Intensive Care Med
DOI 10.1007/s00134-017-4739-7

RESEARCH AGENDA

Intensive care medicine research agenda on cardiac arrest

Jerry P. Nolan[1,2*], Robert A. Berg[3,4], Stephen Bernard[5], Bentley J. Bobrow[6], Clifton W. Callaway[7], Tobias Cronberg[8], Rudolph W. Koster[9], Peter J. Kudenchuk[10], Graham Nichol[11], Gavin D. Perkins[12], Tom D. Rea[13], Claudio Sandroni[14], Jasmeet Soar[15], Kjetil Sunde[16,17] and Alain Cariou[18]

Abstract

Over the last 15 years, treatment of comatose post-cardiac arrest patients has evolved to include therapeutic strategies such as urgent coronary angiography with percutaneous coronary intervention (PCI), targeted temperature management (TTM)—requiring mechanical ventilation and sedation—and more sophisticated and cautious prognostication. In 2015, collaboration between the European Resuscitation Council (ERC) and the European Society for Intensive Care Medicine (ESICM) resulted in the first European guidelines on post-resuscitation care. This review addresses the major recent advances in the treatment of cardiac arrest, recent trials that have challenged current practice and the remaining areas of uncertainty.

Keywords: Cardiopulmonary resuscitation, Cardiac arrest, Basic life support, Advanced life support, Post-resuscitation care, Prognostication

Current standard of care for treatment of cardiac arrest

The current standard of care for the treatment of cardiac arrest is set out in the 2015 European Resuscitation Council (ERC) and American Heart Association (AHA) cardiopulmonary resuscitation (CPR) guidelines [1, 2], which are underpinned by the 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations [3]. Interest among intensive care clinicians in the treatment of cardiac arrest survivors has increased as it has become clearer that the management of these patients in the intensive care unit (ICU) can impact substantially on their ultimate neurological outcome. Over the last 15 years, treatment of comatose post-cardiac arrest patients has evolved to include therapeutic strategies such as emergent coronary angiography with percutaneous coronary intervention (PCI), targeted temperature management (TTM)—requiring mechanical ventilation and sedation—and more sophisticated and cautious prognostication. A collaboration between the ERC and the European Society for Intensive Care Medicine (ESICM) resulted in the first European guidelines on post-resuscitation care; these define the current standard of care for the treatment of post-cardiac arrest patients [4]. This review addresses the major recent advances in the treatment of cardiac arrest, recent trials that have challenged current practice and the remaining areas of uncertainty. Table 1 lists some key ongoing and planned resuscitation studies, and Table 2 includes some proposals for future studies.

Major recent advances in treatment of cardiac arrest

Early recognition of out-of-hospital cardiac arrest

Early recognition of out-of-hospital cardiac arrest (OHCA) is critical for successful resuscitation, and typically relies on laypeople, with the potential for meaningful involvement from the telecommunicator (emergency dispatcher). When a person has a cardiac arrest, they become

*Correspondence: jerry.nolan@nhs.net
[1] School of Clinical Sciences, University of Bristol, Bristol, UK
Full author information is available at the end of the article

Table 1 Ongoing or planned resuscitation studies listed on clinical trials registries

Topic	Studies	Primary outcome and study status
Airway management in CPR	Tracheal intubation versus laryngeal tube as initial advanced airway in OHCA (PART trial, NCT02419573)	72-h survival Recruiting
	Tracheal intubation versus i-gel as initial advanced airway in OHCA (AIRWAYS-2 study, ISRCTN08256118)	Neurological outcome (mRS) at hospital discharge or 30 days Recruiting
	Tracheal intubation before ROSC versus bag-mask ventilation and tracheal intubation delayed until after ROSC (CAAM study, NCT02327026)	28-day survival with favourable neurological outcome Ongoing study but not recruiting as of 31 Jan 2017
Role of adrenaline in CPR	Placebo-controlled trial of adrenaline in OHCA (PARAMEDIC-2 study, ISRCTN73485024)	30-day survival Recruiting
Extracorporeal CPR	Prospective study of E-CPR versus standard advanced life support for selected OHCAs unresponsive to initial resuscitation (NCT011511666)	Survival with good neurological outcome Recruiting
	Prospective study of E-CPR versus standard advanced life support for selected OHCAs unresponsive to initial resuscitation (NCT01605409)	ROSC Recruiting
Oxygenation and carbon dioxide targets after ROSC	RCT of oxygen titrated to 90–94% versus 98–100% as soon as possible after ROSC and continued until ICU admission (EXACT phase 3 trial)	Survival to hospital discharge Not yet recruiting
	RCT comparing targeted therapeutic mild hypercapnia ($PaCO_2$ 50–55 mmHg) with targeted normocapnia ($PaCO_2$ 35–45 mmHg) (TAME study)	Neurological outcome at 6 months (GOSE) Not yet recruiting
Targeted temperature management and pharmacological neuroprotection	Mild induced hypothermia (33 °C) versus fever control (≤37.8 °C) only (TTM-2, NCT02908308)	Mortality at 6 months Not yet recruiting
	Targeted temperature management after non-shockable cardiac arrest: 32.5–33.5 °C versus 36.5–37.5 °C (NSE-HYPERION study, NCT02722473)	NSE values day 1 to day 3 Recruiting
	Targeted temperature management after cardiac arrest: 33 °C for 24 versus 48 h (TTH48 study, NCT01689077)	Neurological outcome at 6 months (CPC) Finished recruiting
Early coronary angiography after ROSC	Feasibility study—cardiac arrest survivors without ST-elevation randomised to acute coronary angiography versus routine care (DISCO study, NCT02309151)	Feasibility for multiple outcomes Recruiting
	Feasibility study—cardiac arrest survivors without ST-elevation randomised to acute coronary angiography versus standard care (PEARL study, NCT02387398)	Safety and feasibility Recruiting
	Cardiac arrest survivors without ST-elevation randomised to transfer to a cardiac arrest centre and urgent coronary catheterisation versus transfer to a district general hospital (ARREST trial, ISRCTN96585404)	All-cause mortality at 30 days Recruiting
	Emergency versus delayed coronary angiogram in survivors of OHCA with no obvious non-cardiac cause of arrest (EMERGE trial—NCT02876458)	Survival with no or minimal neurological sequel at 180 days Recruiting

