

# Chapter 2

## ALS; Advanced Life Support

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## 1 Cardiac arrest algorithm

When a lay rescuer gives CPR, they should follow the Basic Life Support (BLS) algorithm. But healthcare providers who would treat a cardiac arrest patient in hospital or as their duty are recommended to follow the BLS algorithm for healthcare providers (Figure.1) as a preface of Advanced Life Support (ALS) algorithm (Figure.2). These algorithms are ideal when rescuer can use the devices and drugs if needed. ALS algorithm includes the managements during cardiac arrest and after return of spontaneous circulation.

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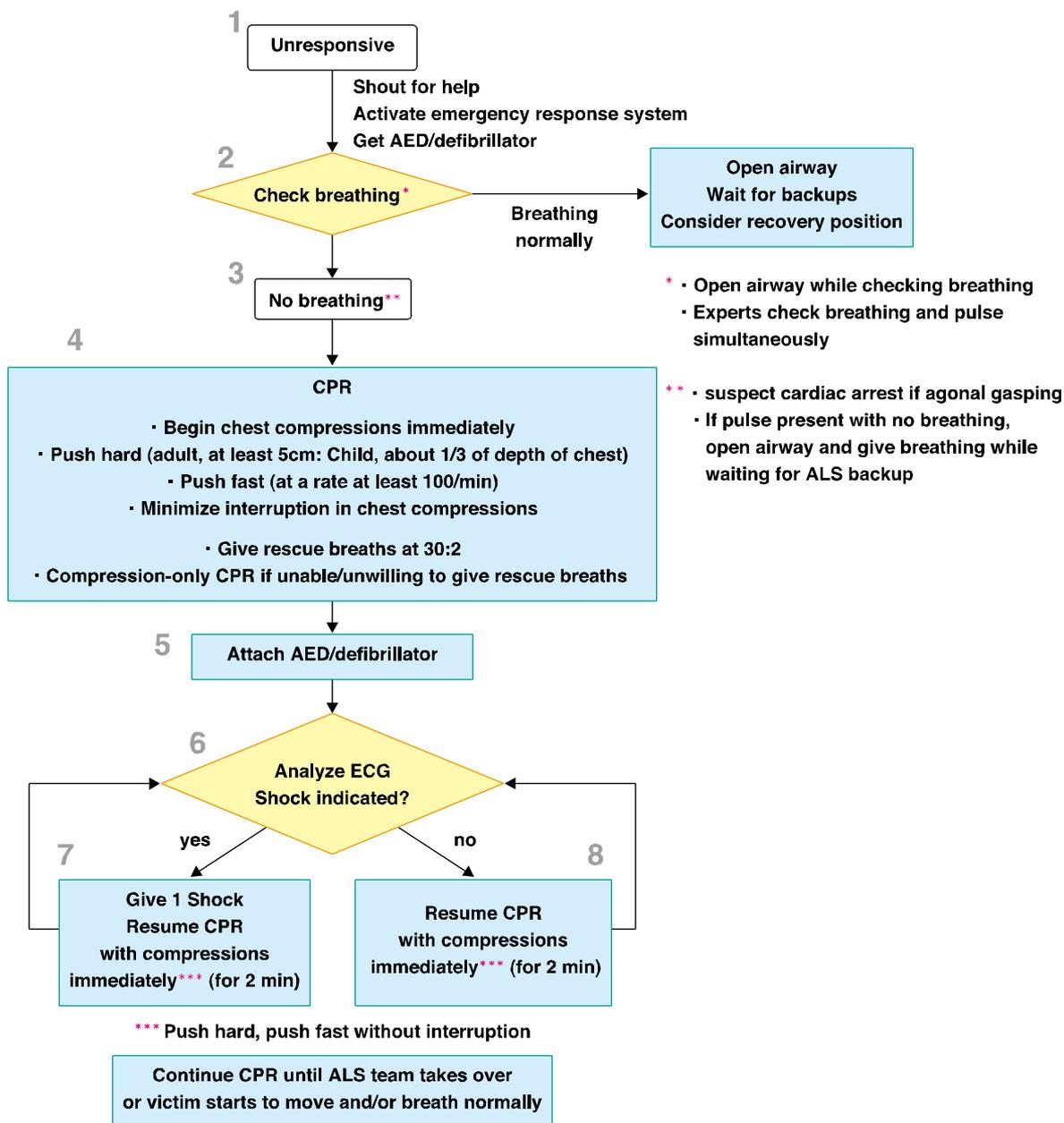


Figure 1. Basic life support for healthcare providers

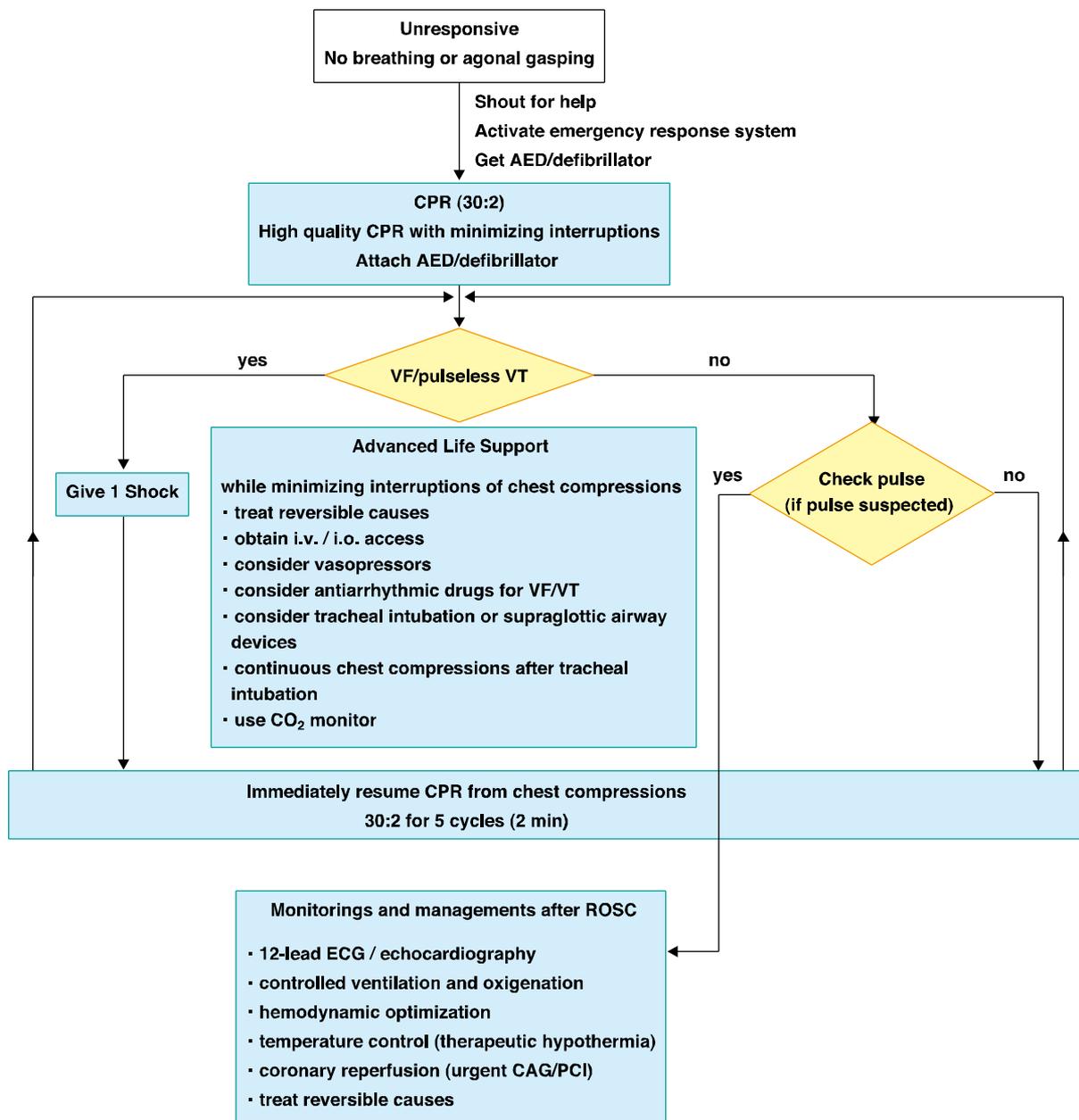


Figure 2 Advance life support

## 2 Airway and ventilation

### 1 Basic Airway Devices

#### 1. Oropharyngeal and Nasopharyngeal Airways

Despite frequent successful use of nasopharyngeal and oropharyngeal airways in the management of non-arrest patients, there are no published data on the use of these airway adjuncts during CPR in humans. When bag-mask ventilation was undertaken with an oral airway and compared with no oral airway, one study in anaesthetized patients demonstrated higher tidal volumes (LOE 5<sup>1</sup>).

In one report, insertion of a nasopharyngeal airway caused some airway bleeding in 30% of cases (LOE 5<sup>2</sup>). One study of nasopharyngeal airways in anesthetized patients showed that nurses inserting nasopharyngeal airways were no more likely than anesthesiologists to cause nasopharyngeal trauma (LOE 5<sup>3</sup>). One study showed that the traditional methods of sizing a nasopharyngeal airway (measurement against the patient's little finger or anterior nares) do not correlate with the airway anatomy and are unreliable (LOE 5<sup>4</sup>). Two case reports reported inadvertent intracranial placement of a nasopharyngeal airway in patients with basal skull fractures (LOE 5<sup>5,6</sup>).

Oro- and nasopharyngeal airways have long been used in cardiac arrest, despite never being studied in this clinical context. It is reasonable to continue to use oro and naso-pharyngeal airways when performing bag-mask ventilation in cardiac arrest (Class IIa), but in the presence of a known or suspected basal skull fracture an oral airway is preferred (Class IIa).

#### 2. Cricoid pressure

No studies addressing the use of cricoid pressure during cardiac arrest were identified. All the identified studies were conducted under anaesthesia or in awake volunteers, cadavers or manikins. (The descriptions of LOE 5\* shown in this chapter are adopted for the studies about non cardiac arrest patients.) The effect of cricoid pressure on gastric inflation during BVM ventilation was examined by 2 adult (LOE 5\* <sup>7,8</sup>) and 2 pediatric studies (LOE 5\* <sup>9,10</sup>). All showed less gastric inflation with cricoid pressure than without, although all of the studies used ventilation volumes higher than those recommended in cardiac arrest.

Nine studies in non arrest adult subjects undergoing anaesthesia showed that cricoid pressure impairs ventilation in many patients, increases peak inspiratory pressures and causes complete obstruction in up to 50% of patients depending on the amount of cricoid pressure (in the range of recommended effective pressure) that is applied (LOE 5\* <sup>7,8,11-16 17</sup>).

One study in anaesthetized patients determined that cricoid pressure prevents correct placement and ventilation with the laryngeal tube (LT) (LOE 5\*<sup>18</sup>). Eight studies in anaesthetized adults showed that when cricoid pressure was used before insertion of a laryngeal mask airway (LMA) there was a reduced proportion of tubes correctly positioned, an increased incidence of failed insertion, and impaired ventilation once the LMA had been placed (LOE 5<sup>19-26</sup>). No significant impairment to

tracheal intubation was found by four studies performed in anaesthetized patients (LOE 5\*<sup>27-30</sup>), while Seven studies (LOE 5\*<sup>19, 31-36</sup>) did show impairment of intubation with increased time to intubation and decreased intubation success rates. One clinical study and One cadaver study demonstrated a worse laryngoscopic view with the application of cricoid pressure (LOE 5\*<sup>37, 38</sup>).

Cricoid pressure prevented movement of liquid from the oesophagus into the pharynx in 5 cadaver studies (LOE 5\*<sup>39-43</sup>) however, in 1 LOE 5\* study<sup>44</sup> of 4891 obstetric patients undergoing anaesthesia, no significant difference was observed in regurgitation rates between patients who received cricoid pressure and those who did not.

The routine use of cricoid pressure to prevent aspiration in cardiac arrest is not recommended (Class III). If cricoid pressure is used during cardiac arrest, the pressure should be adjusted, relaxed or released if it impedes ventilation or placement of an advanced airway.

## 2 Advanced Airway Devices

There is insufficient evidence to support or refute the routine use of specific advanced airway devices during CPR to improve outcome from cardiac arrest. No data support the routine use of a particular device for advanced airway placement during cardiac arrest.

### 1. Timing of Advanced Airway Placement

One registry study evaluated the impact of timing of advanced airway placement during 25,006 in-hospital cardiac arrests (LOE 2<sup>45</sup>). In this study, earlier time to invasive airway (< 5 min) was associated with no improvement in ROSC but improved 24 hour survival (NNT = 48). In an urban out-of-hospital setting, intubation in <12 minutes was associated with better survival than intubation ≥13 minutes<sup>46</sup>. In an out-of-hospital urban and rural setting, patients intubated during resuscitation had better survival than patients not intubated<sup>47</sup>; whereas, in an in-hospital setting, patients requiring intubation during CPR had worse survival<sup>48</sup>. A recent study found that delayed tracheal intubation bundled with passive oxygen delivery and minimally interrupted chest compressions was associated with improved neurologically intact survival after out-of-hospital cardiac arrest in patients with adult, witnessed, ventricular fibrillation/ ventricular tachycardia<sup>49</sup>. The independent contribution of the timing of the advanced airway was not available in the study.

There is inadequate evidence to define the optimal timing of advanced airway placement during cardiac arrest. In the case of shortage of rescuers, early placement of these devices might help the rescuers focus on other effective treatment without having to deal with BVM ventilation.

The tracheal tube was once considered the optimal method of managing the airway in CPR. However, tracheal intubation is a high risk treatment because of esophageal intubation, and requires adequate training and ongoing skills maintenance for secure and prompt intubation. Because prolonged attempts of tracheal intubation are harmful if chest compressions are interrupted, it should be minimized even when performing tracheal intubation (Class I).

## 2. Supraglottic Airway Device Versus Ventilation With Bag-Mask

A retrospective case series (LOE 4) comparing a laryngeal mask airway with bag-mask ventilation in cardiac arrest patients demonstrated a regurgitation rate of 3.5% with use of a laryngeal mask airway and 12.4% with use of bag-mask ventilation<sup>50</sup>. When a variety of supraglottic airway devices were compared with bagmask ventilation in manikin models, six studies showed improved ventilation and a decrease in gastric inflation (LOE 5<sup>51-56</sup>). One pseudorandomized and one nonrandomized clinical trial (LOE 2) found no difference in arterial blood gas values or survival rates when a variety of supraglottic airway devices were compared to bagmask ventilation<sup>57,58</sup>. Three studies performed in manikin cardiac arrest models (LOE 5<sup>59-61</sup>) found that compared with a bag-mask, use of a single-use, disposable laryngeal tube to provide ventilation may decrease no-flow times. Holding the mask to the victim's face with both hands can ensure a better mask seal during bag-mask ventilation(LOE 5<sup>62,63</sup>).

A supraglottic airway device may be considered by healthcare professionals trained in its use as an alternative to bag-mask ventilation during cardiopulmonary resuscitation (Class IIb). When two or more experienced rescuers perform CPR, ventilation with bag-mask is reasonable (Class IIa). It may be beneficial that one rescuer holds the mask with both hands to open the airway and maintain a tight mask-to-face seal while another rescuer compresses the ventilation bag (Class IIa).

### Knowledge Gaps

Further data are needed on the adequacy of ventilation with the various supraglottic airway devices if chest compressions are not interrupted and comparison of the various supraglottic airway devices with bag-mask ventilation and with each other when used clinically by inexperienced and by experienced providers.

## 3. Tracheal Intubation Versus Supraglottic Airway Device

Nine studies compared a variety of supraglottic airway devices with the tracheal tube during cardiac arrest (LOE 1<sup>64</sup>, LOE 2<sup>65-72</sup>) and a further six studies compared a variety of supraglottic airway devices with the tracheal tube in patients undergoing anaesthesia (LOE 5<sup>73-78</sup>). Overall in these studies the supraglottic airway device performed as well as, or better than, the tracheal tube with respect to successful insertion and/or time to tube insertion or to ventilation. One study retrospectively compared outcomes in cardiac arrest patients treated with esophageal-trachealcombitube or tracheal tube and found no difference in ROSC, survival to admission or survival to discharge (LOE 2<sup>71</sup>). One study compared survival in cardiac arrests managed with laryngeal mask airway with an historical control group of cardiac arrests managed with tracheal tube and found that ROSC was significantly higher in the study period (61% vs 36%) (LOE 3<sup>72</sup>).

Nine studies documented that when a supraglottic airway device is used as a rescue airway after failed tracheal intubation, most patients can be ventilated successfully with the supraglottic airway device (LOE 2<sup>65,66,70</sup>, LOE 3<sup>79-82</sup>, LOE 5<sup>74,83</sup>)

Two studies performed while wearing anti-chemical protective clothing, one randomized crossover trial on anaesthetized patients and a second pseudorandomized study on manikins, found increased

time to tracheal tube insertion but not to laryngeal mask airway insertion (LOE 5<sup>75, 84</sup>).

Three manikin studies comparing a supraglottic airway device with the tracheal tube during ongoing chest compressions demonstrated decreased time to intubation with the supraglottic airway device as well as reduced no flow time (LOE 5<sup>85-87</sup>). One non-randomized manikin study found that chest compressions caused only a minor increase in time to tracheal intubation but not to supraglottic airway device insertion (LOE 5<sup>88</sup>).

Healthcare professionals trained to use supraglottic airway devices may consider their use for airway management during cardiac arrest and as a backup or rescue airway in a difficult or failed tracheal intubation (Class IIb). These devices may be used as a backup for a difficult or failed tracheal intubation (Class IIb). Among supraglottic airway devices, there is sufficient evidence to support only for Combitube or LMA as the substitute of tracheal intubation. Although the laryngeal tube is widely used in Japan during CPR, there is insufficient evidence to show its benefit.

## Knowledge Gaps

The adequacy of ventilation with supraglottic airway devices during uninterrupted chest compressions is unknown. The performance of the various supraglottic airway devices should be compared with each other and with the tracheal tube when used in cardiac arrest. Use of the supraglottic airway devices by providers of differing experience should also be studied.

### ■ 3 Confirming tracheal tube Placement

#### 1. Exhaled carbon dioxide detection and esophageal detection devices

Two studies of waveform capnography (LOE 2) to verify tracheal tube position in victims of cardiac arrest after intubation demonstrated 100% sensitivity and 100% specificity in identifying correct tracheal tube placement<sup>89, 90</sup>. Grmec reported that the capnography detected 4 esophageal intubations of 246 cardiac arrests<sup>89</sup>. Silvestri demonstrated that the rate of unrecognized misplaced intubations in the group with continuous ETCO<sub>2</sub> monitoring was zero, and the rate in the group without the monitoring was 23.3%, but this study included non-cardiac arrest patients and did not show the accuracy for cardiac arrest patients<sup>90</sup>.

Three studies (LOE 1<sup>91-93</sup>) with a cumulative total of 194 tracheal and 22 esophageal tube placements demonstrated an overall 64% sensitivity and 100% specificity in identifying correct tracheal tube placement when using the same model capnometer (no waveform capnography) on prehospital cardiac arrest victims. The sensitivity may have been adversely affected by the prolonged resuscitation times and very prolonged transport times of many of the cardiac arrest victims studied. Intubation was performed after arrival at hospital and time to intubation averaged more than 30 minutes.

Studies of colorimetric ETCO<sub>2</sub> detectors, (LOE 2<sup>94, 95</sup>, LOE 4<sup>96-98</sup>, LOE 5<sup>99, 100</sup>), the syringe aspiration esophageal detector device (LOE 1<sup>92</sup>, LOE 4<sup>101</sup>) the self-inflating bulb esophageal detector device (LOE 1<sup>91-93</sup>), and non-waveform end tidal CO<sub>2</sub> capnometers (LOE 2<sup>89, 102</sup>, LOE 4<sup>96</sup>, LOE 5<sup>100</sup>)

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show that the accuracy of these devices is similar to the accuracy of clinical assessment (not uniformly defined across all studies) for confirming the tracheal position of a tracheal tube in victims of cardiac arrest.

Waveform capnography is recommended to confirm and continuously monitor the position of a tracheal tube in victims of cardiac arrest and it should be used in addition to clinical assessment (auscultation and direct visualization is suggested) (Class I).

If waveform capnography is not available, a non-waveform carbon dioxide detector or esophageal detector device in addition to clinical assessment (auscultation and direct visualization is suggested) is an alternative (Class IIa).

## Knowledge Gaps

If a waveform capnography shows zero ETCO<sub>2</sub>, the duration between cardiac arrest and measurement should be considered.

## 2. Thoracic Impedance

Two studies in adults (LOE 5<sup>103, 104</sup>) and one study in children (LOE 5<sup>105</sup>) in patients undergoing anaesthesia demonstrated high sensitivity (0.975-1.0) and specificity (0.925-1.0) of thoracic impedance in diagnosing tracheal and esophageal intubations. One non-randomized trial in immediately post-mortem patients (LOE 2<sup>106</sup>) demonstrated smaller changes in thoracic impedance with esophageal ventilations than with tracheal ventilations. One study (LOE 2<sup>107</sup>) tested impedance-based ventilation recognition during cardiac arrest with ongoing compressions and was able to detect 90.4% of ventilations with a 95.5% positive predictive value. Two case reports comprising a total of 6 cardiac arrest patients with ongoing CPR (LOE 3<sup>108</sup>, LOE 4<sup>109</sup>) demonstrated disappearance of ventilation-induced changes in thoracic impedance after esophageal intubation.

The evidence evaluating the use of thoracic impedance in diagnosing adequacy of ventilation is scant. Supportive evidence from one animal study (LOE 5<sup>110</sup>) demonstrated that the intensity of the thoracic impedance signal was proportional to the observed tidal volumes. An exploratory study conducted in human cardiac arrest patients (LOE 2<sup>111</sup>) demonstrated a strong correlation between thoracic impedance changes and tidal volume changes in the absence of chest compressions, but large variations in measured impedance coefficients ( $\Omega$ /kg/ml) were observed.

Thoracic impedance may be used as an adjunctive measure to diagnose tracheal tube placement in cardiac arrest patients; however, treatment decisions pertaining to accuracy of airway placement should not be based solely upon thoracic impedance measurements until further study has confirmed its utility and accuracy in this population. Thoracic impedance has not been clinically used as a measure to diagnose tracheal tube placement in Japan.

## Knowledge Gaps

More research is needed to clarify the usefulness of thoracic impedance to independently confirm

placement of a tracheal tube and adequacy of ventilation during cardiopulmonary resuscitation.

## 4 Oxygen

### 1. Supplemental oxygen: 100% versus titration

There were no adult (>8 years of age) human studies that addressed directly whether titrated oxygen compared with 100% oxygen during cardiopulmonary resuscitation affects outcome. Two animal studies (LOE 5<sup>112, 113</sup>) using a fibrillatory model of cardiac arrest suggested that use of 100% oxygen during CPR and for 15-60 minutes after return of spontaneous circulation results in worse neurological outcomes compared with normoxic (21% oxygen, room air) resuscitation, whereas one animal study (LOE 5<sup>114</sup>) using an asphyxial model documented that ventilation with either 100% oxygen or 21% oxygen during resuscitation did not affect outcome.

There is insufficient evidence to support or refute the use of a titrated oxygen concentration or constant 21% oxygen (room air) when compared with 100% oxygen during adult cardiac arrest. In the absence of any other data there is no reason to change the current treatment algorithm, which includes use of 100% oxygen during adult cardiac arrest.

### Knowledge Gaps

Prospective clinical trials will be necessary to explore constant (including room air) versus titrated oxygen resuscitation approaches during human adult cardiac arrest.

### 2. Passive oxygen versus positive pressure oxygen during CPR

Two studies (LOE 1<sup>115, 116</sup>) involving ALS providers in- and out-of-hospital settings, and two animal studies (LOE 5<sup>117, 118</sup>) suggested that passive oxygen delivery through a Boussignac tube at a flow of 15 L/min associated with continuous chest compressions (with or without active compression-decompression CPR) generated equal or improved gas exchange and hemodynamics, but without improved outcome (ROSC, hospital discharge survival or neurological outcome), when compared with a standard tracheal tube and positive pressure ventilation.

Four animal models (LOE 5) utilising different devices or approaches (nasal cannula in the oropharynx<sup>119</sup>, pharyngeal-tracheal lumen airway<sup>120</sup> and oxygen catheter tip at the level of the carina<sup>121, 122</sup>) confirmed an equivalent or better gas exchange and/or hemodynamics, with continuous oxygen inflation compared with standard ventilation.

One swine model (LOE 5<sup>123</sup>) demonstrated equivalent gas exchange and 48-hour survival following 4 minutes VF arrest with passive oxygen supplied via tracheal tube compared with oxygen supplied by positive pressure ventilation.

Two studies (LOE 3<sup>124, 125</sup>) of a simplified minimally interrupted cardiac resuscitation (MICR) protocol (concept of cardiocerebral resuscitation), that included passive oxygen delivery via a standard oxygen mask with non-rebreather bag and continuous chest compressions, showed an improvement in neurologically intact survival in adults with bystander-witnessed cardiac arrest and an initially

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shockable rhythm when controlled with historical controls using standard CPR. Another study (LOE 3<sup>49</sup>) demonstrated better survival with passive oxygen delivery than with bag-mask ventilation.

In the three human studies which demonstrated possibility of better neurological outcome, the effective component of the treatment bundle is unknown, because the passive oxygen delivery with continuous chest compressions was compared with the oxygen delivery via bag-mask-ventilation with interruption of chest compressions.

In the studies with a Boussignac tube and some of animal studies, the efficacy of MICR may be reduced, because the passive oxygen delivery was compared with the oxygen delivery through tracheal tube with continuous chest compressions. Arterial blood gas values and circulatory status were certainly improved but there was no difference of the outcome. In addition, these improvements may result from a specific structure of a Boussignac tube itself.

There is insufficient evidence to support or refute the use of passive oxygen delivery during CPR to improve outcomes (ROSC, hospital discharge rate and improve neurological survival) when compared with oxygen delivery by positive pressure ventilation.

## Knowledge Gaps

High-quality controlled clinical trials are required to evaluate the relationship between continuous positive airway pressure and important clinical outcomes and comparison with passive oxygen delivery during cardiopulmonary resuscitation.

## ■ 5 Strategies for Ventilation

### 1. Monitoring ventilatory parameters during CPR

There are no studies that directly addressed the relationship between monitoring of minute ventilation and peak pressure during cardiopulmonary resuscitation and changes in outcome (other than respiratory rate). One animal study (LOE 5<sup>126</sup>) showed that hyperventilation was associated with decreased coronary perfusion pressure and decreased survival. The study also demonstrated that hyperventilation during cardiac arrest is common. One study (LOE 3<sup>127</sup>) demonstrated that real-time feedback during CPR compared with no feedback resulted in a delivered ventilation rate closer to that indicated by current guidelines.

One animal study (LOE 5<sup>128</sup>) showed that during CPR applying PEEP up to 10 cm H<sub>2</sub>O, in addition to intermittent positive pressure ventilation (IPPV), may improve oxygenation compared with IPPV alone. Another study demonstrated that continuous positive airway pressure with pressure support ventilation (CPAP PSV) during resuscitation also may improve oxygenation and outcome (LOE 5<sup>129</sup>).