OHCA out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *E-CPR* extracorporeal cardiopulmonary resuscitation, *GOSE* Glasgow outcome scale extended, *NSE* neuron-specific enolase, *CPC* cerebral performance category

unconscious, pulseless, with agonal breaths or no breathing at all. Because pulse determination is challenging for laypeople, there should be a high suspicion for arrest if an individual is unconscious and not breathing normally. The term 'normally' is essential to help identify agonal gasps, which can be confused for signs of life [5]. The telecommunicator should prioritise the two 'all-caller' questions at the outset: "Is the patient conscious?" and "Is the patient breathing normally?" If both answers are "no", the telecommunicator proceeds to CPR instructions. Efforts to characterise abnormal breathing are not useful and only delay CPR. Although other conditions (e.g. postictal state) may be falsely identified as arrest, the risk of injury from inadvertent layperson CPR is exceedingly low [6]. Real-world experience has informed telecommunicator performance goals for arrest recognition and CPR instruction [7]. Efforts using this approach have been associated with increases in bystander CPR and improvement in survival [8, 9].

Early activation and bystander CPR

Observational studies show that multiple components of lay and emergency medical services (EMS) care are associated with survival after OHCA. These include briefer time from the call for assistance to activation of EMS providers (i.e. activation interval) and briefer time from activation of EMS providers to the arrival of EMS providers on scene (i.e. response time interval) [10]. Briefer pre-shock pauses, greater depth of chest compression and an optimal compression rate are also associated with improved outcomes [11–13]. The relationship between chest compression fraction and outcome is less consistent [14, 15].

Early access to defibrillation

In patients with OHCA, application of an automated external defibrillator (AED) by a layperson before the arrival of EMS providers on scene increases survival significantly compared to a standard community response, but only 25% of ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) cardiac arrests occur in public settings [16]. Solutions for use in a residential environment would reach many more patients but are more difficult to implement because of the large areas to cover, fewer victims per unit area to be covered and lower probability of a nearby and trained rescuer. AEDs in residential areas are uncommon. More effective use of residential AEDs is possible if dispatchers direct rescuers to nearby AEDs. New solutions for these logistic challenges in residential areas involve mobile phones with short message system (SMS) messages or smart phones with geolocation [17, 18] (Fig. 1). These solutions increase the likelihood of bystander CPR [18] and reduce time to defibrillation [17]. AEDs should be accessible at all hours but this is the case for less than 50% of nearby cardiac arrests in public locations during evening, night-time and weekends [19]; AEDs in boxes located outside can resolve this problem.

Rapid response systems for in-hospital cardiac arrest

Rapid response systems (RRS) use multiple interventions to prevent unplanned ICU admissions, unexpected deaths (including from in-hospital cardiac arrest [IHCA]) and improve hospital mortality. Interventions include staff education, monitoring of patients, recognition of patient deterioration, a system to call for help and an effective response—the chain of prevention.

Evidence supporting RRS is largely observational, and the best way of achieving the complex interventions that make up an RRS remain uncertain [20]. Patients sustaining unmonitored cardiac arrest have a worse prognosis than those patients who are monitored, suggesting that approaches to more comprehensively monitor or more precisely allocate monitoring could improve IHCA outcome [21]. Some, but not all, evidence supports the lifesaving potential of the implementation of early warning and response strategies [22]. The variability may depend upon the specific warning algorithm, the patient population, the hospital setting, the composition of the response or the outcome of interest.

Studies suggest multiple interventions may be related to improved outcomes including electronic observation and alerting, staff communication interventions (e.g. situation, background, assessment, recommendation [SBAR]), different triggers for alerting a response (e.g. early warning scoring systems) and differing types of rapid response team [e.g. medical emergency team (MET)]. The responses may result in escalating or limiting treatments, and may include palliative care [23]. RRS are conceptually attractive and this has led to widespread uptake, whereas difficulties in measuring processes and outcomes have led to relatively little high-quality research.

Monitoring during resuscitation

Innovative technology capable of monitoring CPR metrics during resuscitation enables investigators and clinicians to measure the quality of CPR in real time. This has informed optimal resuscitation practice (e.g. minimising pre-shock pause, maximising chest compression fraction and correct chest compression depth [14, 24]). There are two categories of CPR monitoring: physiological (patient response to CPR) and CPR performance (provider CPR delivery) metrics; both enable real-time and retrospective feedback. Invasive haemodynamic monitoring (arterial and central venous pressures when available) along with end-tidal carbon dioxide ($ETCO_2$) values provide pertinent physiological data during CPR, but are seldom available. While the theoretical significance of haemodynamic and $ETCO_2$ monitoring during CPR is accepted, clinical

Table 2 Potential resuscitation studies to be undertaken in the next 10 years and suggested endpoints

Topic	Potential studies	Potential endpoints
Real-time physiological monitoring	Pragmatic RCT comparing standard ALS with measurement of real-time physiological parameters to indicate blood flow and tissue perfusion, e.g. regional cerebral oximetry using NIRS	Mortality Neurological outcome at discharge or 30 days Neurological outcome at 6 months HFS[a]
Rhythm waveform analysis	Smart defibrillators that analyse the VF waveform and indicate the optimal timing of shock delivery depending on prognostic indicators in the VF waveform. Studies needed to develop and validate such technology before an RCT comparing this technology with standard ALS	Shock success Mortality Neurological outcome at discharge or 30 days
Role of adrenaline in CPR	Dose–response study of adrenaline in OHCA	Neurological outcome at discharge or 30 days Neurological outcome at 6 months Mortality
Extracorporeal CPR	Prospective studies of E-CPR versus standard ALS for selected IHCAs unresponsive to initial resuscitation	Neurological outcome at discharge or 30 days Neurological outcome at 6 months Mortality
Targeted temperature management and pharmacological neuroprotection	RCT phase 3 trial testing new neuroprotective drugs (e.g. xenon) Nitrite infusion to replenish nitric oxide Optimal haemodynamic management and different target temperatures	Mid- and long-term neurological recovery
Prognostication in comatose patients after ROSC	A prospective validation study of current neuroprognostication guidelines. Treating team blinded to the results of prognostication indices to eliminate self-fulfilling prophecy. Standardised sedation and, ideally, monitoring of drug plasma levels	Prediction with false positive rate close to zero and narrow confidence intervals The predictive value of combinations of predictors
Rehabilitation	Best practice follow-up and rehabilitation after cardiac arrest against standard care Screening for cognitive impairment and intervention against cardiovascular risk-factors including physical inactivity. 5-year follow-up of cognitive function, HRQoL and participation	Mortality HRQoL, participation and cognitive function Cost-effectiveness

RCT randomised controlled trial, *ALS* advanced life support, *NIRS* near-infrared spectroscopy, *RCT* randomised controlled trial, *E-CPR* extracorporeal cardiopulmonary resuscitation, *HFS* hospital-free survival, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *IHCA* in-hospital cardiac arrest, *HRQoL* health-related quality of life

[a] In comparison with a dichotomous analysis of ordered outcomes, use of HFS can reduce the number of patients required to detect a difference in outcome. HFS is defined as the number of days alive and permanently out of hospital during the first 30 days after the acute event and is like 'home time', which has been used in some stroke, heart failure and intensive care trials

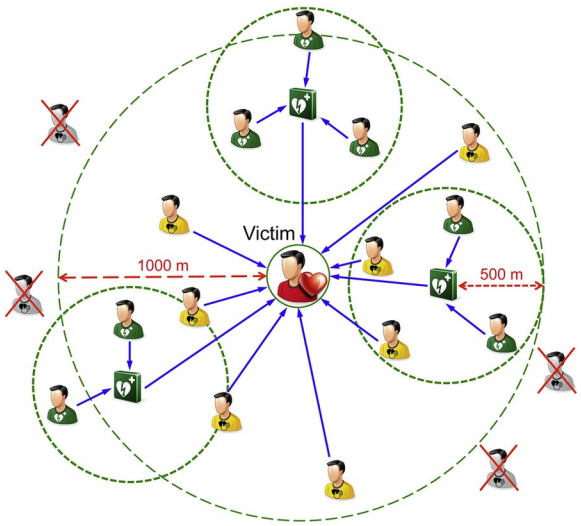

Fig. 1 A text message (TM) alert system in North Holland. When a dispatcher suspects an out-of-hospital cardiac arrest, trained first responders within 1000 m are alerted to either first retrieve an automated external defibrillator (if within 500 m) and then go to the victim or to go directly to the victim and start CPR [17]. Reproduced with permission from Resuscitation

studies have yet to identify the optimal values during human CPR. Nonetheless, an AHA consensus statement recommends monitoring haemodynamic response with techniques such as arterial lines when available (maintaining diastolic blood pressure >25 mmHg in adults), and $ETCO_2$ monitoring when available [optimising CPR performance to a goal of $ETCO_2$ > 2.6 kPa (20 mmHg)] [25]. However, inter-individual differences, cause of arrest and comorbidities impact these values, questioning clinical decision-making based on specific threshold values.

Post-resuscitation care

'Post-resuscitation disease' was described first by Negovsky in 1971 and was redefined in more detail in 2008 as the post-cardiac arrest syndrome (PCAS) [26]. PCAS is complex. Most resuscitated cardiac arrest patients are comatose and critically ill and require extensive intensive care treatment depending on the cause of the arrest, severity of the reperfusion injury and the extent of myocardial dysfunction [26]. PCAS is best treated with a goal-directed approach including immediate access to coronary angiography and PCI, early implementation of TTM, and a well-defined standardised treatment plan including prognostication [27, 28]. There are large interhospital differences in treatment and outcome [28], and a standardised treatment plan enables the focus to be on optimising treatment for each individual cardiac arrest patient. As an important part of the chain of survival, improvement in hospital treatment after ROSC has increased survival rates worldwide. Importantly, there are still several knowledge gaps related to optimal post resuscitation care, e.g. haemodynamic goals [4].

Common beliefs contradicted by recent trial results

Mechanical compression devices

Intuitively, the use of mechanical compression devices, which deliver consistent, high-quality chest compressions, should improve outcomes. Five, moderate- to high-quality randomised trials enrolled over 12,000 patients with an OHCA. Meta-analysis comparing mechanical CPR with manual CPR found no significant improvement in initial survival, survival to discharge/30 days [odds ratio (OR) 0.89, (95% confidence interval (CI) 0.77–1.02)] (Fig. 2) or favourable neurological outcome [OR 0.76, (95% CI 0.53, 1.11)] [29]. For IHCA, three randomised trials and six observational studies comparing mechanical CPR with manual CPR and involving 689 patients found evidence of significantly improved short-term (53.2% versus 35.2%; OR 2.14, 95% CI 1.11–4.13) and hospital or 30-day survival (26.7% versus 12.2%; OR 2.34, 95% CI 1.42–3.85) suggesting the need for further research in this setting [30].