There is insufficient evidence to support or refute the use of peak pressure and minute ventilation monitoring to improve outcome from cardiac arrest. There is indirect evidence that monitoring the respiratory rate with real time feedback is effective in avoiding hyperventilation and achieving ventilation rates closer to recommended values, but there is no evidence that ROSC or survival is improved.

### Knowledge Gaps

Clinical trials evaluating ventilation monitoring during cardiac arrest resuscitation for all outcomes are needed. There is limited information on the accuracy of ventilation rate monitoring in the new defibrillator software that evaluates CPR process measures. This initial work would be helpful to enable controlled trials to determine the optimal ventilation rate associated with survival.

### 2. Monitoring physiological parameters during

None of the 17 studies that were reviewed evaluated physiological feedback (ETCO<sub>2</sub>, coronary perfusion pressure, superior vena caval central venous oxygen saturation, bispectral index monitoring) specifically as a tool to guide resuscitation intervention in real time to improve outcomes from cardiac arrest. Eleven studies showed that physiologic monitoring values (end tidal CO<sub>2</sub>, coronary perfusion pressure, venous oxygen saturation) increased when return of spontaneous circulation was achieved (LOE 4<sup>94, 130-139</sup>) and may be an indication of ROSC before it can be seen in vital signs<sup>140</sup>.

Five of the studies found that ETCO<sub>2</sub> was accurate for predicting patients who could not be resuscitated; some giving a time frame for that prediction of 20 minutes (LOE 4<sup>95, 133, 137, 141, 142</sup>). However, two studies documented patients who did not meet the ETCO<sub>2</sub> range but who survived (LOE 4<sup>133, 143</sup>). Multiple studies by one group (LOE 4<sup>134-136</sup>) showed that when ETCO<sub>2</sub> exceeded 10 mmHg, all patients achieved ROSC. In one of these studies all the survivors had an initial ETCO<sub>2</sub>

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higher than 10 mmHg<sup>135</sup>. Similarly, two studies showed that if the ETCO<sub>2</sub> did not exceed 10 mmHg, survival was zero (LOE 4<sup>141, 142</sup>).

One study showed no correlation between BIS values during cardiopulmonary resuscitation and ROSC and survival (LOE 4<sup>144</sup>).

Continuous capnography or capnometry monitoring may be beneficial by providing feedback on the effectiveness of chest compressions (Class IIb). The prognostic value of end tidal CO<sub>2</sub> is further reviewed in the section on prognostication.

## Knowledge Gaps

Animal and human studies evaluating the effects of modification of resuscitation based on physiologic feedback would be helpful.

## ■ 6 Automatic Transport Ventilators

### 1. Automatic ventilators vs manual ventilation during CPR

One pseudo-randomized study suggests that use of an automatic transport ventilator with intubated patients may enable the EMS team to perform more tasks while subjectively providing similar ventilation to that of a bag-valve device (LOE 2<sup>145</sup>). One study suggests that use of an automatic transport ventilator with intubated patients provides similar oxygenation and ventilation as use of a bag-valve device with no difference in survival (LOE 2<sup>146</sup>).

There is insufficient evidence to support or refute the use of an automatic transport ventilator over manual ventilation during resuscitation of the intubated cardiac arrest victim.

## Knowledge Gaps

Studies evaluating adequacy of oxygenation, difference between volume and pressure cycled ventilation, survival and complication rates when comparing manual ventilation versus automatic transport ventilator in cardiopulmonary resuscitation with an advanced airway in place are needed to advance the science in this area.

## 2 Supporting the circulation during cardiac arrest

Questions related to circulatory support during cardiac arrest that were discussed during the 2010 Consensus Conference are categorized as (1) timing of drug delivery, (2) vasopressors during cardiac arrest, (3) other drugs during cardiac arrest (4) intravenous fluids and (5) extracorporeal support. It is recognised that the vast majority of studies assessing the effects of drugs on survival have not been able to control for the quality of cardiopulmonary resuscitation. Furthermore, most drug evaluations to date have been conducted before recent advances in post-cardiac arrest care including therapeutic hypothermia. Since most drug trials have, at most, demonstrated only short-term outcome advantage it may be important to evaluate long-term outcome when these drugs are combined with optimized post-cardiac arrest care. One study (LOE 1<sup>147</sup>) compared the use of all drugs (adrenaline, amiodarone, atropine, vasopressin), without isolating the effect of each individual drug alone, with placebo in adult out-of-hospital cardiopulmonary resuscitation and demonstrated improvement in return of spontaneous circulation and survival to hospital and intensive care unit admission, but no difference in survival to discharge or neurologic outcomes at discharge and at 1-year follow-up; however, this study 17 was not powered to detect clinically meaningful differences in long-term outcome. Similarly one study (LOE 3<sup>148</sup>) with a before and after design, compared various outcomes after out-of-hospital cardiac arrest, and was not able to demonstrate any improvements after introduction of advanced life support (adrenaline, atropine, lidocaine). Neither of these studies was able to isolate outcomes specifically related to individual drug administration.

### ■ 1 Timing of drug delivery

There are no studies that addressed the order of drug administration. Subgroup analyses from two clinical studies reported decreased survival for every minute drug delivery was delayed, measured from call received at EMS dispatch (LOE 4<sup>149, 150</sup>). This finding was likely to be biased by a concomitant delay in onset of ALS. In one study the interval from the first shock to the injection of the drug was a significant predictor of survival (LOE 4<sup>149</sup>). One animal study reported lower coronary perfusion pressure when delivery of vasopressor was delayed (LOE 5<sup>151</sup>). Time to drug administration was a predictor of return of spontaneous circulation in a retrospective analysis of swine cardiac arrest (LOE 5<sup>152</sup>).

There is inadequate evidence to define the optimal timing or order for drug administration. An incomplete review of animal studies suggests that timing of vasopressor administration may affect circulation and further investigations are important to help guide the timing of drug administration.

### Knowledge Gaps

Advancing the science in the timing of drug administration is closely related to the need to conduct

placebo-controlled trials to determine the efficacy of some drugs in cardiopulmonary resuscitation. The timing of drug administration and route of delivery are important data points to be captured in future studies. Animal models and clinical trials addressing efficacy can also be designed to provide substantial information on how timing and delivery can impact on outcome. In future, inclusion of 18 studies on pharmacokinetics combined with dose response, as well as studies addressing the impact of timing of defibrillation on circulation and drug effect might better address the question of optimal timing of drug delivery.

## ■ 2 Vasopressors

One study retrospectively compared adrenaline with no adrenaline for sustained VF and PEA/asystole and found improved ROSC with adrenaline for both rhythms but no difference in survival (LOE 2<sup>153</sup>). In a large retrospective registry-based study from Sweden adrenaline was an independent predictor of poor outcome (LOE 2<sup>154</sup>)

Three studies (LOE 1<sup>155-157</sup>) and a meta-analysis (LOE 1<sup>158</sup>) demonstrated no difference in outcomes (ROSC, survival to discharge, or neurologic outcome) with vasopressin when compared with adrenaline as a first line vasopressor in cardiac arrest. Also one study (J-LOE 1<sup>159</sup>) that compared outcomes in out-of-hospital cardiac arrest patients treated with vasopressin or adrenaline, shows no significant difference in ROSC, 24 hour survival or survival to discharge. Two studies (LOE 2<sup>160, 161</sup>) demonstrated no difference in outcomes (ROSC, survival to discharge, or neurologic) comparing adrenaline in combination with vasopressin with adrenaline alone in cardiac arrest. No study demonstrated a survival benefit with high-dose versus standard-dose adrenaline in cardiac arrest.

Two studies (LOE 1<sup>162, 163</sup>) reported improvement in ROSC using high-dose adrenaline. One meta-analysis (LOE 1<sup>164</sup>) 204 of pooled data 19 from 5 studies<sup>162, 163, 165-167</sup> supported improvement in ROSC with high-dose adrenaline but no change in survival outcomes.

Although there is evidence that vasopressors (adrenaline or vasopressin) may improve return of spontaneous circulation and short-term survival, there is insufficient evidence to suggest that vasopressors improve survival to discharge and neurologic outcome. There is insufficient evidence to suggest the optimal dosage of any vasopressor in the treatment of adult cardiac arrest. Given the observed benefit in short-term outcomes, the use of adrenaline or vasopressin may be considered in adult cardiac arrest (Class IIb).

### Knowledge Gaps

Placebo-controlled trials to evaluate the use of any vasopressor in adult and paediatric cardiac arrest are needed.

## ■ 3 Other drugs during cardiac arrest

## 1. Atropine

Three studies (LOE 4<sup>168-170</sup>) documented improvement in survival when atropine was given to patients in asystole; Two of them are in combination with adrenaline<sup>168, 169</sup> and the rest one was the use of atropine for asystole following induction with succinylcholine and fentanyl<sup>170</sup>. One study documented improvement in ROSC (14% versus 0%) when atropine was given to adults in asystolic out-of-hospital cardiac arrest in combination with adrenaline and sodium bicarbonate, but none survived to discharge (LOE 3<sup>171</sup>).

Three studies suggested that the use of atropine for treatment of cardiac arrest was not associated with any change in survival (LOE 2<sup>172</sup>, LOE 5<sup>173, 174</sup>). Four human studies suggested that the use of atropine was associated with poor survival (LOE 4<sup>48, 175-177</sup>).

One study about out-of-hospital cardiac arrest in Japan revealed that atropine increased ROSC and survival rate to hospital admission in patients with asystole, however, it decreased 30-day survival rate in patients with PEA (J-LOE 2<sup>178</sup>) .

Routine use of atropine for asystole and PEA is not recommended (Class III). Atropine may be considered when adrenaline is not effective in asystole (Class IIb).

### Knowledge Gaps

Randomised placebo-controlled trials are required to define the role of atropine in PEA and asystolic cardiac arrest.

## 2. Antiarrhythmic drug

There was little evidence to suggest the advantages in outcomes (e.g., ROSC, survival-to-discharge) with any antiarrhythmic drug (lidocaine, procainamide, amiodarone, bretylium ) used during resuscitation from out-of-hospital or in-hospital cardiac arrest.

### 1) Amiodarone

Two randomised trials for shock refractory or recurrent VT/VF had been performed. One RCT<sup>150</sup> compared 300mg amiodarone with placebo and the other<sup>149</sup> compared amiodarone (initially 5mg/kg, followed by 2.5mg/kg as the second dose ) with lidocaine (initially 1.5mg/kg, followed by 1.5mg/kg as the second dose) demonstrated the benefit of amiodarone on survival to hospital admission, however, it showed no significant difference about survival to hospital discharge.

### 2) Nifekalant

One randomised trial (J-LOE 2<sup>179</sup>) for out-of-hospital cardiac arrest due to shock refractory or recurrent VT/VF was performed. The trial compared the outcome of the patients who administered 0.3mg/kg nifekalant intravenously with 1.5mg/kg lidocaine intravenously. Nifekalant demonstrated the benefit on survival to hospital admission and 24-hour survival rate, while there was no significant difference about the neurological outcome on discharge. Also in the other two studies (J-LOE 2<sup>180</sup>,

## Advanced Life Support (ALS)

J-LOE 3<sup>181</sup>), nifekalant improved ROSC and survival to admission. Combined administration of lidocaine and nifekalant revealed advantage in 24-hour survival rate compared to only lidocaine, however, there was no significant difference about neurological outcome at 30-day of admission (J-LOE 5<sup>182</sup>).

### 3) Lidocaine

Lidocaine (50mg intravenously, up to 4 times) improved survival to admission for out-of-hospital VF in one study (LOE 4<sup>183</sup>).

### 4) Procainamide

A retrospective review found procainamide was associated with increased survival to 1-h postarrest in patients with VF in hospital (LOE 4<sup>174</sup>).

### 5) Magnesium

Four studies comparing magnesium with placebo showed no advantages in ROSC and survival rate (LOE 1<sup>184-187</sup>).

Amiodarone may be considered for those who have refractory VT/VF, defined as VT/VF not terminated by defibrillation, or VT/VF recurrence in out-of-hospital cardiac arrest or in-hospital cardiac arrest (Class IIb). Nifekalant may be considered for those who have electrical shock-refractory VT/VF, or VT/VF recurrence out-of-hospital cardiac arrest or in-hospital cardiac arrest (Class IIb). Lidocaine may be considered when amiodarone or nifekalant is not available, however the efficacy is inferior (Class IIb).

## Knowledge Gaps

All the studies to date were done with stacked shocks; it may be helpful to re-evaluate the efficacy of amiodarone in the setting of a single-shock defibrillation strategy.

## 3. Calcium

Three randomised control trials (LOE 1<sup>188-190</sup>) and three cohort studies (LOE 2<sup>174, 177, 191</sup>) and 1 case series (LOE 4<sup>192</sup>) demonstrated no effect on survival when calcium was given to in-hospital or out-of-hospital cardiac arrest patients. Two adult studies suggest that calcium administration during cardiac arrest was associated with decreased survival to hospital discharge (LOE 2<sup>177, 193</sup>).

In VF, calcium did not restore a spontaneous circulation (LOE 4<sup>192</sup>). In one study of PEA arrests, calcium demonstrated improved ROSC, without reporting long-term survival, but only in a subgroup of patients with wide QRS (LOE 1<sup>189</sup>). Another study showed improved ROSC and survival to hospital arrival; however, there was no significant effect on survival (LOE 4<sup>192</sup>). Another study showed decreased rate of ROSC in the calcium group (LOE 2<sup>193</sup>). In two studies of asystole calcium administration failed to show any improvement in ROSC or survival to hospital discharge (LOE 1<sup>188</sup>,

<sup>190</sup>). One study showed reduced ROSC in the calcium group (LOE 2<sup>193</sup>).

Routine administration of calcium for treatment of in-hospital and out-of-hospital cardiac arrest is not recommended (Class III).

## Knowledge Gaps

More data are needed on the administration of calcium for specific circumstances, such as hyperkalaemia, documented hypocalcaemia, hypermagnesaemia, calcium channel blocker overdose, or wide QRS complexes.

## 4. Steroid and hormonal therapy

There were no human or animal studies that directly addressed the use of the estrogen, progesterone, insulin, or insulin-like growth factor in cardiac arrest. Early observational studies of the use of corticosteroids during cardiac arrest suggested possible benefit (LOE 4<sup>194, 195</sup>). One complex randomised pilot study (LOE 1<sup>196</sup>) and one nonrandomised human study (LOE 2<sup>197</sup>) suggested benefit with corticosteroids, whereas one small, older, human prehospital controlled clinical trial suggested no benefit (LOE 1<sup>198</sup>). One animal study of corticosteroids suggested possible benefit (LOE 5<sup>199</sup>).

There is insufficient evidence to support or refute the use of corticosteroids alone or in combination with other drugs during cardiac arrest.

## Knowledge Gaps

High-quality clinical trials are required to determine if there is a role in cardiopulmonary resuscitation for hormonal therapy with or without vasopressor while controlling for in-hospital use of hormonal therapy postarrest.

## 5. Sodium bicarbonate

Two studies evaluated buffering agents during CPR (LOE 1<sup>200, 201</sup>). Both had limitations but showed no improvement in outcome. Two retrospective cohort studies also showed no benefit in the use of buffering agents during CPR (LOE 2<sup>202, 203</sup>). Two studies demonstrated increased ROSC, hospital admission, and survival at hospital discharge with bicarbonate use (LOE 2<sup>204</sup>, LOE 3<sup>205</sup>). Four cohort studies reported that bicarbonate use was associated with poor short- and long-term outcome (LOE 2<sup>177, 206-208</sup>).

Routine administration of sodium bicarbonate for treatment of in-hospital and out-of-hospital cardiac arrest is not recommended (Class III). For patients with cardiac arrest due to poisoning tricyclic antidepressants may consider the administration of sodium bicarbonate (Class IIb).

## Knowledge Gaps

There are large differences in direction and effect between results from the laboratory and those derived from clinical trials; therefore, well-designed trials, using bicarbonate or non-CO<sub>2</sub> generating buffers, are necessary to clarify the role of buffers in the treatment of short or prolonged cardiac arrest.

## 6. Fibrinolytics

Two studies failed to show any improvement in short- or long-term outcomes with the use of fibrinolytics (LOE 1<sup>209, 210</sup>). One study showed an increased risk of intracranial bleeding associated with the routine use of fibrinolytics during cardiac arrest (LOE 1<sup>210</sup>). Seven studies showed benefit from fibrinolytic therapy in the treatment of victims of cardiopulmonary arrest unresponsive to standard therapy; however, those studies had significant limitations (LOE 1<sup>211</sup>, LOE 2<sup>212-215</sup>, LOE 3<sup>216, 217</sup>).

Routine administration of fibrinolytics for the treatment of in-hospital and out-of-hospital cardiac arrest is not recommended (**Class III**). Administration of fibrinolytics may be considered for cardiac arrest caused by pulmonary embolus (Class IIb). (Pulmonary embolus is described in the section of Chapter 2 [7] Cardiac arrest in special situations.)

## Knowledge Gaps

The potential role of adjuvant antithrombotic and antiplatelet drugs needs exploration.

## **4 Intravenous fluids during cardiac arrest**

Two animal studies reported that normothermic fluid infusion during CPR causes a decrease in coronary perfusion pressure (LOE 5<sup>218, 219</sup>), and another animal study showed that the coronary perfusion pressure rise with adrenaline during CPR is not improved with the addition of a fluid infusion (LOE 5<sup>220</sup>). Most animal studies of fluid infusion during CPR lack a control group that receives no fluids; without a control group, it is difficult to assess of benefit or harm from fluid therapy (LOE 5<sup>221-232</sup>).

### 1. Hypertonic Fluid

One small randomized clinical trial (RCT) in adults found no significant ROSC or survival benefit with hypertonic intravenous fluid infusion when compared to isotonic intravenous fluid infusion during CPR (LOE 5<sup>221</sup>). One animal study showed that hypertonic saline improves cerebral blood flow during CPR (LOE 5<sup>227</sup>). Two animal studies found neither benefit nor harm with infusion of hypertonic saline (LOE 5<sup>225, 232</sup>).

## 2. Chilled fluid vs room-temperature fluid

Two adult studies (LOE 5<sup>223, 226</sup>) and 2 animal studies (LOE 5<sup>230, 231</sup>) showed no improvement in ROSC when cold intravenous fluids (compared with room temperature intravenous fluids) were infused during CPR. One of the reported animal studies showed that the infusion of cold fluids during CPR caused a decrease in coronary perfusion pressure when compared to no fluids (LOE 5<sup>233</sup>).

There is insufficient evidence to recommend for or against the routine infusion of intravenous fluids during cardiac arrest resuscitation.

## **5 Extracorporeal circulatory support during cardiac arrest**

All the studies on this topic were small and there was a lack of consistency in the management before and after extracorporeal-CPR (ECPR). Three studies documented improvement in outcome in patients 70 years old, without significant comorbid conditions and with potential reversible/correctable conditions, when using ECMO (Extracorporeal Membrane Oxigenation) /PCPS (Percutaneous Cardiopulmonary Support) compared with traditional CPR (LOE 2<sup>234, 235</sup>, LOE 3<sup>236</sup>). Two prospective studies demonstrated that 12-52% of out-of-hospital cardiac arrest patients showed improvements in neurological outcomes. These patients had been unresponsive with ordinary CPR and treated with a combination of circulatory support using PCPS and therapeutic hypothermia at 34°C (J-LOE 4<sup>237, 238</sup>). One study demonstrated a 3-month survival of 22.7% for ECPR during out-of-hospital cardiac arrest unresponsive to advance life support after 20 minutes, with 10.6% having a Cerebral Performance Category (CPC) of 1 (LOE 2<sup>235</sup>). However, the ECPR group was more likely to have had a witnessed arrest, received bystander CPR, and be younger (with a mean age of 52 years, compared with 70 years in the standard treatment group).

ECPR (mainly PCPS) may be considered if the duration of circulatory arrest is relatively short and the cause of cardiac arrest (accidental hypothermia, drug intoxication or STEMI) is expected to treat (Class IIb).

### Knowledge Gaps

Future research should define the criteria for ECPR after out-of-hospital cardiac arrest and the criteria for ECPR as a bridge to left ventricular assist device (LVAD) or transplant. In addition, the role of IABP during CPR needs to be studied.

## 4 CPR Techniques and Devices

### 1 Introduction

The success of any technique or device depends on the education and training of the rescuers and as well as on resources (including personnel). In the hands of some groups, novel techniques and adjuncts may produce better short- or long-term outcome than standard CPR. However, a device or technique that provides good quality CPR when used by a highly trained team or in a test setting may show poor quality and create frequent interruptions in CPR when used in an uncontrolled clinical setting<sup>239</sup>.

While no circulatory adjunct is currently recommended instead of manual CPR for routine use, some circulatory adjuncts are being routinely used in both out-of-hospital and in-hospital resuscitation. If a circulatory adjunct is used, rescuers should be well-trained and a program of continuous surveillance should be in place to ensure that use of the adjunct does not adversely affect survival.

The following CPR techniques and devices were reviewed during C2010. It should be noted that interposed abdominal compression has not been studied on humans since 1994 and active compression-decompression has not been studied in humans since 2003. Therefore, these techniques have not been evaluated against the international resuscitation guideline changes of 2000 and 2005 (for interposed abdominal compression) and 2005 (for active compression- decompression).

### 2 Interposed Abdominal Compression CPR (IAC-CPR)

Two randomized controlled trials in in-hospital cardiac arrests, showed improved ROSC and survival to hospital discharge when interposed abdominal compressions (IAC)-CPR was compared with standard CPR (LOE 1<sup>240</sup>, LOE 2<sup>241</sup>). However, there were no differences in neurologically intact survival.

One randomized controlled trial in out-of-hospital cardiac arrest was unable to show any consistent benefits when IAC-CPR was compared with standard CPR (LOE 2<sup>242</sup>).

Evidence from LOE 3<sup>243, 244</sup> and LOE 5<sup>245</sup> in-hospital studies suggests better or neutral<sup>246, 247</sup> hemodynamics with IAC-CPR compared with standard CPR.

There is insufficient evidence to support or refute the use of IAC-CPR.

### 3 Active Compression-Decompression CPR (ACD-CPR)

Five randomized controlled trials (LOE 1<sup>248-252</sup>) and three controlled trials (LOE 2<sup>253-255</sup>) failed to show a difference in ROSC or survival with use of ACD-CPR compared with standard CPR. Six studies (LOE 2<sup>256-261</sup>) demonstrated improved ROSC or survival to hospital discharge although there were no statistically significant differences in neurologically intact survival. A meta-analysis<sup>252</sup> of two trials (826 patients) comparing ACD-CPR with standard CPR after in- hospital cardiac arrest did not

detect a significant increase in rates of immediate survival or hospital discharge.

There is insufficient evidence to support or refute the use of ACD-CPR.

#### ■ 4 Open-Chest CPR

There are no published randomized controlled trials and very limited data in humans comparing open chest CPR to standard CPR in cardiac arrest. One retrospective clinical trial (LOE 3<sup>262</sup>) demonstrated ROSC was improved by open chest CPR in OHCA. One case series in victims of OHCA who had failed standard CPR (LOE 4<sup>263</sup>) reported ROSC in 13 of 33 highly selected patients of whom two survived to hospital discharge.

Multiple animals studies (LOE 5<sup>264-282</sup>) utilizing a variety of endpoints demonstrated benefit with open chest CPR.

There is insufficient evidence to support or refute the routine use of open-chest CPR in cardiac arrest.

#### ■ 5 Load Distributing Band CPR (LDB-CPR)

One multicenter randomized control trial in over 1000 adults documented no improvement in 4-hour survival and significantly worse neurological outcome when LDB-CPR administered by EMS providers was compared with traditional CPR for primary out-of-hospital cardiac arrest (LOE 1<sup>283</sup>). However, a post-hoc analysis of this study revealed significant heterogeneity between study sites (LOE 1<sup>284</sup>).

In one LOE 3 study<sup>285</sup> the use of LDB-CPR was associated with lower odds of 30-day survival (OR 0.4). However, when a smaller (77 patient) subgroup of LDB-CPR treated patients was analyzed against concurrent controls, increased rate of ROSC was noted.<sup>47</sup>

Other non-randomized human series (LOE 3<sup>286, 287</sup>) have reported increased rates of sustained ROSC and increased survival to discharge<sup>49</sup> following out-of-hospital cardiac arrest (OHCA) and improved hemodynamics following failed resuscitation from in-hospital cardiac arrest (LOE 4<sup>288</sup>). In a prospective before-after study (LOE 3<sup>289</sup>) the mean no-flow ratio with manual CPR was 0.28 in the first 5 minutes of CPR compared to 0.40 with LDB-CPR. However between 5 and 10 minutes, no-flow time with manual CPR was 0.34 and 0.21 with LDB-CPR.

Evidence from both clinical (LOE 1<sup>283, 284</sup>) and simulation (LOE 5<sup>290</sup>) studies suggest that site-specific factors may influence resuscitation quality and device efficacy.

A case report documented successful performance of a CT scan while the LDB CPR was used (LOE 4<sup>291</sup>).

There are insufficient data to support or refute the routine use of the load-distributing band (LDB) instead of manual CPR. It may be reasonable to consider LDB to maintain continuous chest compression while undergoing CT scan or similar diagnostic studies, when provision of manual CPR would be difficult (Class IIb).

## ■ 6 Mechanical (Piston) CPR

When a piston CPR device was compared with manual CPR, one randomized controlled trial documented no improvement in ROSC or survival among adults in cardiac arrest (LOE 1<sup>292</sup>).

Supportive data from one prospective, randomized crossover designed study (LOE 1<sup>293</sup>), and one paired cohort study (LOE 2<sup>294</sup>) documented that the use of a piston CPR device improved hemodynamics during CPR in adult cardiac arrest victims.

One prospective pseudorandomized trial documented improvement in hemodynamic variables during CPR in adult cardiac arrest victims but no improvement in ROSC or survival (LOE 2<sup>295</sup>).

Data from one, prospective cohort study comparing the use of a piston CPR device with manual CPR documented that the use of a piston CPR device increased interruption in CPR because time was required to set up and remove the device from patients during transportation in out-of-hospital adult cardiac arrest (LOE 2<sup>296</sup>).

There is insufficient evidence to support or refute the use of a piston CPR instead of manual CPR for adult victims of cardiac arrest.

## ■ 7 Lund University Cardiac Arrest System CPR (LUCAS-CPR)

There are no RCTs evaluating the LUCAS device in human cardiac arrests.

One study using concurrent controls in witnessed OHCA was unable to show any benefit (ROSC, survival to hospital or survival to hospital discharge) with the use of the LUCAS device over standard CPR (LOE 2<sup>297</sup>).

One postmortem study showed similar injuries with LUCAS and standard CPR (LOE 2<sup>298</sup>).

Six case series involving approximately 200 patients have reported variable success in use of the LUCAS device, when implemented after an unsuccessful period of manual CPR (LOE 4<sup>299-304</sup>).

Six adult human studies (LOE 4<sup>300, 301, 304-307</sup>) and one animal study (LOE 5<sup>306</sup>) reported that the use of a mechanical chest compression device in cardiac arrest during percutaneous coronary intervention maintained circulation and enabled the procedure to be completed. A small number of patients in the case series survived.

Two case reports demonstrated that a CT scan could be performed during CPR with the LUCAS device (LOE 4<sup>291</sup>).

There are insufficient data to support or refute the use of LUCAS-CPR instead of manual CPR. It may be reasonable to consider LUCAS-CPR to maintain continuous chest compression while undergoing CT scan or similar diagnostic studies, when provision of manual CPR would be difficult (Class IIb).