Antiarrhythmic drugs

Antiarrhythmic drugs are typically administered for their immediate effects in cardiac arrest, namely to terminate life-threatening arrhythmias and restore spontaneous circulation. These benefits, though realised across virtually all studies, have not been accompanied by improved survival [31], fuelling the common belief that this goal may not be achievable pharmacologically. Such pessimism was seemingly reinforced by a recent antiarrhythmic drug trial [32]. But cardiac arrest interventions are very time-sensitive and when analysed in the context of the probable time from collapse to treatment (which is estimated more accurately in bystander-witnessed than unwitnessed arrests), antiarrhythmics significantly improved survival in the trial (Fig. 3) [33]. Thus, like all cardiovascular emergencies, the effect of antiarrhythmic therapies in cardiac arrest also hinges on both what is given and, importantly, when they are received.

Pharmacological neuroprotection

Although return of spontaneous circulation (ROSC) is the primary therapeutic objective of cardiac resuscitation, reflow after whole-body ischaemia might activate detrimental pathways during reperfusion, causing tissue injury, particularly in the brain. Several drugs which are known to inhibit the intracellular process of ischaemia–reperfusion were shown to decrease the severity of the post-resuscitation syndrome in animal experiments.

However, the results of recent large clinical studies are disappointing. Ciclosporin, exenatide (a glucagon-like peptide-1 analogue) and erythropoietin analogues all failed to show any protective effect when administered to OHCA patients [34–36] (Fig. 4).

Optimal target temperature for targeted temperature management

Animal data indicate several different mechanisms for the impact of temperature on reperfusion injury [26]. Mild induced hypothermia (32–34 °C) was recommended by the International Liaison Committee on Resuscitation (ILCOR) in 2003 as a neuroprotective strategy for OHCA patients in coma after a VF/pVT cardiac arrest. At that time, the supporting evidence was based on experimental animal data, non-randomised clinical trials and two small randomised trials [26]. Gradual implementation followed worldwide despite methodological limitations in the two pivotal clinical trials. After the neutral results of the TTM Trial comparing 36 versus 33 °C [37] current recommendations have been modified to include a broader range of target temperature and the quality of evidence supporting TTM has been downgraded to very low to low depending on initial rhythm [38].

Remaining areas of uncertainty

Extracorporeal cardiopulmonary resuscitation (E-CPR)

In the 1990s several studies established that 30–50% of children with prolonged CPR (30–80 min) could survive when extracorporeal CPR (E-CPR) was used as salvage therapy during CPR [39]. Similar remarkable outcomes were reported for adults with prolonged IHCA [40] and OHCA (e.g. as a bridge to enable successful PCI). The logic was simple: E-CPR, a cardiopulmonary bridge therapy, could provide adequate blood flow to the brain and heart for hours to days until potentially reversible processes resolve. However, data over the last decade have also shown that patients can survive after prolonged high-quality CPR without E-CPR [41]. Some retrospective studies show better outcomes with E-CPR for IHCAs compared with prolonged standard CPR [39, 40], whereas others do not [42]. Several ongoing trials are intended to clarify whether E-CPR results in better outcome (e.g. NCT01511666).

Airway management

The ideal airway management strategy during CPR remains unclear. In practice, there is often a progression in complexity of airway management, from no intervention (compression only CPR), mouth-to-mouth, and bag-mask ventilation, through to supraglottic airway (SGA) devices and tracheal intubation. The best airway is likely to vary depending on the time-point in the resuscitation process, and the skill set of the attending rescuers [43]. Several observational studies on airway management during OHCA have been published but they are prone to selection bias, e.g. patients who recover rapidly from a cardiac arrest, and therefore likely to have a better outcome, are less likely to require advanced airway management. Propensity analysis is often use to adjust for such confounders, but can only ever include data that has been collected and reported. There may be hidden confounders that account for the apparent differences in outcome. In comparison with tracheal intubation, SGAs require less training for successful insertion and may cause less interruption of chest compressions than tracheal intubation [44]. Three ongoing prospective OHCA studies, one randomised clinical trial of tracheal intubation versus bag-mask ventilation (CAAM study, NCT02327026) and

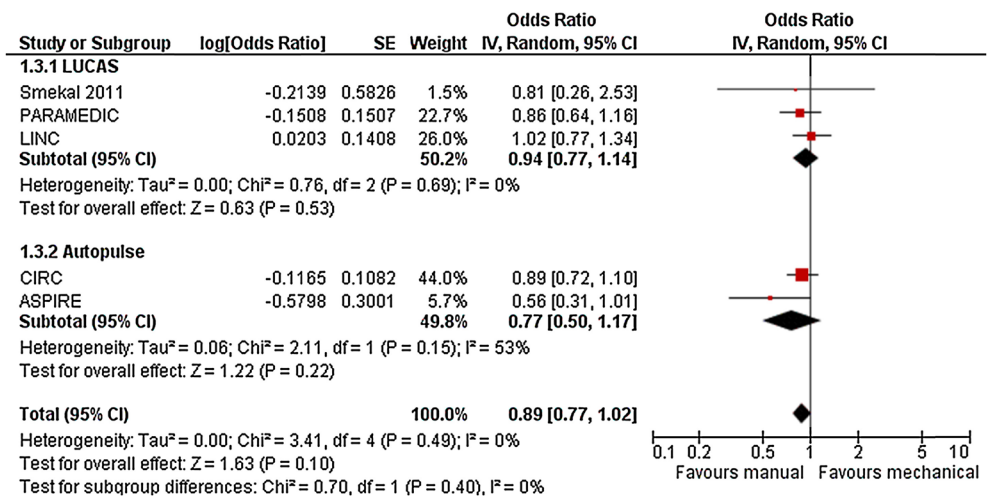

Fig. 2 Meta-analysis of studies of mechanical chest compression for out-of-hospital cardiac arrest—survival to hospital discharge or 30 days. Reproduced from Gates et al. *Resuscitation* 2015 [29]