## ■ 8 Impedance Threshold Device (ITD)

One meta-analysis that pooled the data from both conventional CPR and ACD-CPR randomized

controlled trials (RCTs) demonstrated improved ROSC and short-term survival but no significant improvement in either survival to discharge or neurologically intact survival to discharge associated with the use of an ITD in the management of adult OHCA patients (LOE 1<sup>308</sup>).

One randomized controlled trial suggested that the use of an ITD in combination with ACD-CPR improved 24 hour survival and survival to ICU admission in adult OHCA patients, compared with ACD-CPR and a sham ITD (LOE 1<sup>309</sup>). This contrasts with another randomized controlled trial which compared ITD plus ACD-CPR with ACD-CPR plus a sham ITD that did not show significant improvement in ROSC or 24hour survival with use of the ITD (LOE 1<sup>310</sup>).

One randomized controlled trial reported that the use of an ITD in combination with standard CPR (CPR) did not significantly improve ROSC, 24 hour survival or survival to ICU admission in adult OHCA patients, compared with CPR and a sham ITD (LOE 1<sup>311</sup>).

One randomized controlled trial comparing ACD-CPR plus ITD with CPR in adult OHCA patients showed improved ROSC and 24hour survival rates associated with ACD-CPR plus ITD, but no significant improvement in hospital discharge or intact neurologic survival to hospital discharge rates (LOE 1<sup>312</sup>).

One prospective cohort study (with historical control) of CPR plus ITD vs. CPR (without ITD) in OHCA reported improved survival to ED admission for OHCA patients presenting in any rhythm (LOE 3<sup>313</sup>).

Three cohort studies comparing CPR using 2005 Guidelines plus ITD, with historic controls of CPR using 2000 Guidelines, demonstrated improved survival to hospital discharge in out of hospital cardiac arrest (LOE 3<sup>314-316</sup>). It was not possible to determine the relative contribution of the ITD to the improved outcome.

In a porcine model of cardiac arrest, 8 studies demonstrated improved hemodynamic variables during CPR with use of the ITD (LOE 5<sup>128, 317-323</sup>). A further three animal studies (LOE 5<sup>324-326</sup>) showed no difference in survival or in any hemodynamic variable and two animal studies (LOE 5<sup>325, 327</sup>) reported evidence of a decrease in ROSC, 20minute survival and arterial oxygen saturation associated with the use of an ITD.

There is insufficient data to support or refute the use of the ITD. (ITD is unapproved per the Pharmaceutical Affairs Law in Japan.)

## 5 Defibrillation

### 1 Introduction

The 2010 Defibrillation Task Force considered many questions related to defibrillation. In general, the 2010 International Consensus on Science with Treatment Recommendations statement contains no major differences or dramatic changes from the 2005 International Consensus statement. The questions have been grouped into the following categories: (1)CPR Before Defibrillation, (2)Electrode-Patient Interface, (3)Defibrillation strategy, (4)Special Circumstances and (5)Related defibrillation topics.

Science and treatment recommendations dealing with the infant or child requiring defibrillation can be found in the "Pediatric Basic and Advanced Life Support" chapter. The only two treatment recommendations that differ for adult and pediatric patients are defibrillation dose and AED use.

There are several Knowledge Gaps created by the lack of high-quality, large clinical studies. These include: the minimal acceptable first shock success rate; the characteristics of the optimal biphasic waveform; the optimal energy levels for specific waveforms; and the best shock strategy (fixed versus escalating).

### 2 Integration of CPR and defibrillation

Whether a period of CPR should be performed before defibrillation in ventricular fibrillation (VF), especially after long response times, has recently been the subject of intense debate. The theoretical rationale for CPR before shock delivery is to improve coronary perfusion and thereby the chances of achieving sustained return of spontaneous circulation (ROSC).

#### 1. CPR before defibrillation

In two randomized controlled trials (LOE 1<sup>328, 329</sup>), a period of 1.5 to 3 minutes of CPR by EMS personnel before defibrillation did not improve return of spontaneous circulation (ROSC) or survival to hospital discharge in patients with out-of-hospital VF or pulseless ventricular tachycardia (VT), regardless of EMS response interval. One before and after study (LOE 3<sup>330</sup>) and another study (LOE 4<sup>331</sup>) failed to demonstrate significant improvements in ROSC or survival to hospital discharge when a strategy of CPR before defibrillation (CPR first) was compared to a shock first strategy. In the Hayakawa study, the CPR first group showed a higher rate of favorable neurologic outcome 30 days and one year after cardiac arrest.

One randomized controlled trial (LOE 1<sup>332</sup>) and one clinical trial with historic controls (LOE 3<sup>333</sup>) comparing CPR first versus shock first also found no overall difference in outcomes. However, in both studies, improvements in ROSC, survival to hospital discharge, neurologic outcome and one-year survival were observed in a subgroup of patients who received CPR first where the EMS response interval was greater than 4 to 5 minutes.

There is inconsistent evidence to support or refute delay in defibrillation to provide a period of CPR (90 seconds to 3 minutes) for patients in ventricular fibrillation/pulseless VT cardiac arrest.

## 2. Use of filtering devices for rhythm analysis during CPR

As chest compressions produce artifacts, it is difficult to analyze the ECG during CPR. Therefore once AED starts ECG analysis, chest compressions are forced to be interrupted. However, interruptions of chest compressions decrease the rate of ROSC, survival, and myocardial function after ROSC. Especially the time for ECG analysis by AED is one of the main cause of the interruption. On the other hand, there is a possibility to shorten the interruption of compression by using a filtering devices for rhythm analysis.

In six studies (LOE 5<sup>334-339</sup>) using human-derived ECG recordings with actual or simulated CPR artifacts and one study in a swine model of VF (LOE 5<sup>340</sup>), the use of computerized algorithms that removed compression artifacts from the ECG during CPR reduced the accuracy of rhythm analysis relative to rhythm analysis during pauses. Sensitivity was between 90% and 98%, which would cause inappropriate prolongations in chest compression for shockable rhythms in up to 1 out of 10 patients. Specificity was between 80% and 89%, which could result in inappropriate interruptions in chest compression for shock delivery in victims who actually had nonshockable rhythms.

There is insufficient evidence to support or refute the use of artifact-filtering algorithms for analysis of ECG rhythm during CPR.

## **3** Electrode–patient interface

Studies on defibrillation for cardiac arrest and on cardioversion for atrial fibrillation (AF) are both included here. While few studies compared differences in outcome, many studies compared secondary end points such as effect on transthoracic impedance (TTI). In ventricular arrhythmias, however, there is no direct evidence that TTI affects shock success.

### 1. Self-adhesive defibrillation pads compared with paddles

Since 2005 there have been no new studies comparing selfadhesive defibrillation pads with paddles in cardiac arrest. Evidence from one small, good-quality controlled study (LOE 3<sup>341</sup>) in 1987 showed that self-adhesive pads were associated with a significantly improved rate of ROSC and hospital admission compared with hand-held paddles. Several studies have shown the practical benefits of pads over paddles for routine monitoring and defibrillation<sup>342-346</sup>.

One prospective study (LOE 3<sup>347</sup>) found lower TTI when paddles applied at an optimal force of 8 kg were compared with pads. In a cohort study in patients with atrial fibrillation (LOE 2<sup>348</sup>) the use of hand-held paddles placed in the anterior–posterior position increased the success rate of monophasic cardioversion compared with similarly placed self-adhesive electrodes for monophasic defibrillation. The overall cardioversion success rate for biphasic defibrillators was high (>95%) in all groups. In the majority of other studies, self-adhesive electrodes were associated with similarly high cardioversion success rates.

For both defibrillation and AF cardioversion, when using biphasic defibrillators, self-adhesive defibrillation pads are safe and effective and are an acceptable alternative to standard defibrillation paddles (Class IIb). In AF cardioversion using monophasic defibrillators, hand-held paddles are preferable (Class IIa).

## 2. Placement of paddles/pads

There are no studies in patients with VF/pulseless VT directly comparing the effects of various positions of paddle/pad placement on defibrillation success and ROSC. Most studies evaluate cardioversion (e.g., AF) or secondary end points (e.g., TTI). Eleven studies (LOE 5<sup>349-359</sup>) found all four positions (anterior–apex, anterior–posterior, anterior–left infrascapular, anterior–right infrascapular) to be equally effective in defibrillation (for VF/pulseless VT) or elective AF cardioversion success. Four studies support the anterior–posterior position (LOE 5<sup>360-364</sup>), one study supports the anterior–lateral position (LOE 5<sup>365</sup>), and one study supports the anterior–apex position (LOE 5<sup>366</sup>).

Five studies (LOE 5<sup>350, 355-358</sup>) found no effect of electrode position on TTI. One study showed that paddles/pads should be placed under the breast tissue (LOE 5<sup>367</sup>) and two studies showed that hirsute males should be shaved before the application of pads (LOE 5<sup>368, 369</sup>). Of the 36 studies reviewed, only four examined biphasic waveforms (LOE 5<sup>352, 359, 363, 370</sup>) that have gained widespread use.

It is reasonable to place paddles/pads on the exposed chest in an anterior–lateral position (Class IIa). Acceptable alternative positions are anterior–posterior (for paddles/pads) and apex–posterior (for pads). In large-breasted individuals it is reasonable to place the left electrode paddle/pad lateral to or underneath the left breast, avoiding breast tissue (Class IIa). Consideration should be given to the rapid removal of excessive chest hair before the application of paddles/pads but emphasis must be on minimizing delay in shock delivery.

## 3. Size of paddles/pads

No new clinical study on this topic has been published since 2005. One study demonstrated that TTI decreased and shock success increased with increasing pad size (from 8 to 12 cm) (LOE 3<sup>371</sup>). Ten other studies showed that larger paddle/pad sizes (8- to 12-cm diameter) lowered TTI and that maximum paddle/pad size was limited by the chest wall size and anatomy (LOE 3<sup>372</sup>, LOE 5<sup>357, 370, 373-379</sup>). No data related to survival outcome was included in these studies.

There is insufficient evidence to recommend a specific electrode size for optimal external defibrillation in adults. However, it is reasonable to use a paddle/pad size >8 cm (Class IIa).

## 4. Composition of conductive material

Fourteen studies showed that the composition of the conductive material (e.g., saline, hypertonic sodium chloride [NaCl] solution, or silver-silver chloride) may alter TTI by more than 20% (LOE 2<sup>373</sup>,

<sup>380, 381</sup>, LOE 3<sup>371</sup>, LOE 4<sup>382</sup>, LOE 5<sup>368, 383-390</sup>). Five studies (LOE 3<sup>391, 392</sup>, LOE 5<sup>393-395</sup>) showed that TTI was not affected by electrode composition. The end point for all of these studies was TTI, and no studies involved outcomes following cardiac arrest.

The composition of the conductive material of defibrillation electrodes influences TTI. In terms of cardiac arrest outcomes, there is insufficient evidence to recommend a specific composition of the defibrillation electrode conductive material.

## 4 Waveforms, energy levels, and strategies

All new defibrillators currently deliver shocks using biphasic waveforms. Although it has not been demonstrated conclusively in randomised clinical studies that biphasic defibrillators save more lives than monophasic defibrillators, biphasic defibrillators achieve higher first-shock success rates. Shock success is usually defined as termination of VF 5 seconds after the shock.

### 1. Biphasic compared with monophasic defibrillation waveform

In three randomised trials (LOE 1<sup>396-398</sup>) and four other human studies (LOE 3<sup>399-401</sup>) biphasic waveforms had higher shock-success rates compared with monophasic defibrillation. One randomised study comparing transthoracic incremental monophasic with biphasic defibrillation for out-of-hospital pulseless VT/VF cardiac arrest failed to demonstrate any significant differences in any outcome (LOE 1<sup>402</sup>). A single-cohort study (LOE 3<sup>403</sup>) using the 2000 International Guidelines<sup>404</sup> demonstrated better hospital discharge and neurological survival with biphasic than with monophasic waveforms. However, there were confounding factors in that the intervals between the first and second shocks (of three-stacked shocks) were shorter with the biphasic defibrillators.

There is no clinical evidence for superiority of any specific biphasic waveform over another.

Biphasic waveforms are more effective in terminating VF when compared with monophasic waveforms (Class IIb). There is insufficient evidence to recommend any specific biphasic waveform. In the absence of biphasic defibrillators, monophasic defibrillators are acceptable.

### 2. Multiphasic compared with biphasic defibrillation waveform

There are no human studies to support the use of multiphasic waveforms over biphasic waveforms for defibrillation. Animal data suggests that multiphasic waveforms may defibrillate at lower energies and induce less postshock myocardial dysfunction<sup>405, 406</sup>. These results are limited because in all studies duration of VF was very short (approximately 30 s) and results have not been validated in human studies.

Currently, multiphasic defibrillators are not commercially available.

### 3. Waveforms, energy levels, and myocardial damage

Several different biphasic waveforms are used in commercially available defibrillators, but no

human studies have directly compared these waveforms or compared them at different energy levels related to defibrillation success or survival.

### 1) Biphasic truncated exponential (BTE) waveform

Evidence from one well-conducted randomised trial (LOE 1<sup>407</sup>) and one other human study (LOE 2<sup>408</sup>) employing BTE waveforms suggested that higher energy levels are associated with higher shock-success rates. In the randomised trial, the first-shock success rate was similar with 150 J and 200 J<sup>407</sup>.

### 2) Pulsed biphasic waveform

In one study using pulsed biphasic waveforms at 130 J the first-shock success rate was 90% (LOE 4<sup>409</sup>).

### 3) Rectilinear biphasic waveform

When defibrillation success was defined as ROSC (this differs from the definition in other studies), one study using a rectilinear biphasic waveform showed that an organised rhythm was restored by the first shock (120 J) in 23% of cases (LOE 1<sup>396</sup>). Success rate for the termination of VF at 5 s was not published for this waveform.

For the different biphasic waveforms, studies of different size and quality have been performed and are presented separately. For all waveforms, insufficient evidence exists to make clear recommendations.

### 4) Monophasic waveform (damped sinusoid or truncated exponential)

Evidence from three studies of monophasic defibrillation suggested equivalent outcomes with lower and higher starting energies (LOE 1<sup>410</sup>, LOE 2<sup>411, 412</sup>).

### 5) Myocardial damage associated with higher energy level shocks

Several animal studies have suggested the potential for myocardial damage with higher energy shocks using BTE or monophasic waveforms (LOE 5<sup>370, 413-415</sup>). Human studies involving BTE waveforms<sup>407, 416</sup> with energy levels up to 360 J have not shown harm as indicated by biomarker levels, ECG findings, and ejection fractions.

It is reasonable to start at a selected energy level of 150–200 J for a BTE waveform for defibrillation of pulseless VT/VF cardiac arrest (**Class I**). There is insufficient evidence to determine the initial energy levels for any other biphasic waveform. Although evidence is limited, because of the lower total shock success for monophasic defibrillation, initial and subsequent shocks using this waveform should be at 360 J.

## 6) One-shock compared with three-stacked shock protocols

One study showed no survival benefit from a protocol that included a single-shock protocol compared to a three-shock protocol (LOE 1<sup>417</sup>). Evidence from three pre–post design studies suggested significant survival benefit with a single-shock defibrillation protocol compared with three-stacked shock protocols (LOE 3<sup>285, 418, 419</sup>). However, these studies included confounders related to pre–post design and the multiple interventions that were included as part of the defibrillation protocol. Another pre–post study, with fewer confounding factors, showed a significantly lower hands-off ratio (i.e., percentage of total CPR timewhen no compressions were provided) with the one-shock protocol but no statistical difference in survival (LOE 3<sup>420</sup>).

One observational study of fixed-dose biphasic defibrillation suggested higher defibrillation success with three shocks (LOE 4<sup>421</sup>). The same study also suggested that chest compressions immediately following a shock did not result in recurrence of VF. In contrast another study showed earlier recurrence of VF when chest compressions were resumed immediately after the shock compared with delayed resumption of compressions (LOE 1<sup>422</sup>). There was no significant difference in total incidence of recurrent VF or outcome. A single study demonstrated that early termination of recurrent VF was associated with increased ROSC, but quality of CPR was poor and few patients achieved ROSC (LOE 4<sup>423</sup>). Another study showed decreased survival when defibrillation for recurrent VF was, for a variety of reasons, delayed (LOE 4<sup>424</sup>).

When defibrillation is required, a single shock should be provided with immediate resumption of chest compressions after the shock (**Class I**). Chest compressions should not be delayed for rhythm reanalysis or pulse check immediately after a shock. CPR should not be interrupted until rhythm reanalysis is undertaken.

## 7) Fixed versus escalating defibrillation energy protocol

One randomised trial (LOE 1<sup>407</sup>) of 150-J fixed versus 200-J to 300-J to 360-J shocks and one LOE 2 study<sup>408</sup> of 150-J fixed versus 100-J to 150-J to 200-J shocks supported the use of an escalatingenergy biphasic defibrillation protocol compared with a fixed-dose defibrillation protocol. In one study (escalating 200-J to 200-J to 360-J shocks), the success rate of defibrillation for recurrent VF declined with the number of recurrences (LOE 4<sup>425</sup>). However, these studies were not designed to demonstrate an improvement in the rate of ROSC or survival to hospital discharge. One study of fixeddose biphasic defibrillation suggested that defibrillation success improved with three shocks (LOE 4<sup>421</sup>). All of these studies were done with the three-shock protocol (before the change in Guidelines 2005).

For second and subsequent biphasic shocks the same initial energy level is acceptable (**Class IIb**). It is reasonable to increase the energy level when possible (**Class IIa**).

## 8) Shock using manual versus semiautomatic mode

Modern defibrillators can be operated in both manual and semiautomatic (AED-similar) modes.

However, few studies compare these two options. One randomised controlled study showed no significant difference in survival-to-hospital-discharge rate but significant reduction in time to first shock in the AED group versus the manual group (1.1 min versus 2.0 min) (LOE 1<sup>426</sup>). One good concurrent controlled OHCA study in 36 rural communities showed no improvements in ROSC, survival, or neurological outcome but significantly shorter times to first shock and higher VF conversion rates when paramedics used AEDs in semiautomatic mode compared with manual mode (LOE 2<sup>427</sup>). One retrospective study demonstrated no improvement in survival to hospital discharge for adult IHCA when comparing AED with manual defibrillators (LOE 4<sup>428</sup>). In patients with initial asystole or pulseless electric activity (PEA), AEDs were associated with a significantly lower survival (15%) compared with manual defibrillators (23%, P = 0.04)<sup>428</sup>.

In a study of three different EMS systems and one in-hospital centre, manual mode of defibrillation was associated with a lower total hands-off ratio (i.e., percentage of total CPR time when no compressions were provided) than AED mode (LOE 3<sup>429</sup>). However, more shocks were delivered inappropriately by rescuers using manual defibrillators (26% manual versus 6% AEDs). A randomised manikin study simulating cardiac arrest showed a lower handsoff ratio, mainly due to a shorter preshock pause, when trained paramedics used the defibrillator in manual mode compared with semiautomatic mode (LOE 5<sup>430</sup>). More inappropriate shocks (12% versus 0) were delivered in manual mode. All episodes of VF were detected and shocked appropriately. A shorter preshock pause and lower total hands-off ratio increased vital organ perfusion and the probability of ROSC (LOE 5<sup>431-433</sup>).

No significant survival differences have been demonstrated between defibrillation in semiautomatic and manual modes during out-of-hospital or in-hospital resuscitation; however, the semiautomatic mode is preferred because it is easier to use and may deliver fewer inappropriate shocks.

Trained personnel may deliver defibrillation in manual mode (**Class IIb**). Use of the manual mode enables chest compressions to be continued during charging, thereby minimizing the preshock pause. When using the defibrillator in manual mode, frequent team training and ECG recognition skills are essential.

The defibrillation mode that results in the best outcome will be influenced by the system of care and by provider skills, training, and ECG recognition.

## 9) Cardioversion strategy in atrial fibrillation

Twenty-two studies have compared specific cardioversion strategies (monophasic vs biphasic defibrillators, different energy levels) administered by cardiologists in the hospital setting to patients with atrial fibrillation (both acute/chronic) (LOE 1<sup>348, 351, 360, 361, 365, 434-447</sup>, LOE 2<sup>448, 449</sup>). Most of these studies document that biphasic shocks were more effective than monophasic shocks for cardioversion.

Studies with varying strategies (fixed and escalating) and energy levels all resulted in high cardioversion rates for a variety of biphasic waveforms, with no clear evidence of superiority. For monophasic defibrillation, higher initial energy levels (360J) were associated with higher cardioversion rates and less total energy used than escalating from lower to higher energy levels. Body weight may affect cardioversion success, and one study suggested that initial shock should be 200J for patients < 90 kg and 360 J if > 90 kg (LOE 1<sup>450</sup>). In general, increased total energy use was associated

with more dermal injury and post-procedural pain (LOE 1<sup>435, 444, 451</sup>).

Biphasic defibrillators are preferred for cardioversion of atrial fibrillation (Class IIa). There is no evidence to recommend a specific waveform, energy level or strategy (fixed vs escalating) when using biphasic defibrillators. For monophasic defibrillators, a high initial energy (360 J) seems preferable (Class IIb).

## ■ 5 Special circumstances

Some special circumstances, such as if pacing is ever indicated during cardiac arrest, or how to respond in cardiac arrest if the patient has a pacemaker or an internal defibrillator are presented and discussed in this section.

### 1. Precordial thump

In five prospective case series of out-of-hospital (LOE 4<sup>452-456</sup>) and two series (LOE 4<sup>453, 454</sup>) of in-hospital VF cardiac arrest, healthcare provider administration of the precordial thump did not result in ROSC. In three prospective case series of VT in the electrophysiology laboratory (LOE 4<sup>453, 457, 458</sup>), administration of the precordial thump by experienced cardiologists was of limited use (1.3% ROSC). When events occurred outside of the electrophysiology laboratory, in six case series of in- and out-of-hospital VT (LOE 4<sup>454-456, 459-461</sup>), the precordial thump was followed by ROSC in 19% of patients. Rhythm deterioration following precordial thump occurred in 3% of patients and was observed predominantly in patients with prolonged ischaemia or digitalis-induced toxicity.

Two case series (LOE 4<sup>456, 462</sup>) and a case report (LOE 5<sup>463</sup>) documented the potential for complications from use of the precordial thump, including sternal fracture, osteomyelitis, stroke, and rhythm deterioration in adults and children.

The precordial thump is relatively ineffective for VF, and it should not be used for unwitnessed OHCA (Class III). The precordial thump may be considered for patients with monitored, unstable VT if a defibrillator is not immediately available (Class IIb). There is insufficient evidence to recommend for or against the use of the precordial thump for witnessed onset of asystole caused by atrioventricular conduction disturbance.

### 2. Pacing (e.g., transcutaneous [TC], transvenous [TV], needle, and fist)

Four studies addressed the efficacy of pacing in cardiac arrest (LOE 2<sup>464-466</sup>, LOE 3<sup>467</sup>). These studies found no benefit from routine pacing in cardiac arrest patients. Use of pacing (transcutaneous, transvenous, needle) in cardiac arrest (in-hospital or out-of-hospital) did not improve ROSC or survival. There was no apparent benefit related to the time at which pacing was initiated (early or delayed in established asystole), location of arrest (in-hospital or out-of-hospital), or primary cardiac rhythm (asystole, PEA). Five case series (LOE 4<sup>468-472</sup>), a review with two additional case reports<sup>473</sup>, and a moderate sized case series (LOE 4<sup>474</sup>), support percussion pacing in p-wave asystolic cardiac arrest/complete heart block or hemodynamically unstable patients with bradycardia. In these reports,

sinus rhythm with a pulse was restored using different pacing techniques.

Electrical pacing is not effective as routine treatment in patients with asystolic cardiac arrest (Class III). Percussion pacing is not recommended in cardiac arrest in general (Class III). However, fist pacing may be considered in hemodynamically unstable bradyarrhythmias until an electrical pacemaker (transcutaneous or transvenous) is available (Class IIb). The use of epicardial wires to pace the myocardium following cardiac surgery is effective and discussed elsewhere (Class I).

### 3. Implantable cardioverter defibrillator or pacemaker

Two case series reported pacemaker or implantable cardioverter defibrillator (ICD) malfunction after external defibrillation when the pads were placed in close proximity to the device generator (LOE 4<sup>475, 476</sup>). One small study on atrial cardioversion demonstrated that positioning the pads on the chest at least 8 cm from the device generator did not produce significant damage to pacing sensing and capturing (LOE 4<sup>475</sup>).

One case report suggested that pacemaker spikes generated by devices programmed to unipolar pacing may confuse AED software and emergency personnel and may prevent the detection of VF (LOE 4<sup>477</sup>).

In patients with an ICD or a permanent pacemaker, the placement of pads/paddles should not delay defibrillation (Class I). In this case, it is reasonable to avoid placing the pads/paddles directly over the implanted device (Class IIa). Although some reports suggest that the pads/paddles should be placed on the chest wall ideally at least 8 cm from the generator position, shock delivery should not be delayed for ideal pads/paddles placement.

## **6 Defibrillation-related topics**

### 1. Predicting success of defibrillation and outcome (VF waveform analysis)

VF waveform analysis has been shown to correlate with myocardial perfusion/coronary perfusion pressure. In theory waveform analysis could be a tool for predicting outcome of defibrillation and therefore indicate the optimal time for shock delivery.

Retrospective analysis of the VF waveform in multiple clinical (LOE 1<sup>478, 479</sup>, LOE 4<sup>480, 481</sup>, LOE 5<sup>482, 483</sup>) and animal studies (LOE 5<sup>484-486</sup>) and theoretical models suggested that it is possible to predict the success of defibrillation from the fibrillation waveform with varying reliability. One animal study was neutral (LOE 5<sup>487</sup>). No human studies have specifically evaluated whether treatment altered by predicting success of defibrillation can improve successful defibrillation, ROSC, or survival from cardiac arrest. Multiple waveform parameters have been examined without consensus on the most important parameters to predict outcome.

There is insufficient evidence to support routine use of VF waveform analysis to guide defibrillation

management in adult cardiac arrest in- or out-of-hospital.

## 2. Defibrillation in the immediate vicinity of supplementary oxygen

Four case reports involving adults (LOE 4<sup>488-491</sup>) and one case report involving a neonate (LOE 4<sup>492</sup>) described fires caused by sparks generated during defibrillation attempts when paddles were used in the vicinity of high-flow (>10 L/min) oxygen. There are no case reports of fires caused by sparking when shocks were delivered using adhesive pads. In two manikin studies the oxygen concentration in the zone of defibrillation was not increased when ventilation devices (self-inflating bag, and more) were left attached to a tracheal tube or when the oxygen source was vented at least one metre behind the patient's mouth (LOE 5<sup>493, 494</sup>). One study described higher oxygen concentrations and longer washout periods when oxygen was administered in confined spaces without adequate ventilation (LOE 5<sup>495</sup>).

Rescuers should take precautions to minimise sparking (by paying attention to pad/paddle placement, contact, etc.) during attempted defibrillation (Class I). Rescuers should try to ensure that defibrillation is not attempted in an oxygen-enriched atmosphere (e.g., when high-flow oxygen is directed across the chest) (Class I).

## 6 Antiarrhythmic therapies during periarrest

### 1 Overview

When you recognize arrhythmias of the patients as healthcare providers, you should check airway, breathing and pulse immediately. CPR should be started promptly in cardiac arrest. You should attach the ECG monitor and pulse oxymeter in non-cardiac arrest case. Oxygen may be given if needed. Then you have to evaluate the patient's symptoms and clinical signs whether the patient's condition is stable or unstable. When an arrhythmia causes a patient unstable, you should establish any venous access for possible emergent medicines. Then you have to assess whether or not decreasing cardiac output by the arrhythmia is a direct cause for the signs and symptoms of the patients. Treat the arrhythmias first in the former cases but the treatment is not necessary in the latter.

For references; Signs and symptoms suggesting the unstable status are as follows:

- symptoms: altered mental status, syncope, ongoing chest pain, dyspnea, etc.
- signs: hypotention, other signs of shock (perspiration, cold clammy skin, oliguria, disturbance of consciousness), etc.

### 2 Bradycardia

#### 1. Algorithm for the management of bradyarrhythmias

Bradycardia is defined as a heart rate of below 60 beats per minute.

##### 1) The key principles of bradyarrhythmias management in adult (Fig.3)

A provider should start the treatment of bradycardia emergently when a patient's condition is unstable and bradycardia is the cause of the signs and symptoms <sup>comment 1)</sup>. As is described later, third-degree (complete) atrioventricular block (AVB) and high-degree AVB <sup>comment 2)</sup> are the exceptions and these heart blocks should always be treated as emergency regardless of the signs and symptoms. The provider will contact the specialist of the cardiovascular diseases and begin treatment immediately according to the algorithm. Well-trained athletes often show their heart rate around 40/min. The heart rates of healthy normal persons are often below 50/min during the sleep. But it is obvious the treatment is not necessary for them. On the other hand, when the patient with AMI becomes hypotensive due to the bradycardia, the patient should be received immediate treatment of the bradycardia because it may trigger the next myocardial ischemic attack. The emergent treatment for the symptomatic bradycardia is indicated when the condition of the patient is unstable. The bradycardia algorithm shows that both the third-degree (complete) AVB and sinus bradycardia can be dealt with the same way. Third-degree (complete) AVB and high-degree AVB need the transvenous pacing regardless of the signs and symptoms. For this reason it is important to identified these heart

blocks. The figure shows the ECG identification of bradyarrhythmias and their therapies.

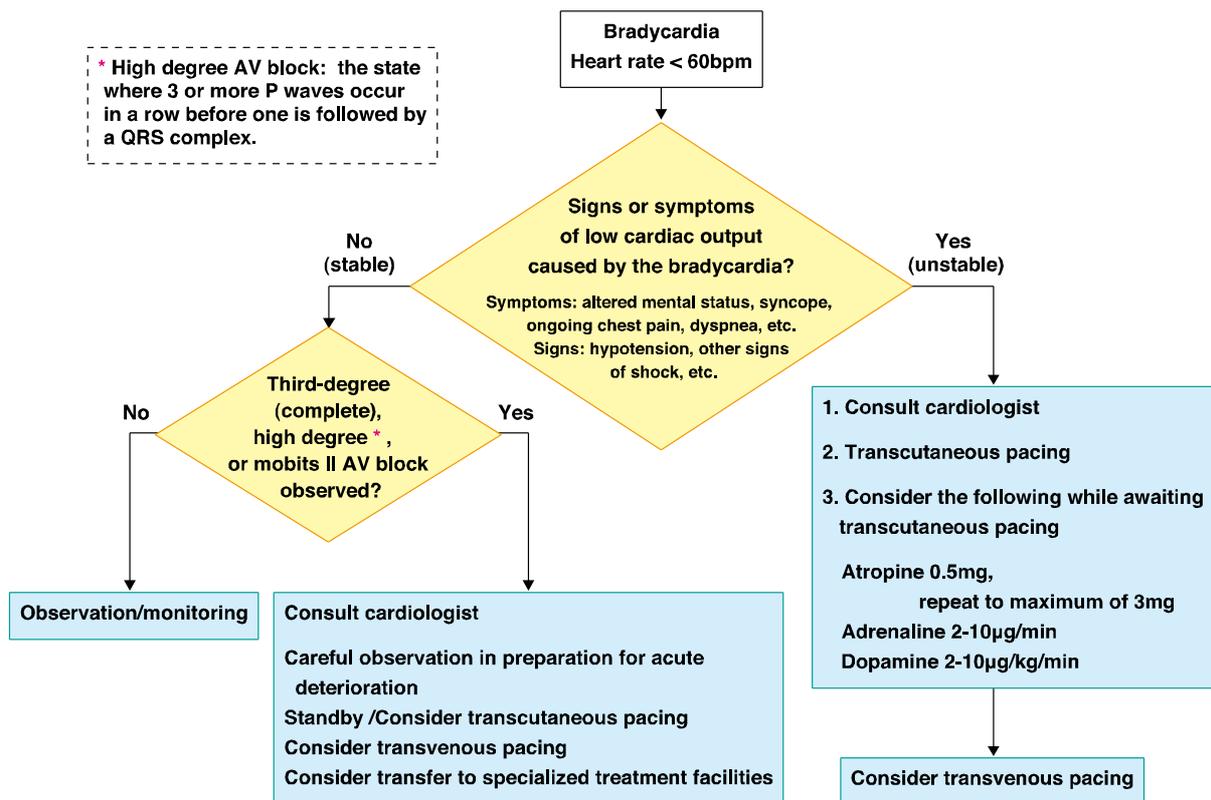


Figure 3 Bradycardia

Comment 1) Relationship between the signs and symptoms with bradycardia: If the patient's condition is unstable while the bradycardia is not the primary cause of instability, you cannot stabilize the condition by the treatment for the bradycardia itself. As the underlying cause of the patient's symptoms are various, such as hypoxemia and electrolytes abnormalities, you should treat these causes for the first which may lead the patient to brady PEA .

Comment 2) Definition of the high degree AV block: Transient atrioventricular block, QRS without P occurs in at least two consecutive waves (that is, three or more P waves occur in a row before one is followed by a QRS complex). High degree AV block does not include three degree (complete) AV block.

## 2. Bradycardia

### 1) Transcutaneous pacing

Four case series (LOE 4) demonstrated that in-hospital transcutaneous pacing had slightly higher success rates for rhythm capture<sup>496</sup> and survival to discharge (18–75%)<sup>497-499</sup> compared with survival-to-discharge rates (69%) when transcutaneous pacing was given for out-of-hospital bradycardia (LOE 1<sup>500</sup>). A systematic review supported this survival-to-discharge rate of 15–70% in the prehospital setting (LOE 3<sup>501</sup>).

## Advanced Life Support (ALS)

Few studies have compared drugs with transcutaneous pacing for the treatment of bradycardia. One feasibility study (LOE 1<sup>500</sup>) compared dopamine with transcutaneous pacing in patients with bradycardia refractory to atropine. There were no differences in outcomes of survival to discharge (70% versus 69%).

### 2) Atropine

One randomized clinical trial (LOE 1<sup>502</sup>), 2 retrospective cohort studies (LOE 4<sup>503, 504</sup>), and 2 additional observational studies (LOE 4<sup>505, 506</sup>) documented that intravenous atropine improved heart rate and symptoms and signs associated with bradycardia. An initial dose of 0.5 to 1 mg, repeated as needed to a total of 1.5 to 3 mg, was effective in both in-hospital and out-of-hospital treatment of symptomatic bradycardia. One study (LOE 4<sup>506</sup>) reported that a  $\geq 0.8$  mg dose increased the incidence of tachycardia. One other study in 10 healthy volunteers (LOE 5<sup>507</sup>) indicated that a 3-mg dose of atropine produces the maximum achievable increase in resting heart rate. Two studies indicated that atropine may paradoxically cause high-degree atrioventricular (AV) block in patients after cardiac transplantation (LOE 5<sup>508</sup>, LOE 4<sup>509</sup>).

### 3) Other drugs

Second-line drug therapy with dopamine (LOE 1<sup>500</sup>) and adrenaline for undifferentiated hemodynamically unstable bradycardia may be successful; it should be tailored according to potential causes in individual patients. For the treatment of bradycardia unresponsive to atropine in post inferior–myocardial infarction, post–cardiac transplant, or post–spinal cord injury, theophylline may be administered (LOE 2<sup>510</sup>, LOE 4<sup>511, 512</sup>, J-LOE 4<sup>513</sup>).

First-line drug treatment for symptomatic bradycardia is atropine 0.5 to 1 mg intravenous (IV) repeated every 3 to 5 minutes as needed up to 1.5 to 3 mg total (Class I). If not effective, then consider adrenaline (2 to 10  $\mu\text{g}/\text{min}$ ) or dopamine (2 to 10  $\mu\text{g}/\text{kg}/\text{min}$ ) (Class IIb). Transcutaneous pacing may be considered when full-dose atropine fails, although it may not be any more effective than second-line drug therapy (Class IIb). Avoid relying on atropine in patients with third-degree AV block accompanied by a wide-QRS escape rhythm. These bradyarrhythmias are not likely to be responsive to atropine and are preferably treated with transcutaneous pacing or second-line drug therapy.

Other second-line choices for symptomatic bradycardia should be tailored according to potential causes. After inferior myocardial infarction, cardiac transplant, or spinal cord injury, theophylline 100 to 200 mg slow injection IV (maximum 250 mg) may be given (Class IIb). Atropine should be used with caution in patients with bradycardia after heart transplant as it may cause paradoxical AV block.

### 4) Transvenous pacing

Transcutaneous pacing or atropine is, at best, a temporizing or emergency measure. If the bradycardia continues, the patient should be prepared for transvenous pacing (Class IIa).

## ■ 3 Tachycardia

### 1. Algorithm for the management of tachyarrhythmias

Definition of tachycardia: The heart rate is more than or equal to 100/min.

#### 1) The key principles of tachyarrhythmias management in adult

As provider, you should identify the patient's condition whether it is stable or unstable by the signs and symptoms (hemodynamic parameter, etc.) and whether these signs and symptoms is related to a suspected arrhythmia or not.

##### (1) Determination of whether stable or unstable

The patient's symptoms suggesting unstable are acute altered mental status, syncope, ongoing chest pain, dyspnea and the signs for unstable conditions are the hypotension, or other signs of shock (perspiration, cold clammy skin, oliguria, disturbance of consciousness). However it cannot be definitively stated that it is unstable even if one of these signs and symptoms can be found in the patient. These signs and symptoms determine whether the condition of the patient is stable or unstable comprehensively. The heart rate of the patient in an unstable condition is generally over 150 beats per minute. In addition, it is important to identify whether the signs and symptoms of instability are caused primarily by the tachycardia or secondary to the underlying diseases.

##### (2) Identification of tachycardia causing other signs or symptoms

If the signs and symptoms are related to a suspected tachyarrhythmia and the patient is unstable, immediate electrical shock should be performed (synchronized or unsynchronized). But the therapy for the tachycardia is not recommended if the signs and symptoms are caused secondary to the underlying diseases. For example, a patient in shock caused by sepsis or bleeding may present sinus tachycardia as a physiologic compensation for maintaining the cardiac output. Treatment for this sinus tachycardia is not favorable. Lowering the heart rate may result in suppression of physiological compensative response and may aggravate the patient's condition to the state of cardiac arrest.

#### 2) Management for unstable tachyarrhythmias in adult (Fig.4)

##### (1) key principles

If a patient is unstable with signs and symptoms related to a suspected tachyarrhythmia, give intervention quickly to this tachyarrhythmia is critically important. The primary intervention to unstable tachycardia is immediate synchronized electrical shock. If no pulse is detected, you should start CPR and switch to the cardiac arrest algorithm.

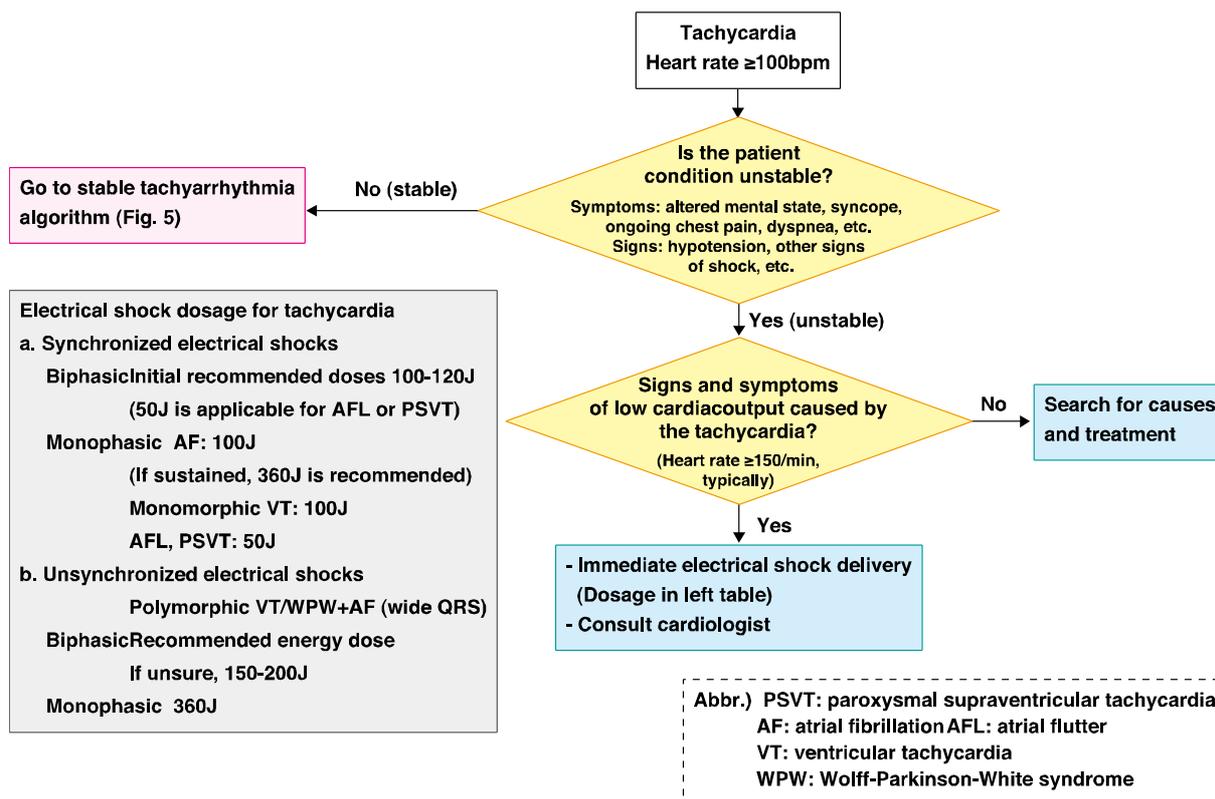


Figure 4 unstable tachyarrhythmia

## (2) Electrical shock

For patients in unstable conditions with tachycardia, perform immediate synchronized shock. The specific practices of electrical shock are described in the paragraph "Defibrillation". Expert consultation may be considered also in unstable patients, however, do not delay the synchronized shock on the excuse of it. We should always remind that the delay in response to a patient with unstable condition might lead to cardiac arrest. Synchronized shocks sometimes take time to implement. So, use unsynchronized shock at the recommended energy doses (defibrillation doses) if the patient's condition is getting aggravated (e.g. increase in heart rate or appearance of the state of the shock) abruptly or the condition has been critically serious. Because unsynchronized electrical shocks may induce cardiac arrest, you should prepare for it. Specific shock energies for each tachyarrhythmias are shown in table 1.

## 3) Management for stable tachyarrhythmias in adult (Fig. 5)

### (1) Key principles

If the patient with tachycardia is judged stable, you can obtain a 12-lead ECG and evaluate the rhythm before treatment. You may consider the expert consultation immediately. When it takes time to prepare a 12-lead ECG, you may print out the monitor recordings to analyze the specific rhythm. As the patient's condition can be aggravated at any time, you should observe the patient continuously while you are waiting for the experts. If the patient became unstable, such as hypotension, follow the algorithm for unstable tachycardia. If the patient loses the consciousness, respiration, and pulse you should proceed to the algorithm to the cardiac arrest. In case no experts are available, follows the

algorithm for the stable tachycardia (Fig 3).

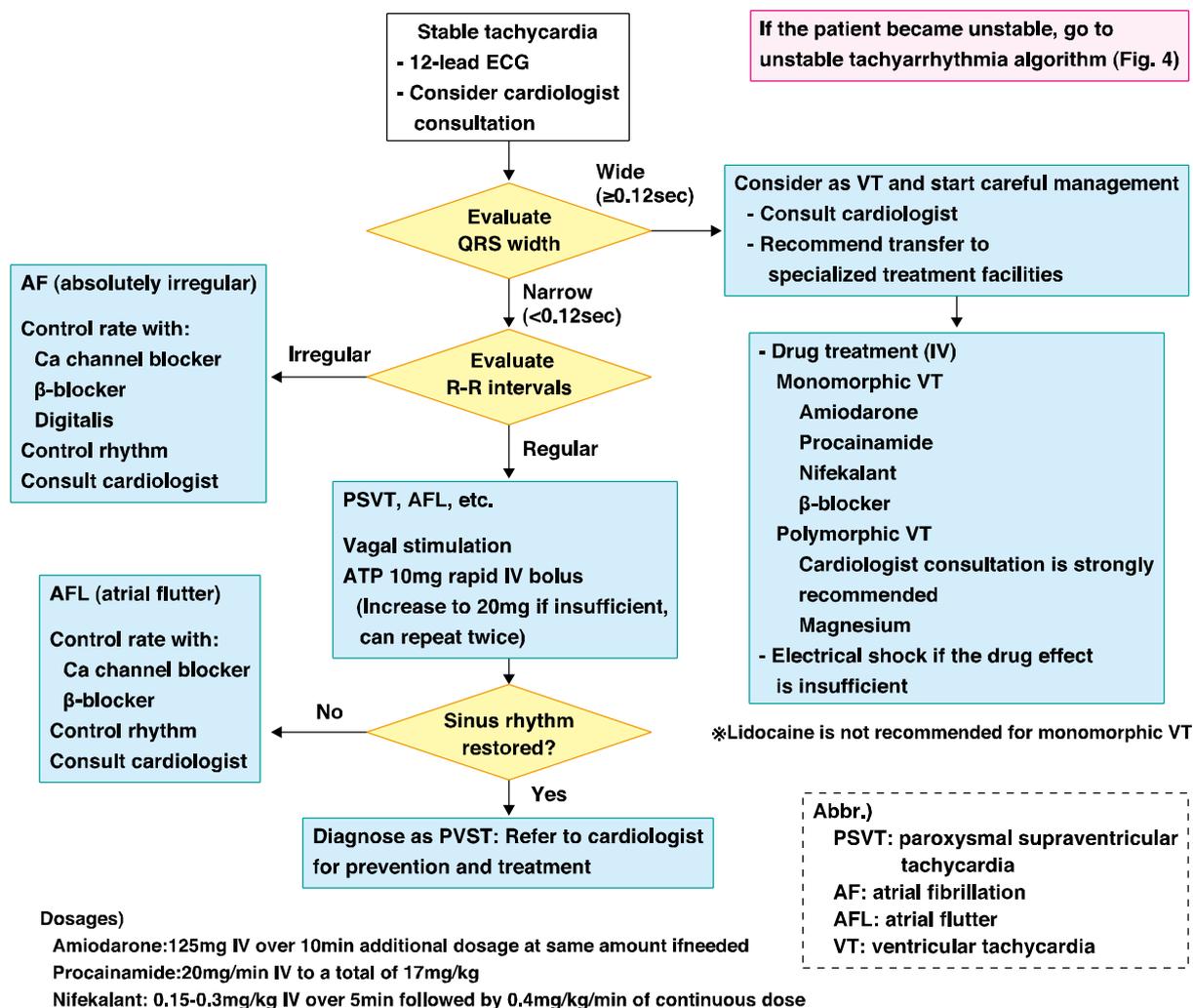


Figure 5 stable tachyarrhythmia

(2) Narrow-complex tachycardia

① Narrow-complex tachycardia excluding atrial fibrillation

There are four options for the treatment of narrow-complex tachycardia in the periarrest setting: electrical conversion, physical maneuver, pharmacological conversion, or rate control. The choice depends on the stability of the patient and the rhythm. In a hemodynamically unstable patient, narrow complex tachycardia is best treated with electrical cardioversion.

Five trials supported the use of adenosine in the treatment of narrow-complex tachycardia (LOE 1<sup>514-518</sup>). Six trials demonstrated the effectiveness of verapamil in conversion to sinus rhythm (LOE 1<sup>514-517, 519, 520</sup>). The effectiveness of diltiazem in conversion to sinus rhythm is supported by four trials (LOE 1<sup>515, 519, 521, 522</sup>). The evidence to support the use of other drugs for conversion to sinus rhythm is limited to a few trials for each drug, including sotalol (LOE 1<sup>523</sup>), amiodarone (LOE 4<sup>524</sup>), propafenone (LOE 1<sup>525</sup>), and nadolol (LOE 1<sup>526</sup>). The study on nadolol suggested treatment effect on rate as well. Cibenzoline terminated narrow-QRS complex tachycardia appeared after surgery (LOE 1<sup>527</sup>). There was no evidence of benefit with magnesium for narrow-complex tachycardia (LOE 1<sup>528</sup>, LOE 4<sup>529</sup>, LOE

<sup>530</sup>). Two studies demonstrated conversion effectiveness of vagal manoeuvres (carotid massage and Valsalva) (LOE 2<sup>531</sup>, LOE 4<sup>532</sup>).

Vagal manoeuvres, IV adenosine, verapamil, and diltiazem are recommended as first-line treatment strategies in the termination of narrow-complex tachycardias (**Class I**). Nadolol, sotalol, propafenone, and amiodarone may be considered (**Class IIb**).

#### □ atrial fibrillation

For the treatment of AF, non-cardiologists are expected to choose rate-control therapy (optimizing heart rate with medication) by suppression of atrioventricular nodal conduction, while rhythm-control therapy (returning to sinus rhythm by medications or electrical shock) needs expert consultation. After the successful rate control, it is recommended to consult a cardiologist about rhythm control and prevention of thrombus formation.

In adult patients in atrial fibrillation either in the prehospital or in-hospital setting, whether or not the use of any drug or combination of drugs improves outcomes compared with not using, has been comprehensively reviewed by the European Society of Cardiology, the American Heart Association, and the American College of Cardiology<sup>533</sup>.

#### ③Rate control in atrial fibrillation

A systematic review (LOE 1<sup>534</sup>) demonstrated superiority for  $\beta$ -blockers (esmolol, metoprolol, and propranolol) with 70% success in meeting target heart rate or verapamil and diltiazem with 54% success<sup>535</sup> as first-line therapy for rate control in atrial fibrillation without a known accessory pathway and amiodarone when an accessory pathway was known and amiodarone or digoxin when fast atrial fibrillation occurred with heart failure (LOE 1<sup>534</sup>).

Four studies showed benefit for diltiazem in controlling rate in hospital (LOE 1<sup>536-538</sup>, LOE 2<sup>539</sup>), and one study for out of hospital (LOE 3<sup>540</sup>). Two studies showed that verapamil is equally effective in rate control for atrial fibrillation (LOE 1<sup>541, 542</sup>). Adverse event rates with calcium channel blockers were reported as 18%<sup>542</sup>.

Amiodarone may control rate and rhythm (LOE 1<sup>543</sup>), but significant complications were described in placebo-controlled trials: the risk of adverse events was 26.8% as a pooled estimate, and the most common side effects encountered were phlebitis, bradycardia, and hypotension (LOE 1<sup>543</sup>).

Digoxin is not effective for cardioversion (LOE 1<sup>544-546</sup>), but in some studies it has been shown to have moderate rate controlling properties (LOE 1<sup>539, 545, 546</sup>).

#### ④Rhythm control in atrial fibrillation

Ibutilide has consistently been more effective in converting atrial fibrillation to sinus rhythm when compared with placebo (LOE 1<sup>547-549</sup>), or other antiarrhythmic drugs (LOE 1: sotalol<sup>550</sup>, procainamide<sup>551</sup>, and amiodarone<sup>552</sup>) and equal to other drugs (LOE 1: flecainide<sup>553</sup>).

Propafenone has been consistently more effective than placebo in converting AF to sinus rhythm (LOE 1<sup>554-556</sup>), but inferior to other drugs (LOE 1: amiodarone<sup>543</sup>, procainamide<sup>557</sup>, and flecainide<sup>558</sup>).

There are also data supporting flecainide (LOE 1<sup>559-562</sup>) and dofetilide (LOE 1<sup>563, 564</sup>) for conversion in patients without coronary artery disease.

## Advanced Life Support (ALS)

Data supporting amiodarone for cardioversion are relatively weak (LOE 1<sup>552, 565-567</sup>); however, amiodarone does have ratecontrolling properties (LOE 1<sup>565, 568</sup>).

Sotalol has consistently been shown to be inferior in conversion compared to other drugs (LOE 1: flecainide<sup>553</sup> and ibutilide<sup>550</sup>), but equal to amiodarone in one study (LOE 1<sup>567</sup>).

Most studies showed no conversion benefit for magnesium (LOE 1<sup>569, 570</sup>), although 1 meta-analysis showed conversion benefit (LOE 1<sup>571</sup>). Most studies showed a benefit for magnesium in rate control (LOE 1<sup>537, 571, 572</sup>), although one study was neutral for magnesium for rate control (LOE 1<sup>570</sup>).

Quinidine has been shown to have greater conversion than sotalol in two studies (LOE 1<sup>573, 574</sup>), although this was with greater toxicity. Clonidine has rate-controlling properties compared with placebo (LOE 1<sup>575, 576</sup>).

Procainamide has shown increased efficacy in conversion of AF to sinus rhythm when compared with placebo<sup>577</sup> and to propafenone<sup>557</sup>, but appears to be as effective as amiodarone<sup>578</sup>.

Patients who are haemodynamically unstable with atrial fibrillation should receive prompt electrical cardioversion (**Class I**).

In the rate control in atrial fibrillation, Beta-blockers and diltiazem are the drugs of choice for acute rate control in most individuals with atrial fibrillation and rapid ventricular response (**Class IIa**). Digoxin and amiodarone may be used in patients with congestive heart failure, and amiodarone may also result in cardioversion to normal sinus rhythm (**Class IIb**). As magnesium and clonidine have rate controlling effects, though there are fewer data supporting their use, they can be used in some cases (**Class IIb**).

In the rhythm control and maintenance of atrial fibrillation, chemical cardioversion can be achieved with ibutilide, dofetilide, and flecainide (**Class IIb**). Amiodarone can also be used for chemical cardioversion, but it is less effective (**Class IIb**). Quinidine, procainamide and propafenone may be useful for cardioversion (**Class IIb**). There is no role for digoxin in chemical cardioversion.

### (3) Wide-complex tachycardia

There are two options for the treatment of wide-complex tachycardia in the periarrest setting: electrical conversion and chemical conversion. Most wide QRS tachycardias are VT. Wide QRS tachycardias should be treated as VT, because even though the patient seems stable, VT may rapidly deteriorate the hemodynamic condition to unstable, inducing pulseless VT or VF (cardiac arrest). The choice depends on the stability of the patient and the rhythm. In a hemodynamically unstable patient, wide complex tachycardia is best treated with electrical synchronized shock (cardioversion).

#### ① Monomorphic VT

In wide QRS tachycardia with uniform QRS morphology (monomorphic VT), the following drugs may be used if the patient's conditions are sufficiently stable. It always should be kept in mind the possibility of sudden change and the defibrillator should be prepared in advance.