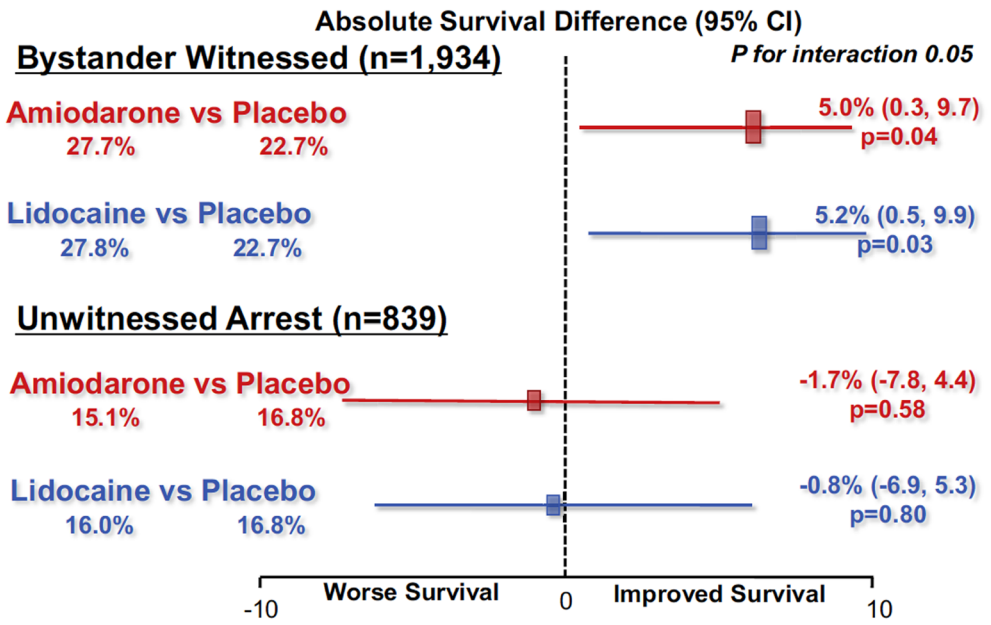

Fig. 3 Absolute differences in survival to hospital discharge between amiodarone versus placebo and lidocaine versus placebo, stratified by whether the OHCA was bystander-witnessed or unwitnessed in the Amiodarone, Lidocaine or Placebo Study (ALPS), an interaction which was statistically significant [33]. Reproduced with permission from Resuscitation

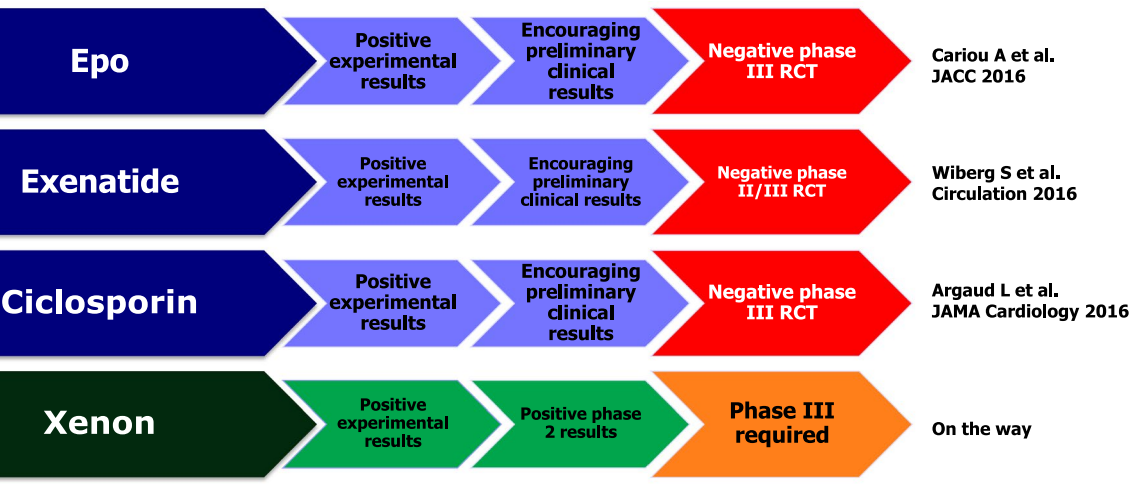

Fig. 4 Neuroprotective drugs recently investigated for the treatment of post-cardiac arrest syndrome

two cluster randomised trials of an SGA versus tracheal intubation [45, 46] should provide useful data on the optimal airway management strategy in OHCA.

Oxygenation and ventilation during cardiopulmonary resuscitation

The optimal approach to oxygenation and ventilation *during* CPR is uncertain, although it may depend upon the pathophysiology of the patient, the type of airway, the mechanics of chest compressions, and the skills and number of rescuers. Different approaches to ventilation and oxygenation can affect intrathoracic pressure, arterial tensions of oxygen and carbon dioxide, and acid–base balance with the confluence potentially affecting coronary and cerebral perfusion, downstream metabolic response and ultimately the likelihood of resuscitation and neurological recovery.

Clinical guidelines have integrated available evidence, understanding there is this uncertainty regarding an optimal strategy. All CPR providers should perform chest compressions for all patients in cardiac arrest. CPR providers trained and able to perform rescue breaths should perform chest compressions and rescue breaths in a ratio of 30 compressions to two breaths.