##### i) Conversion of acute onset of monomorphic (wide-complex) hemodynamically stable VT

- Procainamide: One unblinded study comparing lidocaine with procainamide (LOE 1<sup>579</sup>) documented an improved reversion rate over lidocaine (1.5mg/kg) when procainamide

(10mg/kg) was given to adult patients with haemodynamically stable monomorphic ventricular tachycardia (mVT), but without severe congestive heart failure or acute myocardial infarction in the hospital setting. One retrospective study in Japan also revealed that procainamide ( $358 \pm 50$  mg) was more effective than lidocaine ( $81 \pm 30$  mg) in terminating stable mVT (J-LOE 5<sup>580</sup>). Additional evidence from a case series suggested that procainamide was effective in terminating stable mVT in the hospital setting (LOE 4<sup>581</sup>).

- Sotalol: A double-blind study comparing lidocaine with sotalol documented an improved reversion rate over lidocaine (100 mg) when sotalol (100 mg) was given to patients with spontaneous onset haemodynamically stable sustained mVT in the hospital setting (LOE 1<sup>582</sup>).
- Amiodarone: The evidence on the effectiveness of amiodarone (150–300 mg) in terminating VT is conflicting with reported conversion rates between 20% and 40% based on one controlled trial (LOE 1<sup>583</sup>) and three case series (LOE 4<sup>584-586</sup>) in patients with coronary artery disease with a low left ventricular ejection fraction in the hospital setting. The use of amiodarone (300 mg) was associated with side effects (primarily hypotension) <sup>584, 586</sup>, but the effect of these on outcome remains unclear.
- Lidocaine: Lidocaine was less effective than sotalol (LOE 1<sup>582</sup>), procainamide (LOE 2<sup>579</sup>), and amiodarone (LOE 2<sup>583</sup>) in terminating VT. Three retrospective analyses showed lidocaine was poorly effective when given to patients with or without a history of myocardial infarction with spontaneous sustained stable VT in the hospital setting (LOE 4<sup>587-589</sup>). In one randomised controlled study (LOE 5<sup>590</sup>) lidocaine was injected by paramedics intramuscularly in patients with acute myocardial infarction and VT in the prehospital setting. Lidocaine terminated VT in six of nine patients with an average of 10 minutes after administration while VT was not terminated in none of five patients in control group. Efficacy of intramuscular lidocaine for VT unassociated with acute myocardial infarction in the prehospital setting was 36% (LOE 5<sup>591</sup>). In addition one retrospective study in Japan revealed the efficacy of terminating stable monomorphic VT by lidocaine was 35%, which was not superior to 76% of that of procainamide (J-LOE 5<sup>580</sup>).
- Cibenzoline: One case series suggested cibenzoline ( $70 \pm 12$  mg) may be effective in terminating VT (LOE 4<sup>592</sup>).
- Magnesium: One study suggested magnesium was effective in terminating VT (LOE 5<sup>593</sup>).
- Adenosine: Adenosine may aid in diagnosing VT, but it will not terminate it (LOE 4<sup>594, 595</sup>).
- Calcium channel blockers: The evidence for the use of calcium channel blockers in VT is conflicting, with most studies opposing their use (LOE 4<sup>596-598</sup>), but one study supported the use as long as coronary disease was not present (LOE 5<sup>599</sup>). Calcium channel blockers may terminate some VT (J-LOE 5<sup>600</sup>).
- Nifekalant: There is insufficient evidence about the efficacy of nifekalant for stable mVT, See other sections for the patients with shock refractory VF/VT.

ii) Preventing recurrence and late conversion in refractory ventricular tachyarrhythmias including mVT

- Synchronized electric shock (cardioversion): Electric cardioversion at an early stage or as first-line treatment was reasonable based on a prospective case series (LOE 4<sup>601</sup>). Indirect evidence

was also provided by 3 case studies (LOE 4<sup>587, 602, 603</sup>).

- Amiodarone: Two RCTs (LOE 1) comparing amiodarone with lidocaine<sup>583</sup> or bretylium<sup>604</sup>, two double-blind randomised dose-range studies (LOE 4<sup>605, 606</sup>), and five case series (LOE 4<sup>607-611</sup>) suggested that amiodarone reduced the number of life-threatening arrhythmias (event rate), required shocks, and episodes of symptomatic sustained VT that occurred in patients with recurrent refractory ventricular arrhythmias in hospital. One study in Japan showed amiodarone was suggested to be effective in preventing recurrence of VT (J-LOE 5<sup>612</sup>).
- $\beta$ -blockers: A single prospective case series (LOE 4<sup>613</sup>) suggested that recurrent and refractory ventricular arrhythmias were reduced while long- and short-term survival were improved in patients treated with sympathetic blockade (including  $\beta$ -blockers) during electrical storm. One study in Japan suggested the effectiveness of landiolol (short-acting  $\beta$ -blockers) for the electrical storm (J-LOE 5<sup>614</sup>).
- Nifekalant: Two retrospective control study (LOE 3<sup>615, 616</sup>), one case series (LOE 4<sup>617</sup>), and one other study (LOE 5<sup>618</sup>) suggested that nifekalant showed the improved outcome in patients with shock refractory VF/VT. However, it did not seem to be effective in immediately terminating the arrhythmia (LOE 4<sup>617</sup>).

Procainamide is recommended for patients with hemodynamically stable monomorphic ventricular tachycardia (mVT) who do not have severe congestive heart failure or acute myocardial infarction (**Class I**). Amiodarone is recommended for patients with hemodynamically stable mVT with or without either severe congestive heart failure or acute myocardial infarction (**Class IIa**). Nifekalant may be useful in improving outcomes in shock refractory VF/VT even though it did not seem to be effective in immediately terminating the arrhythmia (**Class IIb**).

Sotalol may be considered for patients with haemodynamically stable sustained mVT, including patients with acute myocardial infarction (**Class IIb**).

### iii) Undifferentiated regular stable wide-complex tachycardia

Five studies involving more than 300 patients (LOE 4<sup>594, 595, 619-621</sup>) demonstrated that adenosine could safely be administered in regular wide-complex tachycardia: it converted wide-complex tachycardia secondary to supraventricular tachycardia to normal sinus rhythm, but rarely terminated VT. One small study showed poor rates of conversion to sinus rhythm in patients known to have VT (LOE 4<sup>587</sup>). No patient in these trials had serious adverse events; however, there are case reports in patients with irregular wide-complex tachycardia (generally pre-excited atrial fibrillation) in whom VF was precipitated by adenosine (LOE 4<sup>622-625</sup>).

Other studies that included lidocaine showed poor rates of conversion to sinus rhythm with lidocaine in patients known to have VT (LOE 4<sup>587</sup>). In one study, 11 of 25 patients known to have VT and treated with verapamil developed profound hypotension (LOE 4<sup>626</sup>).

In undifferentiated regular stable wide-complex tachycardia, IV adenosine may be considered relatively safe, may convert the rhythm to sinus, and may help diagnose the underlying rhythm (**Class IIb**).

### □□ Polymorphic wide-complex tachycardia

In case QRS morphologies of VT are not uniform (polymorphic VT), consultation to cardiologist or transfer to the facilities where specific treatment can be available is strongly recommended. Evidence for benefit from these therapies is limited, mainly anecdotal, extrapolated, or from small, observational studies and based on the presumed mechanism for polymorphic wide-complex tachycardia, which may not always be clinically evident. There are three subtypes of polymorphic VT:

#### i) Polymorphic VT with delayed abnormal repolarization

Torsade de pointes (TdP) is a specific form of polymorphic VT. TdP is characterized by a gradual change in the amplitude and twisting of R wave polarity around the baseline on the ECG. Prolonged QT intervals on 12-lead ECG during sinus rhythm reveal congenital (such as heritable) or acquired (such as drug-induced, resulting from electrolyte disturbances, etc.) long QT syndrome. Therefore, QT measurement on 12-lead ECG is important. There are 2 subtypes of TdP with long QT, as well as “pause-dependent” initiating sequence, and coexisting factors associated with delayed repolarization with 2 subtypes:

- Familial (congenital) long QT (torsades de pointes): Recurrences of polymorphic wide-complex tachycardia associated with congenital long QT may be reduced with IV magnesium, based on extrapolation from a small case series of children (LOE 5<sup>627</sup>); overdrive pacing (atrial or ventricular); or  $\beta$ -blockers derived from extrapolation from two registry case series of secondary prevention in patients with congenital long QT (LOE 5<sup>628, 629</sup>). There is virtually no published experience regarding the acute use of these therapies in such patients.
- Acquired long QT (torsades de pointes): Recurrences of polymorphic wide-complex tachycardia associated with acquired or drug-precipitated Long QT may be reduced with IV magnesium, based on five studies (LOE 3<sup>630</sup>; LOE 4<sup>631</sup>; LOE 5 (paediatrics)<sup>627</sup>; LOE 5 (animals)<sup>632, 633</sup>); overdrive pacing (atrial or ventricular) based on seven studies (LOE 4<sup>631, 634-637</sup>; LOE 5 [extrapolation from secondary prevention in patients with congenital LQTS]<sup>628, 629</sup>); and IV isoprenaline (when not contraindicated by presence of ischaemia or hypertension) is supported by four studies (LOE 4<sup>631, 635</sup>; LOE 5 (animal)<sup>633, 638</sup>) but opposed by one study (LOE 4<sup>635</sup>).

Polymorphic wide-complex tachycardia associated with familial long QT may be treated with IV magnesium, pacing and/or  $\beta$ -blockers (Class I**b**); however, isoprenaline should be avoided (Class I**II**). Polymorphic wide-complex tachycardia associated with acquired long QT may be treated with IV magnesium (Class I**a**). Addition of pacing or IV isoprenaline may be considered when polymorphic wide-complex tachycardia is accompanied by bradycardia or appears to be precipitated by pauses in rhythm (Class I**b**).

#### ii) Polymorphic wide-complex tachycardia associated with acute myocardial ischemia

This tachycardia usually accompanies short QT intervals. The patients presents the feature of acute myocardial ischemia such as the history, signs and symptoms, and electrocardiographic findings. When polymorphic wide-complex tachycardia is caused by acute myocardial ischemia, it may respond

to IV  $\beta$ -blockers in a modestly sized study (LOE 3<sup>613</sup>); however, there was no benefit from IV magnesium in a small study (LOE 3<sup>630</sup>).

iii) Polymorphic VT secondary to other mechanisms

The science on the management of polymorphic wide-complex tachycardia caused by short QT syndrome is limited to case reports involving amiodarone,  $\beta$ -blockers, and quinidine (LOE 4<sup>639, 640</sup>).

A LOE-4 study<sup>641</sup> and extrapolation from a small case series suggested that isoprenaline attenuated the ST elevation associated with Brugada syndrome (LOE 5<sup>642</sup>). Extrapolation from one case series suggested worsened Brugada ST elevation with class IA antiarrhythmics (LOE 5<sup>642</sup>).

A pediatric case report (LOE 5<sup>643</sup>) and extrapolation from a small case series of secondary prevention using oral  $\beta$ -blockers alone (LOE 5<sup>644</sup>) or in combination with verapamil (LOE 5<sup>645, 646</sup>) suggested IV propranolol successfully terminated catecholamine-induced polymorphic wide-complex tachycardia.

Among patients with impaired ventricular function due to structural heart disease (ischaemic, valvular, or cardiomyopathy), in the absence of QT prolongation or drug provocation, treatment of hemodynamically unstable VT with intravenous amiodarone reduced the frequency of recurrent arrhythmias. This evidence rests on extrapolation from three prospective RCTs (LOE 5<sup>604-606</sup>) performed in the in-hospital setting but in which VT morphology was not addressed specifically.

Nifekalant is reported effective for both termination and prevention with hemodynamically unstable VT (LOE 4<sup>615</sup>, J-LOE 4<sup>180, 617, 647, 648</sup>, J-LOE 5<sup>179, 649</sup>) and the effectiveness was same as that of amiodarone.

Polymorphic wide-complex tachycardia without long QT may be responsive to IV  $\beta$ -blockers (for ischaemic VT and catecholaminergic VT) or isoprenaline (for Brugada syndrome) (Class IIb). Amiodarone and nifekalant may be considered for polymorphic wide-complex tachycardia without QT prolongation (Class IIb).

## 7 Cardiac arrest in special situations

### 1 Cardiac arrest caused by avalanche

#### 1. Time of burial and patent airway

Four studies (LOE P3<sup>650-653</sup>) demonstrated a progressive nonlinear reduction in survival as time of burial lengthened. In eight studies (LOE P3<sup>651, 652, 654-657</sup>, LOE P4<sup>658, 659</sup>) victims who were buried beyond 35 min did not survive if they had an obstructed airway (defined as obstructed by avalanche debris or by other means) on uncovering the head. One study (LOE P5<sup>660</sup>) demonstrated that when breathing in simulated air pockets of different volumes, hypoxia and hypercapnia achieved a steady state after 10 min. This finding suggested that long-term survival was possible as long as an air pocket, even as small as 1 L, was present. One study (LOE P5<sup>661</sup>) indicated that deflection of expired air away from an air pocket may slow the development of hypoxia and hypercapnia.

#### 2. Core temperature

Two relevant LOE P3-studies in the general hypothermia literature found that survival decreased with core temperatures less than 32 °C and reported the use of extracorporeal rewarming only when core temperatures were less than 32 °C<sup>662, 663</sup>. One relevant LOE P3-study reported a maximum cooling rate of 8 °C/h in buried victims<sup>664</sup>. An avalanche case report described a maximum cooling rate of 9 °C/h (LOE P4<sup>658</sup>). Those cooling rates suggested that, at 35 min of burial, the core temperature may drop as low as 32 °C. Three relevant studies (LOE P3<sup>655, 664, 665</sup>) and four case series or reports (LOE P4<sup>658, 663, 666, 667</sup>) recorded ROSC in 22, and survival to hospital discharge in 7 of those 22, buried avalanche victims in cardiac arrest with a core temperature less than 32 °C with aggressive rewarming using extracorporeal circulation.

#### 3. Serum potassium

A serum potassium of less than 8 mmol/L on hospital admission was found to be predictive of increased ROSC in avalanche burial victims in one study (LOE P3<sup>655</sup>) and for increased survival to hospital discharge in two studies (LOE P3<sup>654, 664</sup>). Five studies found an inverse correlation between admission potassium concentration and survival to discharge in all-cause hypothermic patients (LOE P3<sup>654, 662, 665, 668, 669</sup>). Four studies (LOE P3<sup>654, 664, 670, 671</sup>) found that high potassium values were associated with asphyxia in all hypothermic patients. The highest reported serum potassium value in an avalanche survivor was 6.4 mmol/L<sup>664</sup>, although survival to hospital discharge from all-cause hypothermia with a potassium concentration as high as 11.8 mmol/L has been documented<sup>672</sup>.

Avalanches occur in areas that are difficult for rescuers to access in a timely manner, and burials frequently involve multiple victims. The decision to initiate full resuscitative measures should be determined by the number of victims and the resources available, and it should be informed by the

likelihood of survival.

Avalanche victims are not likely to survive when they are

- Buried >35 min and in cardiac arrest with an obstructed airway on extrication.
- Buried initially and in cardiac arrest with an obstructed airway on extrication, and an initial core temperature of <32 °C.
- Buried initially and in cardiac arrest on extrication with an initial serum potassium of >8 mmol/L or more.

Full resuscitative measures, including extracorporeal rewarming, when available, are indicated for all other avalanche victims without evidence of an unsurvivable injury (Class I).

## Knowledge Gaps

Prospective validation studies of patient airway, core temperature, and serum potassium as prognostic factors among patients in cardiac arrest on extrication, measurement of core temperature of avalanche victims in cardiac arrest at the time of rescue and prospective studies on effectiveness of prehospital treatment of nonarrested hypothermic avalanche victims would advance the science of avalanche resuscitation.

## ■ 2 Pregnancy

There are no RCTs evaluating the effect of specialised obstetric resuscitation versus standard care in postarrest pregnant women. Many studies of women not in cardiac arrest document the important physiological changes that occur in pregnancy that may influence treatment recommendations and guidelines for resuscitation of cardiac arrest in pregnancy.

### 1. Aortocaval decompression to improve maternal haemodynamics and fetal well-being

In the nonarrest literature, left lateral tilt improved maternal blood pressure, cardiac output, and stroke volume (LOE 5<sup>673-675</sup>) and improved fetal parameters of oxygenation, nonstress test, and fetal heart rate<sup>676-678</sup>. While chest compressions in the left lateral tilt position were shown to be feasible in a manikin study<sup>679</sup>, they have been shown to result in less forceful chest compressions than in the supine position<sup>680</sup>. Two studies found no improvement in maternal haemodynamic or fetal parameters in nonarrest patients with 10–20° left lateral tilt<sup>681, 682</sup>. One study found more aortic compression at 15° left lateral tilt when compared to a full left lateral tilt<sup>677</sup>. In addition, aortic compression has been found to persist at over 30° of tilt<sup>683</sup>; however, the majority of these patients were in labor. Two nonarrest studies found that manual left uterine displacement (which is done with the patient supine) was as good as, or better than, left lateral tilt in relieving aortocaval compression, as assessed by the incidence of hypotension and ephedrine use<sup>684, 685</sup>.

## 2. Respiratory considerations

One study documented that the upper airways in the third trimester of pregnancy are smaller (supine mean difference 0.20; 95% confidence interval [CI] 0.06–0.35) compared with their postpartum state and to nonpregnant controls (LOE 5<sup>686</sup>). One study found increased intrapulmonary shunting in normal pregnancy at 12.8–15.3% compared with the nonpregnant state normal value of 2–5% (LOE 5<sup>687</sup>), suggesting a change in the approach to oxygenation demands and in the size of the advanced airway may be physiologically justifiable in maternal cardiac arrest.

## 3. Perimortem Caesarean section

One retrospective cohort study of 55 maternal cardiac arrests evaluated the incidence of perimortem Caesarean section after the introduction of a targeted training course (Managing Obstetric Emergencies and Trauma; MOET) and compared it with a historical rate (LOE 4<sup>688</sup>). There are no cases where the caesarean section was conducted within 5 minutes of cardiac arrest as recommended in the MOET course. With caesarean sections in cardiac arrest, maternal ROSC rate was 67%, maternal mortality rate was 83%, and infant mortality rate was 58%. One systematic review of perimortem caesarean sections documented 38 cases, with 34 surviving infants and 13 maternal survivors at discharge, suggesting that perimortem caesarean section may have improved maternal and neonatal outcomes (LOE 5<sup>689</sup>). At older gestational ages (30–38 weeks), infant survival was possible even when delivery was after 5min from the onset of maternal cardiac arrest (LOE 5<sup>689</sup>). One retrospective study concluded that for delivery of infants between 22 and 25 weeks gestational age, neonatal outcome is best at 25 weeks, and there was no infant survival when delivery occurred at 22 weeks (LOE 5<sup>690</sup>).

## 4. Changes in pharmacokinetics

One study documented an increase in glomerular filtration rate, cardiac output, and plasma volume early in the first trimester that starts to return to normal in the end of the third trimester, suggesting that known physiological vascular and fluid changes of pregnancy may respond to fluid resuscitation during maternal cardiac arrest (LOE 5<sup>691</sup>).

## 5. Defibrillation

One underpowered case control study reported no difference in transthoracic impedance during pregnancy compared with postpartum, suggesting current energy requirements for adult defibrillation were appropriate (LOE 5<sup>692</sup>).

## 6. Positioning

One study indicated that the human wedge technique can provide left lateral tilt and effective external chest compressions and mouth-to-mouth rescue breathing in a manikin (LOE 5<sup>679</sup>). However, another study found that the estimation of the degree of table tilt is unreliable and often overestimated, suggesting rescuers are more likely to employ an insufficient amount of tilt to achieve the required

haemodynamic benefit (LOE 5<sup>693</sup>). A small study assessed the efficacy of resuscitation at various angles of inclination using a calibrated force transducer (LOE 5<sup>680</sup>). This study found that the maximum possible resuscitative force decreased as the angle of inclination of the plane increased, from 67% of body weight in the supine position to 36% in the full lateral position. Therefore at an inclination of 27° the maximum resuscitative force for chest compressions was only 80% of the force generated at 0° of inclination (supine). Also at an incline of >30° the patient/manikin tended to roll off the incline plane (LOE 5<sup>680</sup>).

## 7. Therapeutic hypothermia postarrest

A single case report suggested that post-cardiac arrest hypothermia was used safely and effectively in early pregnancy with fetal heart monitoring and resulted in favorable maternal and fetal outcome after a term delivery (LOE 5<sup>694</sup>).

There is insufficient evidence to support or refute the use of specialised obstetric resuscitation techniques in maternal cardiac arrest and the use of therapeutic hypothermia in the postarrest period. Treatment may be guided by understanding the physiology of pregnancy, the importance of releasing aortocaval compression, the increased risk for hypovolaemia, the compression advantage through positioning, and the value of perimortem caesarean section early in maternal cardiac arrest.

## Knowledge Gaps

Research in the area of maternal resuscitation is lacking, and most of the science is extrapolated from nonpregnant women, manikin studies, or case reports. Epidemiological studies are needed to document the incidence of cardiac arrest in pregnancy as there is a perception that it is increasing because of increased numbers of women with congenital heart conditions who are now having children.

### **3 Cardiac arrest in morbid obesity**

Evidence from two studies did not find a survival difference associated with obesity following out-of-hospital cardiac arrest (LOE 2<sup>695-697</sup>).

There is insufficient evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for obese patients.

## Knowledge Gaps

There is a paucity of research in this area, and studies looking at epidemiology, current variations from the standard protocol, and associated outcomes, as well as simple experimental studies, would be helpful.

## ■ 4 Cardiac arrest caused by asthma

There are no RCTs that specifically evaluate or compare adjuvant treatment with standard treatment for cardiac arrest in asthmatic patients. Most of the literature comprises case reports and case series.

When ventilation is difficult due to bronchial asthma, it is effective to decrease ventilation by lowering the tidal volume and respiratory rate, and prolonging the expiration time (J-LOE 5<sup>698</sup>). Evidence from three non-cardiac arrest case series involving 35 patients suggests that asthmatic patients are at risk for gas trapping during cardiac arrest, especially if their lungs are ventilated with high tidal volumes and/or rapid rates (LOE 5<sup>699-701</sup>). One volunteer adult study demonstrated that increasing PEEP caused increased transthoracic impedance (LOE 5<sup>702</sup>).

Seven case series involving 37 patients suggested increased ease of ventilation and ROSC with lateral chest compressions at the base of the ribs (LOE 4<sup>703-709</sup>). In a single case report, lateral chest compressions were associated with cardiac arrest and poor cardiac output (LOE 4<sup>710</sup>).

Brief interruptions of ventilation were effective in the case of difficulty of ventilation (J-LOE 4<sup>711-714</sup>). Three single case reports (two intraoperative and one ED) involving cardiac arrest caused by asthma suggested improvement in ease of ventilation and ROSC with thoracotomy and manual lung compression (LOE 4<sup>704, 708, 709</sup>).

There is insufficient evidence to suggest any routine change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by asthma. However, it is reasonable to perform resuscitation, understanding that the fatal bronchial asthma is characterized by distal airway closure and lung hyperinflation, which can cause respiratory arrest resulting in cardiac arrest.

When ventilation for a victim in cardiac arrest caused by asthma is difficult or impossible to perform due to lung hyperinflation from air trapping, interruption of ventilation for 30-60 seconds may be applied (to let the air escape) (Class IIb). Since lung hyperinflation increases transthoracic impedance, if initial defibrillation attempts fail then delivering higher shock energies for defibrillation may be considered (Class IIb). In addition, there is a possibility of pneumothorax with lung hyperinflation, which should be remembered all the time, and releasing air if needed should be considered (Class IIb).

### Knowledge Gaps

Several key areas for research include: the role of disconnecting from positive pressure ventilation and the ideal duration of this disconnection; the role of lateral external compression and the timing with respect to chest compressions; the comparison of these techniques and their cumulative advantage; and the role of magnesium infusions and ECMO in cardiac arrest caused by asthma.

## ■ 5 Cardiac arrest caused by anaphylaxis

There are no RCTs evaluating conventional versus alternative therapies for the treatment of cardiac

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arrest caused by anaphylaxis. Evidence is limited to case reports, extrapolations from nonfatal cases, interpretation of pathophysiology, and animal studies.

One human study of a randomised venom immunotherapy trial where 19 of 21 patients became symptomatic and required emergency treatment suggests that carefully titrated continuous infusion of IV adrenaline in addition to volume infusion may be effective for the treatment of anaphylactic shock (not in cardiac arrest) (LOE 5<sup>715</sup>). One randomised controlled crossover study of animals preshock, but symptomatic with ragweed sensitivity, showed that a continuous IV infusion of 0.01mg/kg adrenaline maintained a mean arterial pressure at 70% of preshock levels better than no treatment or bolus treatment (LOE 5<sup>716</sup>).

A small case series of patients with anaphylactic shock with or without cardiac arrest suggested that patients who did not respond to standard therapy may benefit from vasopressin (LOE 4<sup>717, 718</sup>). A few small case series (LOE 4) have described promising initial findings with  $\alpha$ -agonists such as noradrenaline<sup>719</sup>, methoxamine<sup>720</sup>, terlipressin<sup>721</sup>, and metaraminol<sup>722-724</sup>. A few small case reports (LOE 4) of cardiac arrest suggest cardiopulmonary bypass<sup>725, 726</sup> or mechanical support of circulation (LUCAS)<sup>727</sup> may be helpful in the setting of anaphylaxis. One patient was reported who suffered a cardiac arrest due to drug anaphylaxis despite administration of steroid and antihistamine was successfully resuscitated with prolonged advanced cardiac life support (LOE 5<sup>728</sup>).

There is insufficient evidence to suggest any routine change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by anaphylaxis.

Anaphylaxis accompanied by rapid circulatory collapse and airway obstruction can lead to cardiac arrest. It is important to recognize symptoms in the early stage and start adrenaline administration and fluids treatment (Class I).

## Knowledge Gaps

Future research should consider a comparison between the different IV  $\alpha$ -agonists and a comparison of infusion versus bolus doses for cardiac arrest caused by anaphylaxis. The value of secondary therapies such as glucagon, antihistamines, volume infusions, and steroids should be explored.

## ■ 6 Drug overdose and poisoning

The majority of questions addressing cardiac arrest caused by drug toxicity remain unanswered. Epidemiological studies are required to document the incidence of cardiac arrests caused by drugs, current treatment strategies, and the safety and efficacy of existing treatments. Animal models, controlled clinical trials, and pharmacodynamic studies are needed to advance the treatment of cardiac arrest caused by drugs. Most of the evidence is limited to case reports, extrapolations from nonfatal cases (including severe cardiovascular toxicity cases), and animal studies.

## 1. Cardiac arrest caused by local anaesthetic

Local anaesthetic toxicity typically occurs in the setting of regional anaesthesia, when a bolus of local anaesthetic inadvertently enters the arterial or venous system, leading to refractory seizures and/or rapid cardiovascular collapse. There are no RCTs evaluating conventional versus alternative therapies for the treatment of cardiac arrest caused by local anaesthetics (lidocaine). Evidence is limited to case reports involving cardiac arrest and severe cardiovascular toxicity and animal studies.