In resuscitation involving multiple professional rescuers, guidelines direct repeated cycles of 30 compressions followed by two positive-pressure rescue breaths when an advanced airway is not in place. In this guideline approach, chest compressions are stopped to deliver ventilation whereby each ventilation provides just enough volume to achieve chest rise, occurs in 1–2 s and uses 100% oxygen when available. A large randomised trial of OHCA resuscitation by EMS compared conventional 30:2 sequential delivery of compressions and ventilations with a strategy of continuous compressions with interposed ventilation every tenth compression [47]. In the primary analysis, the continuous compression strategy did not improve clinical outcomes. In a planned secondary analysis, compressions with pauses for ventilations significantly increased hospital-free survival compared with continuous compressions without pauses for ventilations; although the difference was a modest 0.2 days. Once an advanced airway is in place, guidelines recommend continuous compressions with breaths delivered as a positive-pressure ventilation every 6 s [1, 2].

Adrenaline

Adrenaline (epinephrine) has been an integral component of advanced life support treatment guidelines for over 50 years. Despite its widespread use, the safety and effectiveness of adrenaline have never been comprehensively evaluated in a clinical trial. Experimental studies show that adrenaline stimulates alpha receptors causing peripheral vasoconstriction, which increases coronary perfusion pressure thus increasing the chances of ROSC. Harmful effects include increased cardiovascular instability and worsening brain injury. Meta-analysis of the single randomised trial [48] and 14 observational studies [49] which compare adrenaline (1 mg every 3–5 min) with no adrenaline reported that the rate of ROSC doubled [19.7% versus 5.5%; OR 2.85 (95% CI 2.28–3.54)]. By contrast, there was no difference in the chance of survival to discharge/30 days and fewer patients survived with favourable neurological outcomes [(1.9% versus 2.2%; OR 0.51 (95% CI 0.31–0.84)]. ILCOR has called for randomised, placebo-controlled trials to evaluate the safety and effectiveness of adrenaline in cardiac arrest. The PARAMEDIC-2 trial (ISRCTN73485024) is a pragmatic clinical and cost-effectiveness trial comparing adrenaline with placebo [50]. The trial aims to enrol 8000 patients from five ambulance services in the UK. The primary outcome for the trial is survival to discharge. Secondary outcomes will evaluate long-term survival, health-related quality of life and neurological and cognitive outcomes. The trial is due to report in 2019.

Oxygen and carbon dioxide targets after resuscitation from cardiac arrest

In the early period of reperfusion after resuscitation from cardiac arrest, there is a cascade of production of molecules that are known to injure neurones (reperfusion injury). Whilst the reperfusion injury mechanism is complex, one of the major contributors is the generation of oxygen free radicals, and supplementary oxygen increases their production [51]. A detrimental effect of supplemental oxygen has been documented in ST-elevation myocardial infarction (STEMI) [52]. In post-cardiac arrest patients several observational clinical studies comparing normoxia with hyperoxia have come to differing conclusions with some showing an association between hyperoxia and poor outcome [53] and others showing, after correction for illness severity, no such association [54]. These ICU-based studies will have missed the most critical period immediately after ROSC; this can be studied after OHCA only if inspired oxygen concentrations are modified in the prehospital phase. Two such studies have been completed; one showed that most patients had acceptable oxygenation when ventilated with 30% oxygen compared with 100% oxygen [55], but the other was terminated early because of low blood oxygen values in the titrated oxygen group and a high frequency of unreliable pulse oximeter readings [56]. A phase 3 study involving titration of oxygen to a target SpO_2 of 90–94% as soon as possible after ROSC will soon start recruiting.

Cerebral vascular resistance is increased in the early post-resuscitation phase and hypocapnia may exacerbate cerebral ischaemia [57]. Hypercapnia might increase blood flow to ischaemic brain and two observational studies have documented an association between mild hypercapnia and better neurological outcome among post-cardiac arrest patients. A phase 2 study comparing mild hypercapnia with normocapnia in 50 post-cardiac arrest patients documented a lesser increase in neuron-specific enolase (NSE) values in the hypercapnia group [58]. A phase 3 study involving allocation to either normal CO_2 or mild hypercapnia [6.6–7.3 kPa (50–55 mmHg)] as soon as possible after ICU admission will soon start recruiting.

Targeted temperature management after return of spontaneous circulation

Trials have not explored systematically whether specific subgroups of post-cardiac arrest patients benefit from temperature management. For example, lower temperatures can reduce the incidence of seizures,

reduce intracranial pressure (ICP) and minimise cerebral oedema in other conditions albeit with complex effects on patient outcome. TTM at less than 37 °C might benefit only patients with seizures, elevated ICP or cerebral oedema. Furthermore, most TTM studies enrolled OHCA patients and few data support TTM for IHCA patients who have quite different aetiologies and comorbidities.

Optimum timing and duration of hypothermia are unknown and we lack information from systematic meta-analyses of the extensive data from animal experiments. Efforts to reduce temperature quickly using cold intravenous fluid in the prehospital setting did not improve outcome and increased side effects [59]. In laboratory studies, lower temperature during ischaemia and fast cooling reduce brain injury, but no current technology can deliver TTM sufficiently rapidly for clinical trials of intra-arrest hypothermia; moreover, those patients easiest and fastest to cool are those with the most severe reperfusion injury [4], which complicates interpretation of clinical data. No trials have tested the optimum duration of TTM, but some trials are ongoing. Future trials could test titration of TTM duration based on physiological responses or the extent of the reperfusion injury; it is probably not a case of 'one size fits all.' The TTM-2 trial will compare comatose post-OHCA patients treated with temperature control at 33 °C versus standard care avoiding fever (≤37.8 °C) (NCT02908308).

Selection of patients for early coronary angiography

In resuscitated patients with ST-segment elevation (STE) on the post-ROSC ECG, an invasive strategy is widely and routinely applied because an acute coronary occlusion is most often the cause of the arrest and because early coronary revascularisation is associated with a significant clinical benefit. However, up to two-thirds of resuscitated OHCA patients do not have evidence of STE on the post-ROSC ECG. Previous studies have reported variable rates of acute coronary occlusion in these non-STE patients, ranging between 21% and 53% [60]. Retrospective studies of an immediate invasive strategy in non-STE patients resuscitated from OHCA have documented contradictory results [61, 62]. Furthermore, this early invasive strategy is associated with multiple logistical and organisational challenges, and any outcome benefit in these patients is unproven. Several ongoing studies are comparing urgent versus delayed coronary angiography in resuscitated OHCA patients without STE on their ECG (e.g. NCT02309151 and NCT02387398). Prevention of stent thrombosis is another concern because of a higher risk of acute and subacute stent thrombosis in resuscitated patients compared with other settings. Pharmacokinetic changes related to hypothermia treatment and shock may also contribute to this higher risk [63].

New neuroprotective agents

Despite promising experimental results, recent clinical studies failed to demonstrate neuroprotective effects of treatments [34–36]. However, many other drugs have been tested in animal models over the last 10 years including sodium nitrites, epoxide hydrolase inhibitors, caspase inhibitors, endocannabinoids, sodium and hydrogen sulfides, glutamate inhibitors, selenium and coenzyme Q10. Among these treatments, the use of inhaled noble gases (argon, helium and particularly xenon) is probably one of the most exciting ongoing research programs. The neuroprotective properties of xenon have been established in animal studies and are especially evident when combined with mild hypothermia. A randomized phase 2 clinical trial showed that inhaled xenon combined with hypothermia resulted in less white matter damage as measured by fractional anisotropy of diffusion tensor MRI (as compared with hypothermia alone) [64]. However, there was no statistically significant difference in neurological outcomes or mortality at 6 months. A large randomised clinical trial of this therapy is required.

Prognostication

Current prognostication guidelines need prospective validation [65]. A combination of multiple predictors in a multimodal approach may increase accuracy and should be investigated. To adequately account for self-fulfilling prophecy, future prognostication studies should report in detail the criteria for withdrawal of life-sustaining treatment (WLST), with the treating team blinded to the test results whenever possible. The sensitivity and accuracy of prognostication might be increased by combining predictors but this needs confirmation by large prospective studies. Current evidence is based mainly on prediction of poor neurological outcome; however, identification of patients destined for a favourable outcome is also important to avoid inappropriate WLST.

The presence of early myoclonus after cardiac arrest is less accurate as a predictor of poor outcome than previously thought [66]. The nature and the clinical characteristics of post-anoxic myoclonus are insufficiently known and need investigation. Moreover, the definition of status myoclonus is inconsistent in the literature and needs standardisation.

Malignant EEG patterns provide reliable information on prognosis. In future prognostication studies, interpretation of the EEG should comply with recent

recommendations [67, 68]. The term 'status epilepticus' is used inconsistently and should be avoided in assessing prognosis. EEG patterns evolve during the first days after cardiac arrest and the optimal timing for outcome prediction after cardiac arrest using specified patterns including burst-suppression needs to be investigated.

High serum concentrations of biomarkers are associated with false positive rates close to 0% in cardiac arrest patients; however, the thresholds used in the reports are inconsistent. This is partly because measuring techniques vary among studies, and it is an obstacle to widespread clinical implementation of biomarkers for prognostication.

Evidence from imaging studies in comatose survivors of cardiac arrest is limited by small sample size and likely selection bias. Larger prospective studies are needed to confirm the results of the published studies. The severity of brain CT and MRI changes after cardiac arrest will need a standardised description, e.g. using scoring systems like those used for traumatic brain injury.

There is limited evidence on time to awakening in post-arrest comatose patients and the factors affecting this process apart from sedation [69]. Early identification of late awakeners would help establish the optimal timing for neuroprognostication and reduce the risk of inappropriate WLST in these patients.

Rehabilitation

Until recently, rehabilitation of cardiac arrest survivors has been largely neglected and structured follow-up performed mainly to collect data for clinical studies. Knowledge about highly relevant outcomes, such as socio-economic status and level of societal participation, is still limited. This is particularly problematic in the design of rehabilitation studies where increased participation is commonly the goal. In the only randomised study on the effects of a rehabilitation intervention published to date, Dutch investigators showed a more rapid return to work and better quality of life after cardiac arrest using a structured follow-up program [70].

Although brain injury is the major concern for resuscitated patients, remarkably few survive with severe neurological disability. One obvious reason is WLST for patients with presumed poor prognosis; an alternative explanation is that the commonly used outcome measures are too crude to identify effects of mild–moderate brain injury. More detailed cognitive testing has revealed that approximately half of the survivors have some cognitive disability [71]. However, the causal relationship between mild–moderate cognitive dysfunction and the cardiac arrest is not straightforward and a disease-matched control group with myocardial infarction had similar levels of cognitive difficulties as the cardiac arrest patients [71]. The common denominator is likely the cardiovascular burden leading to myocardial infarction and cardiac arrest but also to vascular cognitive impairment, a chronic process rarely considered in the resuscitation literature. Cognitive impairment may decrease compliance with secondary preventive measures, which is of importance since most cardiac arrest patients eventually die from a cardiovascular cause [72].