Five single-case reports describe patients in cardiac arrest attributed to local anaesthetic intoxication, who were refractory to advanced life support conventional treatment, but who obtained ROSC soon after treatment with IV lipid emulsion (LOE 5<sup>729-733</sup>). Five single-case reports (LOE 5) describe patients with acute, life-threatening cardiovascular toxicity from local anaesthetic intoxication, but who were not pulseless at the time of lipid administration. In three cases<sup>734-736</sup> severe cardiovascular toxicity resolved rapidly following IV lipid, but in two other cases<sup>737, 738</sup> the patient's condition deteriorated to cardiac arrest after IV lipid, although the patients were resuscitated and survived to hospital discharge.

Five controlled animal studies demonstrated that a variety of dosages of IV lipid emulsion were more effective than placebo in models of local anaesthetic intoxication with ROSC as the primary outcome (LOE 5<sup>739-743</sup>).

Two controlled animal studies suggested that, in combination with basic life support (BLS), IV lipid emulsion improved the rate of ROSC when compared with vasopressor therapy (vasopressin and adrenaline) (LOE 5<sup>740, 743</sup>). Contrasting results were published in one controlled animal study that demonstrated a survival advantage with vasopressin and adrenaline over lipid emulsion therapy in a model of asystole induced by low-dose bupivacaine and asphyxia (LOE 5<sup>744</sup>). Two controlled animal studies reported no additional benefit from lipid emulsion infusions when combined with high-dose adrenaline 0.1mg/kg (LOE 5<sup>745</sup>) and 0.01 and 0.025mg/kg (LOE 5<sup>746</sup>). Lipid emulsion bolus doses and infusion rates vary across case reports and animal studies. Typical bolus doses were 1–3mL/kg. When infusions were used the typical doses were 0.1–0.3mL/kg/h. A 20% solution of long-chain fatty acid emulsion was used in almost all reports.

Two controlled animal studies showed a survival advantage when cardiac arrest from local anaesthetic toxicity was treated with high-dose insulin (1–2U/kg IV bolus) accompanied by glucose and sometimes potassium, compared with basic life support resuscitation alone (LOE 5<sup>747, 748</sup>). There were no animal studies comparing this intervention with advanced life support resuscitation.

The use of clonidine (150 µg boluses, repeated as needed) to treat cardiac arrest caused by local anaesthetic was described in one human case report (LOE 4<sup>749</sup>) while a second case report (LOE 4<sup>750</sup>) was neutral. An animal study demonstrated partial improvement in bupivacaine-induced intracardiac conduction delays following clonidine administration (0.01mg/kg IV), but nonperfusing rhythms were not studied (LOE 5<sup>751</sup>).

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by local anaesthetics. Animal studies and case reports suggest severe cardiovascular toxicity or cardiac arrest attributable to local anaesthetic intoxication may respond to treatment with IV lipid emulsion (Class IIb).

## 2. Benzodiazepine toxicity

No human studies or reports of any patients who had cardiac arrest solely resulting from benzodiazepine toxicity alone were identified.

Five reports of cardiac arrests resulting from exposure to combinations of medication that included one of the benzodiazepines were identified (LOE 4<sup>752-756</sup>). One case report indicated that standard care alone was sufficient to reverse the severe cardiovascular toxicity attributed to an anaphylactic reaction to a benzodiazepine (LOE 5<sup>757</sup>).

One case report described improved outcome when minor cardiovascular toxicity caused by benzodiazepines was treated with flumazenil (LOE 5<sup>758</sup>). Four studies indicated that flumazenil is unlikely to improve haemodynamic function in the setting of benzodiazepine overdose and may complicate other therapy (LOE 5<sup>755, 759-761</sup>). Two studies described serious adverse effects such as seizure, arrhythmia, hypotension, and withdrawal syndrome after flumazenil was given to patients presenting with decreased level of consciousness attributed to either benzodiazepine toxicity or an unknown cause (LOE 5<sup>755, 762</sup>). These side effects were more common with coingestants (such as tricyclic antidepressant and opioids), chronic benzodiazepine use or abuse, and known seizure disorder.

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by benzodiazepines. Routine use of flumazenil for a victim with impaired consciousness by unknown cause is not recommended (Class III).

## 3. $\beta$ -blocker toxicity

There are no RCTs evaluating conventional versus alternative treatment of cardiac arrest caused by  $\beta$ -blockers. Evidence is limited to case reports, extrapolations from nonfatal cases, severe cardiovascular toxicity cases, and animal studies. The wide variety of  $\beta$ -blockers with differing pharmacological and physiochemical profiles makes it difficult to generalise from the limited data available.

In 13 case studies (n = 16) of human patients with severe cardiovascular toxicity caused by  $\beta$ -blockers refractory to standard treatment, including vasopressors, the administration of glucagon (50–150  $\mu$ g/kg) was followed by haemodynamic improvement and survival (LOE 5<sup>763-775</sup>).

In two animal studies, high-dose insulin infusions (1U/kg/h) given with glucose supplementation and electrolyte monitoring appeared effective (as measured by rates of improved haemodynamic stability and survival) in the setting of cardiovascular toxicity associated with  $\beta$ -blockers (LOE 5<sup>776, 777</sup>). A single human case report documented that high-dose insulin (10U/kg/h IV), given with glucose supplementation and electrolyte monitoring, was followed by improved haemodynamic stability and survival to hospital discharge in the setting of severe cardiovascular toxicity associated with  $\beta$ -blocker toxicity (LOE 5<sup>778</sup>).

Case reports described the use of phosphodiesterase inhibitors (LOE 5<sup>779, 780</sup>), calcium salts (LOE 4<sup>781, 782</sup>), extracorporeal support (LOE 5<sup>783</sup>), intraaortic balloon pumps (LOE 4<sup>784</sup>), and ECMO (Extracorporeal Membrane Oxigenation) (LOE 4<sup>785</sup>).

Animal studies supported the use of the phosphodiesterase inhibitor amrinone (LOE 5<sup>786</sup>). Animal studies suggested that dopamine (LOE 5<sup>787</sup>), a combination of dopamine and isoprenaline (LOE 5<sup>788</sup>), and milrinone (LOE 5<sup>789</sup>) may decrease the effectiveness of glucagon as an antidote for  $\beta$ -blocker toxicity.

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by  $\beta$ -blockers. Animal studies and case reports suggest severe cardiovascular toxicity caused by  $\beta$ -blockers may respond to treatment with intravenous glucagon, high-dose insulin (with glucose supplementation and electrolyte monitoring), or IV calcium salts or extracorporeal-CPR (ECPR) using ECMO/PCPS (Percutaneous Cardiopulmonary Support) in addition to conventional treatment (Class IIb).

#### 4. Calcium channel blocker toxicity

There are no RCTs evaluating conventional versus alternative therapies for the treatment of cardiac arrest caused by calcium channel blockers. Evidence is limited to extrapolations from nonfatal case reports of severe cardiovascular toxicity.

In 16 human case series (n=28) high-dose insulin (bolus 0.5 to 2 U/kg followed by 0.5 U/kg/h infusion) given with glucose supplementation and electrolyte monitoring appeared effective (as measured by improved hemodynamic stability [25/28] and survival [26/28]) in the setting of severe cardiovascular toxicity associated with calcium channel blockers (LOE 5<sup>790-805</sup>)

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by calcium channel blockers. Case reports suggest severe cardiovascular toxicity caused by calcium channel blockers may respond to treatment with high-dose insulin given with glucose supplementation and electrolyte monitoring in addition to conventional treatment (Class IIb).

### Knowledge Gaps

Controlled clinical trials are needed to advance the treatment of cardiac arrest caused by calcium channel blockers. While case reports focus on verapamil toxicity, the different properties of other calcium channel blockers may affect the response to the proposed treatment. Other special interest topics include the use of vasopressin to treat severe cardiovascular toxicity caused by dihydropyridines, the use of combination therapy, sequencing of interventions, and the evaluation of new and emerging therapies, namely intravenous lipid infusion and calcium sensitizers and nonpharmacological interventions.

#### 5. Carbon Monoxide Toxicity

Three studies suggested that most patients who develop cardiac arrest from carbon monoxide poisoning will not survive to hospital discharge, regardless of whether hyperbaric oxygen therapy is administered following ROSC (LOE 4<sup>806-808</sup>).

## Advanced Life Support (ALS)

Two studies (LOE 5) suggested that neurological outcomes were improved in patients (all severity excluding cardiac arrest<sup>809</sup>; and mild-to-moderate, excluding loss of consciousness and cardiac instability<sup>810</sup>) who received hyperbaric oxygen therapy for carbon monoxide poisoning. However, 2 studies found no difference in neurologically intact survival (LOE 5<sup>811, 812</sup>). Two systematic reviews concluded that improvement in neurologically intact survival following the administration of hyperbaric oxygen to carbon monoxide poisoning patients was possible but unproven (LOE 5<sup>813, 814</sup>).

Two studies demonstrated that patients with carbon monoxide toxicity treated with hyperbaric oxygen who developed myocardial infarction have an increased risk of cardiovascular and all-cause mortality lasting at least 7 years after the event (LOE 5<sup>815, 816</sup>).

Patients who develop cardiac arrest caused by carbon monoxide rarely survive to hospital discharge, even if ROSC is achieved; however, 100% oxygen ventilation after ROSC as early as possible is recommended (Class I) and hyperbaric oxygen therapy may be considered (Class IIb) in these patients because it may reduce the risk of developing persistent or delayed neurological injury. The risks inherent in transporting critically ill post arrest patients to a hyperbaric facility may be significant; it must be weighed against the possibility of benefit on a case-by-case basis. Patients who develop myocardial injury caused by carbon monoxide have an increased risk of cardiac and all-cause mortality lasting at least 7 years after the event; it is reasonable to recommend cardiology follow-up for these patients (Class IIa).

## Knowledge Gaps

The epidemiology of cardiac arrest and severe cardiotoxicity caused by carbon monoxide needs further documentation. More precise estimates of the proportion of patients who survive to hospital discharge and who have full neurological recovery following severe carbon monoxide poisoning treated with various interventions are needed. Though challenging, further prospective treatment studies are important and necessary.

## 6. Cocaine Toxicity

There are no RCTs evaluating conventional versus alternative therapies for the treatment of cardiac arrest caused by cocaine. Evidence is limited to a small case series that demonstrated excellent overall and neurologically intact survival (12/22, 55%) in patients with cocaine-associated cardiac arrest treated with standard therapy (LOE 4<sup>817</sup>).

No studies were found that addressed the treatment of severe cardiotoxicity caused by cocaine; however, human studies have evaluated the treatment of cocaine-associated wide-complex tachycardia and ischemic acute coronary syndrome, as well as coronary artery vasospasm caused by cocaine. Thus the benefit or harm of specific agents in cocaine-associated peri-arrest states (defined as severe hypertension, tachycardia, cocaine-induced arrhythmias) is informed by LOE 5-studies (extrapolation for nonarrest patients and, in some cases, cocaine naive patients).

A single study demonstrated reversal of cocaine-induced coronary artery vasospasm in the coronary catheterization laboratory with phentolamine (LOE 5<sup>818</sup>).

A single study (LOE 5<sup>819</sup>) of patients with cocaine-associated chest pain demonstrated improved

autonomic findings and resolution of chest pain when treated with diazepam. An additional study reported no additional benefit associated with benzodiazepine administration in patients already receiving nitroglycerin (LOE 5<sup>820</sup>).

A retrospective case series of patients hospitalized for acute coronary syndrome associated with cocaine use suggested that there was a decrease in the incidence of death and nonfatal myocardial infarction with the use of  $\beta$ -blockers (LOE 5<sup>821</sup>). A prospective clinical trial in cocaine-naive volunteers suggested that propranolol reduced cocaine-induced tachycardia (LOE 5<sup>822</sup>). A prospective clinical trial demonstrated worsening of cocaine-induced coronary artery vasoconstriction following the administration of propranolol to cocaine-naive research subjects (LOE 5<sup>823</sup>). A retrospective case series of 7 ED and hospitalized patients with cocaine-associated cardiovascular toxicity demonstrated no consistent improvement in hypertension or tachycardia following treatment with esmolol (LOE 5<sup>824</sup>). Three of 7 patients developed apparent adverse effects (hypertension, hypotension, and CNS depression with vomiting).

In a pair of double-blind, crossover studies (LOE 5) of volunteers with a history of crack cocaine use, pretreatment with oral carvedilol<sup>825</sup> or labetalol<sup>826</sup> attenuated the cocaine-induced increases in heart rate and blood pressure compared with placebo, without apparent adverse effect. A prospective clinical trial demonstrated no change in cocaine-induced coronary artery vasoconstriction following the administration of labetalol to cocaine-naive research subjects (LOE 5<sup>827</sup>).

One study of cocaine-naive human volunteers demonstrated resolution of cocaine-induced coronary artery vasospasm with verapamil (LOE 5<sup>828</sup>).

A retrospective case series of 29 patients who received lidocaine in the setting of cocaine-associated myocardial infarction included 8 patients with wide-complex tachycardia (2 sustained, 6 nonsustained) (LOE 5<sup>829</sup>). No patient developed complications and all survived the event.

One study of cocaine-naive human volunteers demonstrated that morphine partially reversed cocaine-induced coronary artery vasospasm (LOE 5<sup>830</sup>).

In a clinical trial of cocaine-naive volunteers administration of nitroglycerin reversed cocaine-induced coronary artery vasospasm (LOE 5<sup>831</sup>). In a prospective observational study of patients presenting with cocaine-associated acute coronary syndrome, 37/83 (45%) of patients treated with nitroglycerin reported reduction in the severity of chest pain, while 5 patients had other forms of clinical improvement (resolution of ischemia based on ECG, 2; hypertension, 2; or congestive heart failure, 1) (LOE 5<sup>832</sup>).

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest or cardiotoxicity caused by cocaine. In patients with severe cardiovascular toxicity (defined as severe hypertension, tachycardia, and/or cocaine-induced arrhythmias) it may be reasonable to try drugs known to be effective in acute coronary syndromes:  $\alpha$ -blockers (phentolamine), benzodiazepines (lorazepam, diazepam), calcium channel blockers (verapamil), morphine, and sublingual nitroglycerin (Class IIb). The available data do not support the use of 1 drug over another.

## Knowledge Gaps

Controlled clinical trials are needed to advance the treatment of cardiac arrest and cardiotoxicity due to cocaine. Future studies should evaluate the role of sodium bicarbonate and lidocaine and the safety and effectiveness of other antiarrhythmic drugs, such as amiodarone, in the treatment of cocaine-associated VT.

## 7. Cyanide Toxicity

There are no randomized controlled trials evaluating conventional versus alternative therapies for the treatment of cardiac arrest caused by cyanide. The use of hydroxocobalamin (alone or with sodium thiosulfate) for cardiac arrest caused by cyanide was suggested by three LOE 4 studies<sup>833-835</sup>. The use of hydroxocobalamin (alone or with sodium thiosulfate) in life-threatening cardiovascular toxicity was supported by seven studies (LOE 5<sup>833-839</sup>).

The use of nitrites plus sodium thiosulfate was suggested by three studies, none of which enrolled cardiac arrest patients (LOE 5<sup>837, 840, 841</sup>); however, one additional study found no benefit to this strategy (LOE 5<sup>842</sup>).

Patients with severe cardiotoxicity (cardiac arrest, cardiovascular instability, metabolic acidosis, or altered mental status) caused by known or suspected cyanide poisoning should receive administration of 100% oxygen as early as possible, and cyanide antidote therapy. In addition to standard resuscitation, initial therapy should include a cyanide scavenger (either intravenous hydroxocobalamin [Cyanokit injection 5g/ normal saline 200ml] or a nitrite – i.e. intravenous sodium nitrite and/or inhaled amyl nitrite [inhalation of amyl nitrite 0.25ml or slow intravenous injection of 3% sodium nitrite 10ml]), followed as soon as possible by intravenous sodium thiosulfate [sodium thiosulfate 2g/20mlx6A](Class I). Hydroxocobalamin and nitrites are equally effective but hydroxocobalamin may be safer because it does not cause methemoglobin formation or hypotension. Mouth-to-mouth rescue breathing should not be conducted to avoid secondary cyanide poisoning damage to the rescuer (Class III).

## Knowledge Gaps

Controlled clinical trials are needed to advance the treatment of cardiac arrest and cardiotoxicity caused by cyanide. Comparative studies on antidote therapy and health outcomes including neurological outcomes are required to address the question of which combination of drugs is most effective.

## 8. Tricyclic antidepressant toxicity

There are no randomized controlled trials evaluating conventional versus alternative treatments for cardiac arrest caused by tricyclic antidepressant toxicity. Evidence was limited to a one small case series of cardiac arrest patients, which demonstrated improvement with the use of sodium bicarbonate and adrenaline (LOE 4<sup>843</sup>). Notably, in this case series the pre-arrest use of physostigmine (unavailable

in Japan) was a significant potential confounder.

The evidence for the management of cardiotoxicity caused by tricyclic antidepressant was limited to case reports, case series and animal studies. The use of sodium bicarbonate has been described in two case series (LOE 5<sup>844, 845</sup>) and 6 animal studies (LOE 5<sup>846-851</sup>). The use of hyperventilation was described in one small case series (LOE 5<sup>852</sup>) and one animal study (LOE 5<sup>849</sup>). The evidence for the efficacy of specific antidysrhythmics (lidocaine, magnesium, amiodarone, phenytoin) was limited to negative case reports (LOE 5<sup>849, 853-859</sup>). Specific vasopressors that have been associated with improvement in the treatment of tricyclic-induced hypotension include noradrenaline (LOE 5<sup>855, 860-862</sup>), adrenaline (LOE 5<sup>848, 855, 863</sup>), dopamine (LOE 5<sup>862, 864, 865</sup>), and dobutamine (LOE 5<sup>864</sup>). Diazepam improved seizure control and survival in one animal study (LOE 5<sup>864</sup>). The use of physostigmine (unavailable in Japan) for tricyclic-induced anticholinergic symptoms was not supported by the current literature given the conflicting associations suggested by several case series (LOE 4<sup>850</sup>, LOE 5<sup>845, 866, 867</sup>). Limited animal research demonstrates a benefit for intravenous lipid infusions in models of tricyclic toxicity (LOE 5<sup>868, 869</sup>). Anti-tricyclic Fab (unavailable in Japan) has been beneficial in animal models of varying degrees of tricyclic cardiotoxicity (LOE 5<sup>870-875</sup>), and one small human study (LOE 5<sup>876</sup>) provided evidence of safety and pharmacokinetic advantage; however, clinical benefit has yet to be demonstrated clearly.

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest or cardiotoxicity caused by tricyclic antidepressants.

If patients with cardiotoxicity caused by tricyclic antidepressants (or after resuscitation from cardiac arrest caused by tricyclic antidepressants) show a wide QRS complex ( $\geq 0.12$ sec) administer 1-2mEq/kg of sodium bicarbonate intravenously, and maintain blood pH between 7.45 and 7.55 against tricyclic-induced cardiac conduction abnormalities (Class IIb).

When mechanical ventilation is required respiratory acidosis should be avoided (Class I).

## Knowledge Gaps

Controlled clinical trials are needed to advance the treatment of cardiac arrest and cardiotoxicity caused by tricyclic antidepressants. Future trials exploring novel therapies (FAB, intravenous lipid infusions) and the use of sodium bicarbonate for hypotension in the absence of cardiac conduction abnormalities would be helpful.

## 9. Digoxin Toxicity

There are no randomized controlled trials evaluating conventional versus alternative treatments for cardiac arrest caused by digoxin. Evidence is limited to fourteen studies demonstrating the usefulness of antidigoxin Fab fragments (unavailable in Japan) for severe cardiac glycoside toxicity (LOE 5<sup>877-890</sup>).

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by digoxin.

## Knowledge Gaps

Animal models and controlled clinical trials are needed to advance the treatment of cardiac arrest caused by digoxin. Pharmacokinetic and clinical studies would be helpful to help establish the dosing of anti-digoxin Fab fragment for digoxin cardiotoxicity.

## 10. Opioid Toxicity

Opioids used in Japan are morphine, fentanyl and others. There are no randomized controlled trials evaluating conventional versus alternative treatments for cardiac arrest caused by opioids. Evidence is limited to studies of mild, moderate, and severe cardiovascular toxicity (LOE 5 for cardiac arrest). Evidence from studies assessing other endpoints (efficacy of naloxone), as well as animal studies, support the use of assisted ventilation before giving naloxone in opioid-poisoned patients with severe cardiopulmonary toxicity (LOE 1<sup>891, 892</sup>, LOE 3<sup>893</sup>, LOE 4<sup>894-896</sup>, LOE 5<sup>897</sup>).

The use and safety of naloxone is supported by human studies (LOE 4<sup>894-896, 898-901</sup>), as well as those assessing other endpoints (alternate routes of administration) (LOE 1<sup>891</sup>, LOE 3<sup>893</sup>, LOE 4<sup>902, 903</sup>). Naloxone can be given intravenously (LOE 4<sup>894, 895, 899, 902</sup>), intramuscularly (LOE 1<sup>891</sup>, LOE 4<sup>894, 895</sup>), intranasally (LOE 1<sup>891</sup>, LOE 4<sup>902</sup>), and into the trachea (LOE 5<sup>904</sup>).

There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by opioids. In adults with severe cardiovascular toxicity caused by opioids, ventilation should be assisted using a bag-mask, followed by naloxone, and tracheal intubation if there is no response to naloxone (Class I). Naloxone should be given intravenously or intramuscularly (Class I). Intranasal or tracheal routes may be used if conditions preclude intravenous or intramuscular administration (Class IIb).

## Knowledge Gaps

Animal models and controlled clinical trials are needed to advance the treatment of cardiac arrest caused by opioids. In particular such studies should determine if naloxone has a role in the resuscitation of the cardiac arrest patient pre- or post-ROSC.

## **7 Cardiac Arrest during Coronary Catheterization**

There are no randomized controlled trials evaluating alternative treatment strategies as opposed to standard care for cardiac arrest during PCI. Evidence is limited to case studies for all interventions.

Three adult human case reports (LOE 4<sup>300, 305, 905</sup>), 2 adult human case series (LOE 4<sup>301, 304, 307</sup>), and 1 animal study (LOE 5<sup>306</sup>) reported that the use of a mechanical chest compression device in cardiac arrest during PCI maintained circulation and enabled the procedure to be completed. Although a small proportion of patients in the case series (13/60) survived to hospital discharge, no randomized controlled or comparison study of this intervention has been performed.

One case study suggested that the use of emergency cardiopulmonary bypass to stabilize and

facilitate emergency coronary angioplasty improved the survival of patients who had cardiac arrest during PCI that was unresponsive to advanced life support (LOE 4<sup>906</sup>).

Five studies (LOE 4<sup>907-909</sup>, LOE 5<sup>910, 911</sup>) supported the use of cough CPR as a temporary intervention to maintain adequate blood pressure and level of consciousness in patients who developed ventricular arrhythmias during coronary angiography (CAG) and PCI while definite therapy for malignant arrhythmias was instituted.

There are insufficient data to support or refute the use of mechanical chest compression, cough CPR, or emergency cardiopulmonary bypass to improve outcome of cardiac arrest during PCI. The use of cough CPR may be considered as a temporary intervention in patients who developed ventricular arrhythmias during CAG and PCI while definite therapy was instituted (Class IIb). The use of emergency cardiopulmonary bypass may be considered in patients who had cardiac arrest during PCI that was unresponsive to ALS (Class IIb).

## Knowledge Gaps

Clinical trials, perhaps initially with historical controls, are needed to advance the treatment of cardiac arrest during PCI.

## 8 Cardiac Arrest after Open or Closed Heart Surgery

Eleven studies documented improvement in outcome in patients with cardiac arrest following cardiac surgery who were treated with resternotomy and internal cardiac compression compared with standard protocol, when administered by experienced personnel in intensive care units (LOE 2<sup>912, 913</sup>, LOE 4<sup>914-922</sup>). Five studies neither supported nor opposed this finding (LOE 4<sup>923-926</sup> LOE 5<sup>927</sup>). One study documented that the risk of infection was not significant after resternotomies conducted appropriately outside of the operating room (LOE 4<sup>921</sup>) where as 3 studies demonstrated very poor outcomes when resternotomy was performed outside an intensive care unit (ICU) (LOE 2<sup>912</sup>, LOE 4<sup>918</sup>, LOE 5<sup>927</sup>).

Six studies supported the use of mechanical circulatory support devices during cardiac arrest following cardiac surgery (LOE 3<sup>922</sup>, LOE 4<sup>928-930</sup>, LOE 5<sup>931, 932</sup>). Three studies reported equivocal findings (LOE 5<sup>933-935</sup>). No studies opposed use of mechanical circulatory support. Mechanical circulatory support devices in these studies included extra-corporeal membrane oxygenation or cardiopulmonary bypass.

Two case reports described damage to the heart caused possibly by external chest compressions before resternotomy (LOE 5<sup>936, 937</sup>).

One study reported 2 cases that responded to escalating doses of adrenaline (LOE 4<sup>938</sup>). One study reported 18 cases with VF/VT after cardiac surgery (LOE 4<sup>939</sup>).

Resternotomy for patients with cardiac arrest following cardiac surgery should be considered in an appropriately staffed and equipped ICU (Class IIa). Resternotomy performed outside these specialized

environments has poor results. Chest compressions should not be withheld while preparing for emergency re sternotomy (Class IIa). Mechanical circulatory support may be considered in the setting of cardiac arrest following cardiac surgery (Class IIb).

There is insufficient evidence to make any recommendations about adrenaline dose, antiarrhythmic use, or any other intervention separate from those recommended in standard protocols.

## Knowledge Gaps

Clinical trials are needed to determine the safety and efficacy of mechanical circulatory support devices, chest compressions, and pharmacological adjuncts for the treatment of cardiac arrest after cardiac surgery.

### ■ 9 Cardiac arrest caused by cardiac tamponade

Five studies (LOE 5<sup>940-944</sup>) indicate that echocardiographically guided pericardiocentesis is a safe and effective method of relieving tamponade, especially when used in conjunction with a pericardial drain.

One study (LOE 4<sup>945</sup>) documented 39 patients who received prehospital emergency thoracotomy by physicians to treat cardiac arrest from penetrating trauma. Eighteen patients had cardiac tamponade and 4 (22%) survived. Two additional studies (LOE 4<sup>946, 947</sup>) indicated that emergency department thoracotomy may be beneficial in patients who have cardiac arrest associated with cardiac tamponade and may have improved results over standard needle pericardiocentesis. One study (LOE 2<sup>948</sup>) indicated that emergency department thoracotomy may be especially beneficial if gross blood causes clotting and blocking of a pericardiocentesis needle, and two studies (LOE 4<sup>914, 949</sup>) indicated that emergency thoracotomy may also be beneficial in patients who have post procedure complications. But one study (LOE 5<sup>950</sup>) indicated that a more definitive sternotomy or thoracotomy in an operating room may also be beneficial if transportation to the operating room does not introduce significant delay.

Pericardiocentesis guided by echocardiography should be considered for treatment of cardiac arrest associated with cardiac tamponade (Class IIa) while non-image guided pericardiocentesis is an acceptable alternative if echocardiography is not available (Class IIb). Placement of a pericardial drain may be beneficial (Class IIa) and may obviate the need for subsequent operating room treatment. Emergency department thoracotomy and pericardiotomy should be considered as an acceptable alternative to operating room thoracotomy and pericardiotomy for treatment of traumatic cardiac arrest associated with cardiac tamponade (Class IIb), and can be considered for use in the treatment of nontraumatic cardiac arrest when pericardiocentesis is unsuccessful in relieving cardiac tamponade (Class IIb).

## Knowledge Gaps

Clinical trials should include patients with pericardial tamponade secondary to nontraumatic arrest and compare safety and efficacy of needle drainage versus thoracotomy and prehospital versus emergency department versus operating room thoracotomy

## ■ 10 Cardiac arrest caused by pulmonary embolus

One double-blind randomized control trial (LOE 1<sup>209</sup>) showed no improvement in survival to discharge with the use of tissue plasminogen activator following cardiac arrest with pulseless electrical activity. One randomized controlled trial of fibrinolytics (LOE 1<sup>210</sup>) showed no difference in short- or long-term (30 days) survival or bleeding in patients randomized to receive tenecteplase or placebo during cardiopulmonary resuscitation. Patients with suspected pulmonary embolism were excluded from the study if open thrombolysis was possible in the prehospital setting. Thirty-seven cases with suspected pulmonary embolism were randomized in the trial. Of these, 2 of 15 patients survived when treated with tenecteplase compared with no survivors in the 22 patients in the placebo treated group<sup>210</sup>.

One meta-analysis (LOE 2<sup>951</sup>) of eight retrospective cohort studies with a variety of causes of cardiac arrest (pulmonary embolism (2 studies), myocardial infarctions (4 studies), cardiology diseases (1 study) and non-traumatic etiologies (1 study)) demonstrated an increased rate of return to spontaneous circulation, survival to discharge and long-term neurologic function with fibrinolytic but also increased the risk of severe bleeding.

Nine studies of patients with presumed pulmonary embolism or all patients with cardiopulmonary arrests (LOE 1<sup>211</sup>, LOE 2<sup>213,215</sup>, LOE 3<sup>216</sup>, LOE 4<sup>212,952-955</sup>), showed improvement with fibrinolysis in return of spontaneous circulation and admission to the hospital or intensive care unit, but no improvement in survival to discharge. Three studies (LOE 2<sup>951</sup>, LOE 3<sup>954</sup>, LOE 4<sup>953</sup>) showed good neurological function of those that survived after successful fibrinolysis during cardiopulmonary resuscitation.

Fibrinolytic therapy may be considered when pulmonary embolism is suspected as the cause of the cardiac arrest (Class IIb).

### Knowledge Gaps

The true incidence of pulmonary embolus as a cause of cardiac arrest is not well documented. Surveillance studies of cardiac arrest noting contributing factors and pathological reports may be helpful to define the impact on public health of this cause of cardiac arrest.

## ■ 11 Cardiac arrest caused by electrolyte disorders

### 1. Magnesium

No studies were identified that addressed specifically the correction of low magnesium concentrations. The presence of a low plasma magnesium concentration was associated with poor prognosis in cardiac arrest patients in three studies (LOE 5<sup>956-958</sup>). The use of magnesium in cardiac arrest was supported by five case series (LOE 4<sup>959-963</sup>), however, five randomised controlled trials (LOE 1<sup>184-187,964</sup>), and a systematic review (LOE 1<sup>965</sup>) found no benefit from the use of magnesium in cardiac arrest.

## 2. Calcium

No studies were identified that specifically addressed the treatment of cardiac arrest caused by hypocalcemia or hypercalcemia.

## 3. Potassium

There are no randomized trials on the treatment of potassium abnormalities in the setting of cardiac arrest. The management of hypokalemia and hyperkalemia in the setting of cardiac arrest is based on case reports and animal studies. One case series of 2 patients reported the resolution of torsades de pointes with potassium replacement in patients with hypokalemia (LOE 4<sup>966</sup>). Several clinical studies (LOE 5<sup>956, 967-969</sup>) report an association between hypokalemia and the development of VF, and an animal study (LOE 5<sup>970</sup>) reported that hypokalemia lowers the VF threshold. In an animal model of cardiac arrest (LOE 5<sup>971</sup>), it was reported that hyperkalemic animals had a higher rate of survival.

### Knowledge Gaps

Epidemiological studies are required to document the incidence of cardiac arrests secondary to electrolyte disturbance. Studies are needed to determine the safety and efficacy of current treatments electrolyte replacement strategies during cardiac arrest.

## 8 Intensive Care after ROSC

In the ILCOR statement of Post Cardiac Arrest Syndrome (PCAS)<sup>972</sup>, which was published in 2008, the concept for PCAS included the pathological conditions both before and after ROSC. Since this COSTR 2010 addressed mainly the therapy after ROSC, we have used the term of “Intensive Care After ROSC” rather than “Postresuscitation Care”.

### ■ 1 Comprehensive Treatment Protocol for Post-Cardiac Arrest Syndrome

RCTs addressing the use of comprehensive treatment protocols after sustained ROSC have not been performed. Several retrospective studies documented increases in survival of comatose patients with sustained ROSC after out-of-hospital cardiac arrest with implementation of a comprehensive treatment protocol (LOE 2<sup>973</sup>, LOE 3<sup>905, 974</sup>). Protocols included multiple elements such as therapeutic hypothermia, glucose control, goal-directed hemodynamic optimization, ventilation, and PCI. The independent effect of each element of the bundle treatment could not be established.

A retrospective study showed that if high quality advanced life support in each region is followed by intensive care after ROSC, outcomes in patients with cardiogenic witnessed VF and VT were improved (J-LOE 3<sup>975</sup>).

### Knowledge Gaps

Studies are needed to determine whether a comprehensive treatment protocol after cardiac arrest with a sustained ROSC improves short- and long-term outcomes. Future studies should define what interventions other than hypothermia are important inclusions in an effective comprehensive treatment protocol.

### ■ 2 Ventilation control

#### 1. Ventilation

There were limited studies that addressed alternative ventilation strategies after ROSC. A human study (LOE 2<sup>976</sup>) and studies in animals (LOE 5<sup>977-980</sup>) indicated that hyperventilation reduced cerebral blood flow after ROSC. But, after prolonged cerebral ischemia, the cerebral blood flow response to hyperventilation and to hypoventilation may be absent (LOE 5<sup>981, 982</sup>). Avoiding hyperventilation, as part of a bundle of care, improved long-term outcome in humans (LOE 3<sup>905</sup>) and in dogs (LOE 5<sup>983</sup>), but the independent effect of ventilation could not be determined. A single animal study suggested that hyperventilation reduced degenerating neurons (LOE 5<sup>984, 985</sup>).

Ventilation with tidal volumes  $\leq 9$  mL/kg after ROSC is associated with increased incidence of

atelectasis (LOE 3<sup>986</sup>). In cohort studies, manipulation of tidal volume and PEEP are not associated independently with improved survival in critical patients including those after ROSC (LOE 2<sup>987</sup>, LOE 3<sup>986</sup>).

After ROSC, routine hyperventilation leading to hypocapnia should be avoided in order to prevent additional cerebral ischemia (Class III).

## 2. Controlled Oxygenation

A randomized clinical trial compared ventilation with 30% oxygen or 100% oxygen for the first 60 minutes after ROSC (LOE 1<sup>988</sup>). Mean partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) at 60 minutes after ROSC was 110±25 mm Hg in the 30% oxygen group and 343±174 mm Hg in the 100% oxygen group. No statistical difference was detected in serum biomarkers reflecting acute brain injury, survival, or the percentages of good neurological outcome (cerebral performance category 1 or 2) at hospital discharge. A significant subset of patients in this study (30%) who were ventilated with 30% oxygen after ROSC required increased FiO<sub>2</sub> to maintain a pulse oximetry reading of >95%. The study was underpowered to determine efficacy or harm.

A multi-center cohort study examining the effects of hyperoxia in hypoxic brain damage after ROSC showed that hyperoxia of more than 300 mmHg was associated with an increase in mortality rate in hospital as compared with that in hypoxia less than 60 mmHg and normoxic state (J-LOE 3<sup>989</sup>).

An animal study demonstrated that ventilation with 100% oxygen (generating PaO<sub>2</sub> >450 mmHg) during the first 15 to 60 minutes after ROSC caused neurodegeneration and worse neurological outcome when compared with FiO<sub>2</sub> titrated to an arterial pulse oximetry reading between 94% and 96% (LOE 5<sup>990</sup>).

Six animal studies demonstrated that ventilation with 100% oxygen (generating PaO<sub>2</sub> >250 to 350 mmHg) during the first 10 to 60 minutes after ROSC causes increased brain lipid peroxidation, increased metabolic dysfunction (glucose utilization and mitochondrial dysfunction), increased neurodegeneration, and worse neurological outcome when compared to ventilation with room air (LOE 5<sup>112, 113, 991-994</sup>). But, these studies addressed only short-term evaluation of outcomes (≤24 hours).

An animal study did not detect any difference in outcome at 72 hours when animals were ventilated with 100% oxygen or room air during CPR and for the first hour after ROSC (LOE 5<sup>114</sup>). Another animal study failed to show any difference in outcome when comparing 2 levels of hypoxic FiO<sub>2</sub> (0.085 and 0.12) with normoxic ventilation when given for the intra- and early (15 minutes) period after ROSC (LOE 5<sup>995</sup>). The study did not demonstrate a significant difference in neurological assessment scores at 72 hours or in survival. The study also failed to show a significant difference in the serum biomarkers of oxidative injury.

An animal study reported that a PaO<sub>2</sub> of 250 to 350 mm Hg during the first 10 minutes of cardiopulmonary bypass reperfusion after cardiac arrest resulted in worse cardiac function compared to a PaO<sub>2</sub> 40 to 90 mm Hg during the same time period (LOE 5<sup>996</sup>). A second animal study found no difference in myocardial function or injury when PaO<sub>2</sub> was gradually increased from 40 to 110 mm Hg over the first 15 minutes of cardiopulmonary bypass reperfusion compared to initiating reperfusion at normoxia (LOE 5<sup>997</sup>).

The control of arterial blood oxygen saturation or tension in the early care for patients after ROSC is reasonable (Class IIa).

## Knowledge Gaps

Prospective randomized controlled clinical trials are needed to compare ventilation with 100% oxygen versus ventilation with inspired oxygen titrated to an arterial blood oxygen saturation goal (possibly 94% to 96%) for the first hour after sustained ROSC.

### ■ 3 Support of the Circulation

#### 1. Hemodynamic Optimization

There are no RCTs addressing early hemodynamic optimization after cardiac arrest. A study suggested that hemodynamic optimization (fluids, vasopressors, catecholamines, intra-aortic balloon pump, and PCI) as part of a bundle of interventions improved outcome in comparison with historical controls (LOE 3<sup>905</sup>). The independent effect of early hemodynamic optimization was not assessed in this study. A recent study that included early hemodynamic optimization as part of a post-cardiac arrest treatment bundle was not powered to measure a survival benefit (LOE 3<sup>974</sup>).

Despite limited data, the hemodynamic stabilization according to the pathophysiology of post-cardiac arrest syndrome has a rationale in titrating hemodynamics to optimize organ perfusion.

#### 2. Fluid Therapy

There are no human studies that compare intravenous fluids after ROSC in patients with cardiac dysfunction compared with no intravenous fluids. A small sample human study used intravenous fluid (0.9% saline or lactated Ringer's) as part of early goal-directed therapy in post-cardiac arrest syndrome and found no significant improvements in survival (LOE 5<sup>974</sup>). In an additional before-and-after study (LOE 5), intravenous fluids (0.9% saline, lactated Ringer's, or colloids) were administered as part of a package of care (including PCI and therapeutic hypothermia) that improved survival with favorable neurological outcome in adult patients after ROSC in prehospital or in-hospital settings<sup>905</sup>. The intervention period had a significantly increased positive fluid balance (345 versus 2300 mL). Six human studies showed that rapid infusion of fluids (500 to 3000 mL of 0.9% saline or lactated Ringer's) to induce therapeutic hypothermia after ROSC produced little harm (LOE 5<sup>998-1003</sup>). A human study showed that the deterioration in oxygenation after ROSC was not significantly affected by the infusion of cold 0.9% saline (3427 ±210 mL) (LOE 5<sup>1004</sup>). Three animal studies reported neurological and cardiac protection with the administration of hypertonic fluid compared to normal saline (LOE 5<sup>1005-1007</sup>). An animal study showed an increase in cerebral blood flow with fluid for hemodilution combined with induced hypertension (LOE 5<sup>1008</sup>).

## Advanced Life Support (ALS)

Rapid infusion of cold 0.9% saline or lactated Ringer's appears to be well tolerated when induced therapeutic hypothermia. Based on the pathophysiology of post-cardiac arrest syndrome, it is reasonable to use intravenous fluids as part of a package of post-cardiac arrest care (Class IIa).

### 3. Cardioactive Drugs

There are no clinical trials that have determined the independent effect of vasopressors and/or inotropes after ROSC on cardiovascular dysfunction and/ or survival to discharge. Four clinical trials have suggested improved survival to discharge with vasopressors or inotropes, but they are underpowered for achieving (LOE 3<sup>905, 974, 1009</sup>, LOE 4<sup>1010</sup>). Six experimental studies showed improvement in postresuscitation cardiac dysfunction (left ventricular function) with the administration of cardioactive drugs, such as dobutamine or levosimendan, but none have shown that such improvement in function translates into improved survival (LOE 5<sup>1011-1016</sup>).

There is insufficient evidence to support the routine use of vasopressors and/ or inotropes for improving survival in adult patients with cardiovascular dysfunction after ROSC .

### Knowledge Gaps

Specific clinical research is required to investigate whether treatment of post-cardiac arrest cardiovascular dysfunction with vasopressors and/or inotropes will yield incremental beneficial impact on long-term outcomes beyond those achieved with therapeutic hypothermia alone.

### 4. Antiarrhythmic Drugs

No controlled studies addressed specifically the use of amiodarone, lidocaine, or  $\beta$ -blockers soon after ROSC . One uncontrolled retrospective study did not demonstrate an improvement in 6-month survival when amiodarone or lidocaine was given to patients resuscitated from VF or tachycardia during early (first 72 hours) in-hospital postresuscitation care (LOE 4<sup>1017</sup>). One single prospective nonrandomized study suggested that recurrent VF was reduced and long- and short-term survival were improved in patients treated with  $\beta$ -blockers during electrical storm (LOE 5<sup>613</sup>). One study reported an incidence of approximately 5% for VF or VT in hospitalized post-cardiac arrest patients (LOE 4<sup>1018</sup>). Five RCTs documented consistent improvement in all-cause mortality and sudden death when implantable cardioverter defibrillators were inserted as late, secondary prophylaxis compared with amiodarone or  $\beta$ -blocker administration to patients that survived VF or VT cardiac arrest (LOE 5<sup>1019-1023</sup>).

There are insufficient evidence to support or refute continued administration of amiodarone or lidocaine after ROSC.

## Knowledge Gaps

The incidence of recurrent ventricular arrhythmias after hospital admission following survival of cardiac arrest and the effect of therapeutic hypothermia on their incidence during the early phase of the postresuscitation period should be further investigated.

### 5. Mechanical circulatory support

There are no studies addressing the use of mechanical circulatory support in patients with ROSC but who have cardiovascular dysfunction. A swine study showed worse left ventricular function when an intra-aortic balloon pump was compared with standard treatment including dobutamine after ROSC (LOE 5<sup>1015</sup>). Five studies of nonarrested patients in cardiogenic shock or severe heart failure showed that left ventricular assist device or continuous aortic flow augmentation improved hemodynamics but not survival (LOE 5<sup>1024-1028</sup>). Two case series reported the use of the intraaortic balloon pump in patients with severe myocardial dysfunction after ROSC, but the effect was impossible to isolate from other interventions (LOE 4<sup>905, 1029</sup>).

There is insufficient evidence to support the use of mechanical circulatory support in post-cardiac arrest patients who have cardiovascular dysfunction.

## ■ 4 Temperature control

### 1. Prevention and treatment of hyperthermia

There are no RCTs evaluating the effect of treatment of pyrexia (defined as  $\geq 37.6^{\circ}\text{C}$ ) compared with no temperature control in patients after cardiac arrest. There were eleven studies suggesting an association between pyrexia and poor outcomes (LOE 4<sup>1030-1034</sup>, LOE 5<sup>1035-1040</sup>). Patients with cerebrovascular events who developed pyrexia had worsened short- and long-term outcomes (LOE 5<sup>1035-1040</sup>).

Patients who develop hyperthermia after cardiac arrest have a worse prognosis. Despite the lack of evidence, it is reasonable to treat hyperthermia in the post cardiac arrest period (Class IIa).

### 2. Therapeutic Hypothermia

#### 1) Who to Cool?

All studies of post-cardiac arrest therapeutic hypothermia have included only patients in coma. One trial defined coma as “not responding to verbal commands” (LOE 1<sup>1041</sup>). The other trials defined coma similarly, used the Glasgow Coma Score (GCS)  $\leq 8$ , or did not provide a clear definition.

A randomized trial (LOE 1<sup>1041</sup>) and a pseudorandomized trial (LOE 2<sup>1042</sup>) demonstrated improved neurological outcome at hospital discharge or at 6 months after hospital discharge in comatose patients after out-of-hospital VF cardiac arrest. Cooling was initiated within minutes to hours after ROSC, and a temperature range of 32 to 34°C was maintained for 12 to 24 hours. Two studies with historical control groups (LOE 3<sup>1043, 1044</sup>) showed improvement in neurological outcome after therapeutic

hypothermia for comatose survivors of VF cardiac arrest. One systematic review demonstrated that conventional cooling methods were more likely to reach a best cerebral performance category score of 1 or 2 (5-point scale where 1 is good recovery and 5 is brain death) with a relative risk of 1.55 (99.5% CI 1.22 to 1.96) and more likely to survive to hospital discharge (relative risk of 1.35 95% CI 1.1 to 1.65) compared with standard postresuscitation care (LOE 1<sup>1045</sup>).

One small (n=30) randomized trial showed reduced plasma lactate values and oxygen extraction ratios in a group (n=16) of comatose survivors after cardiac arrest with asystole or PEA who were cooled with a cooling cap (LOE 1<sup>1046</sup>).

Six studies with historical control groups showed benefit using therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest after all-rhythm arrests (LOE 3<sup>905, 1047-1051</sup>). One study with historical controls showed better neurological outcome after VF cardiac arrest but no difference after cardiac arrest from other rhythms (LOE 3<sup>1052</sup>).

Two nonrandomized studies with concurrent controls indicated possible benefit of hypothermia following cardiac arrest from other initial rhythms in- and out-of-hospital (LOE 2<sup>1053, 1054</sup>). One registry study, which included almost 1000 cooled comatose patients following cardiac arrest from all rhythms, showed that survival with good outcome at 6 months was 56% after initial VT/VF, 21% after initial asystole, and 23% after initial PEA (LOE 4<sup>1055</sup>).

A preliminary prospective study about therapeutic hypothermia was performed for 23 patients whose systolic blood pressure more than 90 mmHg and GCS 3 to 5 among 50 patients who did not obtain ROSC after ordinary CPR treated with PCPS and IABP. As a result, 12 patients recovered to good neurological state (J-LOE 4<sup>237</sup>).

Another prospective study about therapeutic hypothermia with PCPS (34 °C for 72 hours, which included patients of starting hypothermia during CPR, with PCI or IABP if necessary) was performed. As a result, the numbers of good neurological outcome decreased when the achieving time to 34 °C from cardiac arrest was delayed (cut-off time of arrest to PCPS: 55.5 minutes in accuracy of 85.4%; PCPS to 34 °C: 21.5 minutes in accuracy of 89.5% ) (J-LOE 4<sup>238</sup>).

## 2) How to Cool?

Nineteen studies indicated that cooling could be initiated safely with intravenous ice-cold fluids (30 mL/kg of saline 0.9% or Ringer's lactate) (LOE 3<sup>905, 974, 1044, 1050, 1052, 1056</sup>, LOE 4<sup>998, 999, 1001-1004, 1029, 1055, 1057-1062</sup>). Six studies indicated that cooling with IV cold saline can be initiated in the prehospital phase (LOE 1<sup>1000, 1063</sup>, LOE 2<sup>1064</sup>, LOE 3<sup>226, 1065</sup>). Thirteen studies documented the use of an intravascular heat exchanger to induce and maintain hypothermia (LOE 2<sup>1053, 1054</sup>, LOE 3<sup>905, 974</sup>, LOE 4<sup>1001, 1058, 1060, 1066-1071</sup>). Twelve studies documented the use of ice packs and either water- or air-circulating blankets to induce and maintain hypothermia (LOE 2<sup>1053</sup>, LOE 3<sup>974, 1044, 1048, 1051, 1052</sup>, LOE 4<sup>974, 1060, 1069, 1072-1074</sup>). Seven studies documented the use of ice packs (sometimes combined with wet towels) alone to induce and maintain hypothermia (LOE 2<sup>1042</sup>, LOE 3<sup>1043, 1047, 1049</sup>, LOE 4<sup>1066, 1068, 1075</sup>). Four studies documented the use of ice packs alone to maintain hypothermia (LOE 3<sup>1056</sup>, LOE 4<sup>1029, 1059, 1062</sup>). Seven studies documented the use of cooling blankets or pads alone to induce and maintain hypothermia (LOE 2<sup>1076</sup>, LOE 3<sup>1077</sup>, LOE 4<sup>1060, 1078-1081</sup>). Eight studies documented the use of water-circulating, gel-coated pads to induce and maintain, or just maintain, hypothermia (LOE 3<sup>905, 1050</sup>, LOE 4<sup>1057, 1060</sup>).

<sup>1061, 1073, 1079, 1082</sup>). One RCT (LOE 1) used a cold-air tent<sup>1041</sup> and another used a cooling helmet<sup>1046</sup> to induce and maintain hypothermia. In a registry study, cooling was maintained with ice packs (17%), air cooling (8%), circulating water blankets (63%), an intravascular cooling device (16%), and other methods (8%) (LOE 4<sup>1055</sup>).

### 3) When to Cool?

One registry-based case series of 986 comatose post–cardiac arrest patients suggested that time to initiation of cooling (median 90 minutes; interquartile range IQR 60 to 165 minutes) was not associated with improved neurological outcome postdischarge (LOE 4<sup>1055</sup>). A case series of 49 consecutive comatose post–cardiac arrest patients who were intravascularly cooled after out-of-hospital cardiac arrest also documented that time to target temperature (median 6.8 hours; IQR 4.5 to 9.2 hours) was not an independent predictor of neurological outcome (LOE 4<sup>1071</sup>).

### 4) The combination of therapeutic hypothermia and primary percutaneous intervention

Five studies indicated that the combination of therapeutic hypothermia and PCI is feasible and safe after cardiac arrest caused by acute myocardial infarction (LOE 3<sup>905, 1056, 1083</sup>, LOE 4<sup>1029, 1055</sup>).

Comatose adult patients (not responding in a meaningful way to verbal commands) with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32 to 34°C for 12 to 24 hours (**Class I**). Induced hypothermia might also benefit comatose adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm, or cardiac arrest in hospital (**Class IIb**). Rapid infusion of ice-cold intravenous fluid 30 mL/kg or ice packs are feasible, safe, and simple methods for initially lowering core temperature up to 1.5°C. When intravenous fluids are used to induce hypothermia, additional cooling strategies will be required to maintain hypothermia. Limited available evidence suggests that PCI during therapeutic hypothermia is feasible and safe and may be associated with improved outcome (**Class IIb**).

### Knowledge Gaps

Although the data support cooling to 32°C to 34°C, the optimal temperature has not been determined. Furthermore the optimal method, onset, duration and rewarming rate, and therapeutic window remain unknown. Further investigation is also needed to determine the benefit of post–cardiac arrest therapeutic hypothermia after nonshockable cardiac arrest, in-hospital cardiac arrest, and in children. Clinical and cost comparisons are required of the methods used for inducing and maintaining therapeutic hypothermia in- and out-of-hospital. The safety and efficacy of therapeutic hypothermia during cardiac arrest resuscitation needs to be explored through controlled clinical trials.

## ■ 5 Seizure control

No controlled clinical trials directly addressed prophylactic treatment for seizures after cardiac arrest. Five studies documented a 3–44% incidence of seizures after sustained ROSC (LOE 4<sup>306, 1033, 1084-1086</sup>). Two studies reported no difference in neurological outcome after use of single-dose diazepam or magnesium or both; or thiopental given after sustained ROSC (LOE 5<sup>963, 1084</sup>). There are no studies addressing prompt and aggressive treatment after the first seizure occurring after circulation was restored. Seizures in the postarrest period may be refractory to multiple medications (LOE 4<sup>1085, 1087</sup>). There was no reported difference in the occurrence of seizures after sustained ROSC in patients treated with therapeutic hypothermia or with normothermia care (LOE 5<sup>974, 1041</sup>).

There are insufficient data to support or refute the use of specific antiseizure medication in the prevention or treatment of seizures after ROSC.

### Knowledge Gaps

Studies need to determine the true incidence of clinical and electrographic seizures in patients after cardiac arrest, particularly in those treated with therapeutic hypothermia.

Clinical trials are required to assess interventions and drugs for the prevention and treatment of seizures. Studies should evaluate whether continuous electroencephalograph (EEG) monitoring to diagnose and treat seizures after cardiac arrest is feasible, interpretable, of prognostic value, and beneficial for patients.

## ■ 6 Other Supportive Therapies

### 1. Blood Glucose Control

One human randomized interventional study that prospectively evaluated strict glucose control ((4–6mmol/L, [72–108mg/dL]) compared with moderate glucose control (6–8mmol/L, [108–144mg/dL]) in patients resuscitated from prehospital cardiac arrest with VF found no survival benefit with strict glucose control (LOE 1<sup>1088</sup>). Five retrospective studies in post–cardiac arrest patients suggested an association of higher glucose levels with increased mortality and worse neurological outcomes, but those findings may be related to other factors (LOE 4<sup>1017, 1033, 1089-1091</sup>). Based on those studies, the suggested target ranges for glucose values have been variable. A good randomized trial of intensive glucose control versus conventional glucose control in the largest number of ICU patients to date reported increased mortality in patients treated with intensive glucose control (LOE 5<sup>1092</sup>). Two meta-analyses of studies of tight glucose control versus conventional glucose control in critically ill patients showed no significant difference in mortality but found tight glucose control was associated with a significantly increased risk of hypoglycemia (LOE 5<sup>1093, 1094</sup>).

Strategies to treat hyperglycemia >10mmol/L (>180mg/dL) should be considered in adult patients with ROSC after cardiac arrest (Class IIb). Hypoglycemia resulting from exceed strict blood glucose control should be avoided.

## 2. Steroid Therapy

Two observational studies (LOE 2<sup>1095, 1096</sup>), and 2 animal studies (LOE 5<sup>1097, 1098</sup>), failed to demonstrate any benefit or harm from the use of steroids after ROSC. One small, single-center randomized placebo-controlled trial showed benefit from the use of a package of care consisting of vasopressin and dexamethasone in addition to adrenaline during cardiopulmonary resuscitation, combined with the treatment of post-cardiac arrest shock with hydrocortisone in the study group (LOE 1<sup>196</sup>). The complex design of this study makes it impossible to determine the independent effect of any interventions on outcome.

There is insufficient evidence to support the use of corticosteroids for patients after ROSC.

## Knowledge Gaps

It is important to determine the incidence of adrenal insufficiency after ROSC. Clinical trials are needed to determine the effect of exogenous steroids administered after cardiac arrest.

## 3. Hemofiltration

One RCT demonstrated no difference in survival or neurological outcome between groups treated with high-volume hemofiltration (200mL/kg/h for 8h) irrespective of inducing mild hypothermia, and control group without hemofiltration (LOE 1<sup>1099</sup>). The combined hemofiltration-only and hemofiltration-plus-hypothermia groups had increased survival at 6 months after cardiac arrest when compared to controls. One study suggested improved survival and neurological outcome in patients treated with high-volume hemofiltration after ROSC (LOE 2<sup>1100</sup>).

There is insufficient evidence to support the use of hemofiltration in patients after ROSC.

## 4. Neuroprotective Therapy

One small pilot study in witnessed, out-of-hospital cardiac arrests of presumed cardiac etiology showed improved survival at 3 months when therapeutic hypothermia (35°C) and the oral administration of coenzyme Q10 (250 mg followed by 150 mg TID for 5 days) was compared with therapeutic hypothermia alone; however, there was no difference in neurologically intact survival (LOE 1<sup>1078</sup>).

Four RCTs (LOE 1) using nimodipine<sup>1101, 1102</sup>, lidoflazine<sup>1103</sup>, or diazepam<sup>964</sup> in out-of-hospital cardiac arrest showed no benefits from any of the drugs when compared with standard care. Two RCTs (LOE 1) using thiopental<sup>1103</sup> or nimodipine<sup>1104</sup> in out-of-hospital cardiac arrest were unable to show any benefits when compared with standard care. A retrospective analysis using glucocorticoids in out-of-hospital cardiac arrest was unable to show any benefits when compared with standard care (LOE 2<sup>1096</sup>).

There are insufficient data to recommend for or against the use of neuroprotective drugs (coenzyme Q10, thiopental, glucocorticoids, nimodipine, lidoflazine, or diazepam) alone or as an adjunct to therapeutic hypothermia in comatose cardiac arrest after ROSC.

## Knowledge Gaps

Specific research and larger clinical trials are required on the use of coenzyme Q10 in patients with therapeutic hypothermia of 33°C on neurologically intact survival.

### ■ 7 Treatment of Precipitating Causes of Cardiac Arrest

There is insufficient evidence about the benefit of fibrinolysis following cardiac arrest in patients with suspected pulmonary embolism is beneficial. Several studies (LOE 5<sup>212, 213, 216, 1105, 1106</sup>) and a case series (LOE 4<sup>1107</sup>) showed no significant increase in survival to hospital discharge. There was an increase in bleeding complications following fibrinolysis in most of those studies. One study suggested that the risk of major hemorrhage is further increased in patients who have undergone CPR (LOE 5<sup>212</sup>).

Five reviews demonstrated that pulmonary embolectomy after cardiac arrest caused a high mortality rate (LOE 4<sup>1108-1112</sup>). One study showed that percutaneous cardiopulmonary support (PCPS) may be beneficial in the management of shock caused by massive pulmonary embolism (J-LOE 5<sup>1113</sup>). One case series reported outcomes of 7 patients after cardiac arrest caused by pulmonary embolism and they were treated with percutaneous mechanical thrombectomy (LOE 4<sup>952</sup>); 3 patients also received recombinant tissue plasminogen activator. Only 1 of the 7 patients died and pulmonary perfusion was restored in the majority (85.7%).

In patients with diagnosed or suspected pulmonary embolism after ROSC, there is inadequate evidence to recommend for fibrinolytic therapy in addition to heparin. The mortality with surgical embolectomy for suspected or diagnosed pulmonary embolism in cardiac arrest patients is high, so that it should be avoided in patients who have received CPR (Class III), especially with fibrinolytic therapy. There are few data on percutaneous mechanical thromboembolectomy, but it may be beneficial and may be considered in patients sustaining cardiac arrest from a pulmonary embolism who are not candidates for fibrinolytic therapy (Class IIb).

## 9 Prognostication

### ■ 1 Prognostication During Cardiac Arrest

#### 1. End-Tidal CO<sub>2</sub> and Prediction of Outcome

Thirteen studies (LOE P2<sup>135-137, 141, 142, 1114, 1115</sup>, LOE P3<sup>1116</sup>, LOE P5<sup>99, 139, 1117-1119</sup>) indicated that higher maximal end-tidal CO<sub>2</sub> levels can predict ROSC. Seven studies demonstrate that end-tidal CO<sub>2</sub> values <1.33kPa (10mmHg) obtained after intubation and during CPR efforts are associated with a low probability of survival from cardiac arrest (LOE P2<sup>135-137, 141, 142, 1114, 1115</sup>). Two prospective human studies demonstrated a significant increase in end-tidal CO<sub>2</sub> when ROSC occurs (LOE 5<sup>99, 139</sup>).

Quantitative measurement of end tidal CO<sub>2</sub> may be a safe and effective noninvasive indicator of cardiac output during CPR and may be an early indicator of ROSC in intubated patients (Class IIa). Although low values of end tidal CO<sub>2</sub> are associated with a low probability of survival, there are insufficient data to support a specific cutoff of end tidal CO<sub>2</sub> at different time intervals as a prognostic indicator of outcome during adult cardiac arrest.

#### Knowledge Gaps

More well-designed prognostic studies of end tidal CO<sub>2</sub> monitoring designed to measure long-term morbidity, mortality, and neurological survivability are recommended.

In future studies the cause of cardiac arrest should be documented. Use of vasopressors and ventilation rates may lower end-tidal CO<sub>2</sub>; and this effect should be controlled in future studies. Evaluation of end-tidal CO<sub>2</sub> for prognosis should be repeated with supraglottic airway devices.

#### 2. Ultrasound During Cardiac Arrest

No studies examined the impact of ultrasound or echocardiography on patient outcomes in cardiac arrest specifically. Three studies examined the prognostic value of the presence or absence of sonographic cardiac motion in cardiac arrest (LOE 4<sup>143, 1120, 1121</sup>). One retrospective chart review (LOE 4<sup>1122</sup>) and 1 prospective comparison (LOE 4<sup>1123</sup>) documented the diagnostic accuracy of transesophageal ultrasound in detecting the cause of circulatory collapse. One study documented the frequency of pulmonary embolism in PEA arrest as detected with transesophageal ultrasound (LOE 4<sup>1124</sup>). An additional 2 prospective observational studies examined the use of transthoracic ultrasound by “nonexpert” sonographers to detect pericardial effusion and other causes of PEA (LOE 4<sup>1125</sup>, LOE 5<sup>1126</sup>).

Three prospective studies examined ultrasound determination of cardiac standstill as a predictor of clinical outcomes and ROSC in patients in cardiac arrest (LOE 4<sup>143, 1120, 1121</sup>). Absence of cardiac

motion on sonography during resuscitation of patients in cardiac arrest was highly predictive of death: of the 341 patients from the 3 studies, 218 had no detectable cardiac activity and only 2 of those had ROSC (no data on survival to hospital discharge).

There is insufficient evidence to support or refute the routine use of ultrasound or echocardiography to guide cardiac arrest resuscitation.

## Knowledge Gaps

Future research should address the role ultrasound (both transesophageal and transtracheal) can perform as a targeted intervention (detection of potential causes, guidance of key procedures) during cardiac arrest resuscitation. With increasing emphasis on uninterrupted chest compressions, there is the potential for harm with the use of transthoracic ultrasound because it often requires interruption of compressions and ventilation to acquire adequate images. This is less of a concern with transesophageal or intracardiac echocardiography.

## ■ 2 Prognostication after resuscitation

### 1. Clinical Examination

In adult patients comatose after cardiac arrest who had not been treated with therapeutic hypothermia, the following parameters predicted poor outcome (CPC 4 or 5) with a false-positive rate (FPR) of 0%: absent vestibulo-ocular reflexes at  $\geq 24$  hours [(95% CI 0% to 14%)] (LOE P1<sup>1127, 1128</sup>); absence of pupillary light *and* corneal reflex at 72 hours [(95% CI 0% to 9%)](LOE P1<sup>1129</sup>); GCS  $< 5$  at 48 hours (95% CI 0% to 13%) (LOE P1<sup>1130</sup>) and on day 3 (95% CI 0% to 6%) (LOE P2<sup>1131</sup>) and a clinical examination score  $< 15$  on day 4 [(95% CI 0% to 18%)](LOE P1<sup>1132</sup>). However, in 1 study an absent motor response (GCS motor=1) at 72 hours after cardiac arrest predicted poor outcome with a FPR of 5% [(95%CI 2% to 9%)](LOE P1<sup>1129</sup>). The presence of myoclonus status in adults was strongly associated with poor outcome (LOE P1<sup>1085, 1129</sup>, LOE P3<sup>1087, 1133</sup>, LOE P4<sup>1134</sup>), but rare cases of good neurological recovery have been described and accurate diagnosis was problematic<sup>1135-1139</sup>.

There are no clinical neurologic signs that reliably predict poor outcome  $< 24$  hours after ROSC. In adult patients who are comatose after cardiac arrest, have *not been treated with hypothermia* and have no confounding factors (eg, hypotension, sedatives or neuromuscular blockers), the absence of both pupillary light and corneal reflex at  $\geq 72$  hours reliably predicts poor outcome. Absence of vestibulo-ocular reflexes at  $\geq 24$  hours and a GCS motor score of 2 or less at  $\geq 72$  hours are less reliable. Other clinical signs, including myoclonus, are not recommended for predicting poor outcome (Class III).

## 2. Biochemical Markers

Serum neuronal-specific enolase (NSE) elevations are associated with poor outcome for comatose patients after cardiac arrest (LOE P1<sup>1140, 1141</sup>, LOE P2<sup>1071, 1129, 1132, 1142-1155</sup>, LOE P3<sup>1156, 1157</sup>). Although specific cutoff values with a FPR of 0% have been reported, clinical application is limited due to variability in the 0% FPR cutoff values reported among various studies.

Serum S100 elevations are associated with poor outcome for comatose patients after cardiac arrest (LOE P1<sup>1140, 1141</sup>, LOE P2<sup>1129, 1132, 1142, 1148, 1150, 1152, 1153, 1158-1163</sup>, LOE P3<sup>1156</sup>).

Many other serum markers measured after sustained ROSC have been associated with poor outcome after cardiac arrest, including brain natriuretic peptide (BNP) (LOE P3<sup>1164</sup>), vWF (LOE P3<sup>1165</sup>), ICAM-1 (LOE P3<sup>1165</sup>), procalcitonin (LOE P2<sup>1159</sup>), IL-1ra, RANTES, sTNFR2, IL-6, IL-8 and IL-10 (LOE P3<sup>1166</sup>). However, other studies found no relationship between outcome and serum IL-8 (LOE P1<sup>1158</sup>), and procalcitonin and sTREM-1 (LOE P3<sup>1167</sup>).

Worse outcomes for comatose survivors of cardiac arrest are also associated with increased levels of cerebrospinal fluid (CSF)-CK (LOE P2<sup>1168, 1169</sup>) and cerebrospinal fluid-CKBB (LOE P1<sup>1140, 1141</sup>, LOE P2<sup>1143, 1154, 1169, 1170</sup>, LOE P3<sup>1171-1173</sup>). However, A study found no relationship between cerebrospinal fluid-CKBB and prognosis (LOE P2<sup>1174</sup>).

Outcomes are also associated with increased cerebrospinal fluid levels of other markers including NSE (LOE P1<sup>1141</sup>, LOE P2<sup>1150, 1154</sup>); S100 (LOE P2<sup>1150</sup>), LDH, GOT (LOE P2<sup>1143, 1169</sup>) neurofilament (LOE P3<sup>1175</sup>); and acid phosphatase and lactate (LOE P2<sup>1169</sup>). Cerebrospinal fluid levels of  $\beta$ -D-N-acetylglucosaminidase and pyruvate were not associated with the prognosis of cardiac arrest (LOE P2<sup>1169</sup>).

Evidence does not support the use of serum or cerebrospinal fluid biomarkers alone as predictors of poor outcomes in comatose patients after cardiac arrest with or without treatment with therapeutic hypothermia. Limitations included small numbers of patients and/or inconsistency in cutoff values for predicting poor outcome.

### Knowledge Gaps

Future studies should identify and resolve the heterogeneity of cutoff values used to predict poor outcome with a FPR of zero. Studies also must account for confounders that may alter levels or predictive performance of various markers (eg, hypothermia, underlying disease, pregnancy, intra-aortic balloon pump, brain instrumentation, hemodialysis, or other organ failure). Studies examining whether biomarkers can be used to monitor ongoing injury and response to therapy may be useful.

## 3. Electrophysiological Studies (Comatose adult patients after ROSC)

### 1) Somatosensory evoked potentials

Somatosensory evoked potentials measured between 4 hours and 2 weeks after cardiac arrest were associated with poor outcome in 14 studies (LOE P1<sup>1128, 1129, 1140, 1176-1181</sup>, LOE P2<sup>1132</sup>, LOE P3<sup>1171</sup>).

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<sup>1182-1184</sup>). In a meta-analysis of patients not treated with therapeutic hypothermia, the absence of cortical N20 response to median nerve stimulation at 24 to 72 hours after cardiac arrest predicted poor outcome (death or Cerebral Performance Category 3 to 4) with a FPR of 0.7% (95% CI 0.1 to 3.7) (LOE P1 <sup>1140</sup>).

## 2) Abnormal Brain Stem Auditory Evoked Potentials

Abnormal brain stem auditory evoked potentials recorded 1 to 56 days after cardiac arrest in patients not treated with hypothermia predicted poor outcome with a FPR of 0% (95% CI 0 to 14) in 1 LOE P1-study<sup>1177</sup>. Abnormal brainstem auditory evoked potentials recorded 55 to 235 minutes after cardiac arrest before initiation of therapeutic hypothermia predicted poor outcome with a FPR of 0% (95% CI 0 to 32) (LOE P1 <sup>1185</sup>). One study found no predictive value with brainstem auditory evoked potentials (LOE P1 <sup>1181</sup>). In patients not treated with therapeutic hypothermia, medium-latency auditory evoked potentials predicted poor outcome after cardiac arrest in 1 LOE P1-study with a FPR of 0% (95% CI 0 to 14<sup>1177</sup>) and in 1 LOE P3-study<sup>1183</sup>. Auditory N100 and mismatch negativity was also associated with poor outcome in 1 LOE P1-study<sup>1177</sup>.

## 3) Electroencephalography

Electroencephalography predicted poor outcome in comatose survivors of cardiac arrest within 1 week after cardiac arrest in 12 studies (LOE P1 <sup>1128, 1129, 1140, 1176, 1186-1188</sup>, LOE P3 <sup>1189, 1190</sup>, LOE P4 <sup>1191, 1192</sup>, LOE P5<sup>1193</sup>). In a meta-analysis, EEG showing generalized suppression to less than 20 $\mu$ V, burst-suppression pattern associated with generalized epileptic activity, or diffuse periodic complexes on a flat background 12 to 72 hours after sustained ROSC predicted a poor outcome (FPR of 3%, 95% CI 0.9% to 11%) in patients not receiving therapeutic hypothermia (LOE P1 <sup>1140</sup>).

No electrophysiological study reliably predicts outcome of comatose patient after cardiac arrest in the first 24 hours treated without therapeutic hypothermia. After 24 hours, bilateral absence of the N20 cortical response to median nerve stimulation predicts poor outcome in comatose cardiac arrest survivors not treated with therapeutic hypothermia. In the absence of confounding circumstances, such as sedatives, hypotension, hypothermia, or hypoxemia, it is reasonable to use unprocessed electroencephalography interpretation (specifically identifying generalized suppression to less than 20  $\mu$ V, burst suppression pattern with generalized epileptic activity, or diffuse periodic complexes on a flat background) observed between 24 and 72 hours after sustained ROSC to assist the prediction of a poor outcome in comatose survivors of cardiac arrest not treated with hypothermia (Class IIa).

## 4. Imaging studies

### 1) Computerized Tomography

There are no LOE P1 or LOE P2 studies that support the use of computerized tomography imaging to predict outcome of comatose cardiac arrest survivors. Use of computerized tomography imaging is supported by twenty-two studies (LOE P3 <sup>1194</sup>, LOE P4 <sup>1195-1205</sup>, LOE P5 <sup>1206-1213</sup>). The timing of

computerized tomography in these studies ranged from 1 hour to 20 days after sustained return of spontaneous circulation. Computerized tomography parameters associated with poor outcome included grey matter to white matter Hounsfield unit ratio <1.22, cerebral atrophy (chronic), low cerebral blood flow, low acetazolamide reactivity, bicaudate ratio, low Hounsfield number in putamen and cortex, low density in basal ganglia and thalamus, diffuse mass effect, and global cortical gray matter density. Overall, these studies were limited by small sample sizes, variable time of imaging (many very late in the course of the event), lack of comparison with a standardized method of prognostication, and early withdrawal of care. Two LOE P3 studies found computerized tomography did not predict outcome<sup>1189, 1214</sup>, and one LOE P4 study was neutral in its findings<sup>1215</sup>. The timing of computerized tomography in these studies ranged from <72 hours to 96 hours after return of spontaneous circulation. Computerized tomography parameters not associated with poor outcome included normal scans. Overall, these studies were limited by small sample sizes, imaging performed too early in the clinical course, non-modern computerized tomography imaging, and early withdrawal of care.

## 2) Magnetic Resonance Imaging

There are no LOE P1 or LOE P2 studies that support the use of magnetic resonance imaging to predict outcome of comatose cardiac arrest survivors. Use of magnetic resonance imaging to predict outcome is supported by thirty-two studies (LOE P3<sup>1216-1220</sup>, LOE P4<sup>1195, 1221-1232</sup>, LOE P5<sup>1196, 1206-1208, 1233-1242</sup>). The timing of magnetic resonance imaging in these studies ranged from 1 day to 10 months after sustained return of spontaneous circulation. Magnetic resonance imaging parameters associated with poor outcome included lower gray matter volume, lower hippocampal volume, global cerebral atrophy, higher number of neuroradiologic findings, extensive abnormalities on digital weight imaging, increased lactate on magnetic resonance spectroscopy, hyperintense lesions in basal ganglia, extensive digital weight imaging abnormalities, global apparent diffusion coefficient depression, extensive white matter abnormalities, and cortical laminar enhancement. Overall these studies were limited by small sample sizes, variable time of imaging (many very late in the course of the event), lack of comparison with a standardized method of prognostication, often non-modern magnetic resonance imaging techniques, and early withdrawal of care. One study found that magnetic resonance imaging performed on comatose cardiac arrest survivors 1-47 days after sustained return of spontaneous circulation did not correlate with outcome (LOE P2<sup>1243</sup>). Magnetic resonance imaging parameters used in this study were leukoaraiosis, cerebral infarcts, and edema. Modern magnetic resonance imaging techniques (i.e. diffusion-weighted imaging) were not used in this study.

## 3) Single photon emission CT (SPECT)

Single Photon Emission Computed Tomography is supported by three LOE P5 studies<sup>1213, 1242, 1244</sup> and is opposed by one LOE P2 study<sup>1245</sup>. The timing of single photon emission computed tomography in these studies ranged from 1-23 days after sustained return of spontaneous circulation. Single photon emission computed tomography parameters associated with poor outcome included diminished cerebral blood flow, particularly frontal and temporal, particularly when persistent on repeated imaging. Single photon emission computed tomography parameters not associated with

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outcome included the anterior:posterior perfusion ratio. These studies were limited by small samples sizes, variable imaging times, early withdrawal of care, and lack of comparison with a standardized method of prognostication.

#### 4) Cerebral angiography

Cerebral angiography has been reported by one case report (LOE P5<sup>1206</sup>). The timing of cerebral angiography was 1 day after sustained return of spontaneous circulation. Cerebral angiography parameters associated with poor outcome included delayed cerebral circulation time.

#### 5) Transcranial Doppler (TCD)

Transcranial Doppler was evaluated in one study (LOE P4<sup>1232</sup>). The timing of transcranial Doppler in this study ranged from 4 to 120 hours after return of spontaneous circulation. Transcranial Doppler parameters associated with poor outcome included delayed hyperemia. This study was limited by a small sample size, early withdrawal of care, and lack of comparison with a standardized method of prognostication.

#### 6) Nuclear medicine

One case report was supportive of nuclear medicine studies (LOE P5<sup>1208</sup>), but the timing of the images after sustained return of spontaneous circulation was not described. Nuclear medicine parameters associated with poor outcome included abnormal tracer uptake in the cerebral cortices. This case report included only a limited description of the findings and was further limited lack of comparison with a standardized method of prognostication.

#### 7) Near infra-red spectroscopy:

One study of near infra-red spectroscopy was not supportive (LOE P3<sup>1246</sup>). The timing of near infra-red spectroscopy in this study ranged from 6-24 hours after sustained return of spontaneous circulation. This study was limited by a small sample size, early withdrawal of care, inclusion of non-cardiac arrest patients, and lack of comparison with a standardized method of prognostication.

There is insufficient evidence to recommend the routine use of neuroimaging to predict outcome of adult cardiac arrest survivors.

### [5. Impact of Therapeutic Hypothermia on Accuracy of Post-Cardiac Arrest Prognostication](#)

Two studies (LOE P1<sup>1133, 1181</sup>) provided evidence that status myoclonus (FPR 0%, 95% CI 0% to 40%), absence of corneal and pupillary reflexes at 3 days postsustained ROSC (FPR 0%, 95% CI 0% to 48%), and bilateral absence of N20 peak on somatosensory evoked potentials at 24 hours postsustained ROSC (FPR 0%, 95% CI 0% to 69%) in patients treated with therapeutic hypothermia

predict poor outcome. One study evaluated somatosensory evoked potential responses in 112 postarrest patients more than 24 hours after cardiac arrest who were treated with hypothermia and found that 35 of 36 patients with bilateral absent N20 cortical response had a poor outcome (FPR 3%, 95% CI 0% to 14%<sup>1247</sup>). One patient with bilaterally absent N20 and another with a barely detectable N20 had a good recovery; both were evaluated at 3 days post–cardiac arrest (LOE P1<sup>1247</sup>). One LOE P1-study<sup>1133</sup> provided evidence that a Glasgow Coma Motor Score of 2 or less at 3 days after sustained ROSC in patients treated with therapeutic hypothermia has a FPR of 14% (95% CI 3% to 44%) for poor outcome. Two studies provided evidence that status epilepticus in postarrest patients treated with hypothermia has a FPR of 7% (95% CI 1% to 25%) to 11.5% (95% CI 3% to 31%) for predicting poor outcome (LOE P2<sup>1248</sup>, LOE P3<sup>1190</sup>). One study (LOE P3<sup>1249</sup>) suggested that glial fibrillary acidic protein level >1.0 ng/dL drawn 12 to 48 hours after sustained ROSC predicts poor outcome (defined as CPC score 3 to 5 at 6 months) both in post–cardiac arrest patients treated with normothermia (FPR 0% 95% CI 0% to 27%) or hypothermia (FPR 0% 95% CI 0% to 48%). One study provided evidence that NSE and S-100b protein cutoff values that reliably predict poor outcome are significantly higher in post–cardiac arrest patients treated with hypothermia compared with those not treated with hypothermia (LOE P2<sup>1152</sup>). Two studies prospectively measured NSE in cohorts of patients treated with post–cardiac arrest hypothermia and reported cutoff values for 0% FPR (LOE P2<sup>1250, 1251</sup>): 1 study<sup>1250</sup> reported that all patients with a 48-hour NSE value >33 µg/L had a poor outcome (FPR 0%, 95% CI 0% to 23%); the other study<sup>1251</sup> reported that all patients with a 48-hour NSE >28 µg/L had a poor outcome (FPR 0%, 95% CI 0% to 18%). Variability in 0% FPR cutoff values from these derivation cohorts potentially results from variability among assays and performance sites. In one study of patients treated with therapeutic hypothermia, the BNP cutoff value for a poor neurological outcome was 80 pg/ml (accuracy of 87.2%)(J-LOE 4<sup>1252</sup>). Two studies examined the utility of bispectral index monitoring in prognosticating poor outcome in post–cardiac arrest patients treated with hypothermia who were under neuromuscular blockade (LOE P1<sup>1188, 1253</sup>). One study reported that an initial bispectral index monitoring score of  $\geq 22$  predicted poor outcome with a FPR of 6% (19 patients having a positive test), and a suppression ratio  $\geq 48$  predicted poor outcome with a FPR of 7% [(95% CI 1% to 26%)]<sup>1254</sup>. The other study reported that a bispectral index monitoring level of 0 at any time in the first 72 hours after cardiac arrest predicted poor outcome with a FPR of 0% [0% to 27%]<sup>1188</sup>. Finally, 1 study (LOE P1<sup>1255</sup>) of 111 post–cardiac arrest patients treated with therapeutic hypothermia attempted to validate prognostic criteria proposed by the American Academy of Neurology<sup>1140</sup>. That study demonstrated that clinical examination findings at 36 to 72 hours were unreliable predictors of poor neurological outcome [motor response less than flexion (FPR 16%, 95% CI 6% to 35%);  $\geq 1$  brainstem reflexes absent (FPR 8%, 95% CI 2% to 25%); early myoclonus (FPR 4%, 95% CI 1% to 19%), while bilaterally absent N20 peak on somatosensory evoked potentials (FPR 0%, 95% CI 0% to 13%) and unreactive electroencephalogram background (FPR 0%, 95% CI 0% to 13%) were the most reliable. A decision rule derived using that dataset demonstrated that the presence of 2 independent predictors of poor neurological outcome (incomplete recovery brainstem reflexes, early myoclonus, unreactive electroencephalogram, and bilaterally absent cortical somatosensory evoked potentials) predicted poor neurological outcome with a FPR of 0% (95% CI 0% to 14%).

There is inadequate evidence to recommend a specific approach to prognosticating poor outcome in

post–cardiac arrest patients treated with therapeutic hypothermia. There are no clinical neurological signs, electrophysiological studies, biomarkers, or imaging modalities that can reliably predict neurological outcome in the first 24 hours after cardiac arrest. Beyond 24 hours, no single parameter for predicting poor neurological outcome in post–cardiac arrest patients treated with hypothermia is without reported false-positives. Based on limited available evidence, potentially reliable prognosticators of poor outcome in patients treated with therapeutic hypothermia after cardiac arrest include bilateral absence of N20 peak on somatosensory evoked potential  $\geq 24$  hours after cardiac arrest or unreactive electroencephalogram background at 36 to 72 hours; and the absence of both corneal and pupillary reflexes  $>72$  hours after cardiac arrest. Limited available evidence also suggests that a Glasgow Coma Motor Score of 2 or less at 3 days after sustained ROSC and the presence of status epilepticus are potentially unreliable prognosticators of poor outcome in post–cardiac arrest patients treated with therapeutic hypothermia. Serum biomarkers such as NSE are potentially valuable as adjunctive studies in prognostication of poor outcome in patients treated with hypothermia, but their reliability is limited by the relatively few patients who have been studied and lack of assay standardization. Given the limited available evidence, prognostication for poor outcome should be done at least 72 hours after ROSC (Class IIa), and decisions to limit care should not be made based on the results of a single prognostication tool (Class III).

## Knowledge Gaps

Further research is needed to elucidate the impact of therapeutic hypothermia on the accuracy and timing of post–cardiac arrest prognostication tools. Prospective derivation and validation of a clinical decision rule for early prediction of poor outcome in post–cardiac arrest patients treated with or without hypothermia are urgently needed.

## ■ 3 Organ Donation

Three studies suggested no difference in functional outcomes of organs transplanted from patients who were determined to be brain dead as a consequence of cardiac arrest when compared with donors who were brain dead from other causes (LOE 2<sup>1256-1258</sup>).

Adult patients who progress to brain death after resuscitation from out-of-hospital cardiac arrest should be considered for organ donation (Class IIa).

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