Study design

Randomised controlled trials, the gold standard in study design, should form part of a pathway of evaluation from proof of concept to confirmation in clinical practice. Animal and laboratory studies provide mechanistic insights leading to a better understanding of the pathophysiology and effects of therapeutic interventions. Proof of concept can be extended from the bench to bedside through high-quality observational studies and clinical efficacy trials. Efficacy trials (also known as explanatory trials) examine interventions under ideal and controlled circumstances and may have intermediate outcomes such as ROSC. Effectiveness (also known as pragmatic) trials seek to evaluate interventions in real-life settings and focus on longer-term outcomes. Some commentators argue that the inclusion of patients with consistently poor outcome (e.g. those with an initial monitored rhythm of asystole randomised before ROSC) in such pragmatic trials dilutes any potential benefit of the therapy under investigation [73]. ILCOR is developing a core outcome set for use in cardiac arrest (COSCA). The transition from efficacy to effectiveness trials is a continuum rather than dichotomy. New approaches to clinical trial design (e.g. personalised medicine, adaptive trial design and registry-based trials) may improve efficiency, reduce cost and produce meaningful results for the resuscitation community and patients.

Author details

[1] School of Clinical Sciences, University of Bristol, Bristol, UK. [2] Anaesthesia and Intensive Care Medicine, Royal United Hospital, Bath, UK. [3] Pediatric Critical Care Medicine, Russell Raphaely Endowed Chair of Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, USA. [4] Anesthesiology and Critical Care Medicine, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, USA. [5] Ambulance Victoria, Victoria, Australia. [6] Department of Emergency Medicine, University of Arizona College of Medicine, Tucson, AZ, USA. [7] Department of Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. [8] Department of Clinical Sciences Lund, Neurology, Skane University Hospital, Lund University, Lund, Sweden. [9] Department of Cardiology, Academic Medical Center, Meibergdreef, Amsterdam, The Netherlands. [10] Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA, USA. [11] University of Washington-Harborview Center for Prehospital Emergency Care, University of Washington, Seattle, WA, USA. [12] Critical Care Medicine, Warwick Medical School and Heart of England NHS Foundation Trust, University of Warwick, Coventry CV4 7AL, UK. [13] University of Washington, Seattle, WA, USA. [14] Department of Anaesthesiology and Intensive Care, Catholic University School of Medicine, Largo Gemelli, 8, 00168 Rome, Italy. [15] Anaesthesia and Intensive

Care Medicine, North Bristol NHS Trust, Southmead Hospital, Bristol BS10 5NB, UK. [16] Department of Anaesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway. [17] Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [18] Medical ICU, Cochin Hospital (AP-HP), Paris-Cardiovascular-Research-Centre, INSERM U970 (Sudden Death Expertize Centre), Université Paris-Descartes-Sorbonne-Paris-Cité, Paris, France.

Compliance with ethical standards

Conflicts of interest

JPN: Editor-in-Chief, ***Resuscitation***; funding from the National Institute for Health Research to evaluate interventions in cardiac arrest including airway management (AIRWAYS-2 study) and adrenaline (PARAMEDIC-2 study). RAB: None declared SB: National Health and Medical Research Grants to undertake clinical trials in controlled oxygenation and mild hypercarbia after cardiac arrest. BJB: None declared. CC: None declared. TC: Co-investigator TTM trial; senior investigator TTM-2 trial. RWK: Research grants for studies on AED use from Physio-Control, Philips Medical, Zoll Medical, Cardiac Science, Defibtech. Advisor (unpaid) for Physio-Control and HeartSine. PJK: PI for the NIH-supported Resuscitation Outcomes Consortium, University of Washington. GN: None declared. GDP: Funding from the National Institute for Health Research to evaluate interventions in cardiac arrest including mechanical CPR and adrenaline (PARAMEDIC-2 study). TDR: None declared. CS: None declared. JS: None declared. KS: Speakers fees and travel grants from Bard Medical. AC: Speakers fees and travel grants from Bard Medical.

Received: 12 December 2016 Accepted: 23 February 2017
Published online: 11 March 2017

References

1. Monsieurs KG, Nolan JP, Bossaert LL et al (2015) European Resuscitation Council guidelines for resuscitation 2015: section 1. Executive summary. Resuscitation 95:1–80
2. Neumar RW, Shuster M, Callaway CW et al (2015) Part 1: executive summary: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 132:S315–S367
3. Nolan JP, Hazinski MF, Aickin R et al (2015) Part 1: executive summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 95:e1–e31
4. Nolan JP, Soar J, Cariou A et al (2015) European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med 41:2039–2056
5. Bobrow BJ, Zuercher M, Ewy GA et al (2008) Gasping during cardiac arrest in humans is frequent and associated with improved survival. Circulation 118:2550–2554
6. White L, Rogers J, Bloomingdale M et al (2010) Dispatcher-assisted cardiopulmonary resuscitation: risks for patients not in cardiac arrest. Circulation 121:91–97
7. Lewis M, Stubbs BA, Eisenberg MS (2013) Dispatcher-assisted cardiopulmonary resuscitation: time to identify cardiac arrest and deliver chest compression instructions. Circulation 128:1522–1530
8. Ro YS, Shin SD, Lee YJ et al (2016) Effect of dispatcher-assisted cardiopulmonary resuscitation program and location of out-of-hospital cardiac arrest on survival and neurologic outcome. Ann Emerg Med 69:52–61.e1
9. Bobrow BJ, Spaite DW, Vadeboncoeur TF et al (2016) Implementation of a regional telephone cardiopulmonary resuscitation program and outcomes after out-of-hospital cardiac arrest. JAMA Cardiol 1:294–302
10. Nichol G, Cobb LA, Yin L et al (2016) Briefer activation time is associated with better outcomes after out-of-hospital cardiac arrest. Resuscitation 107:139–144
11. Cheskes S, Schmicker RH, Verbeek PR et al (2014) The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. Resuscitation 85:336–342
12. Stiell IG, Brown SP, Nichol G et al (2014) What is the optimal chest compression depth during out-of-hospital cardiac arrest resuscitation of adult patients? Circulation 130:1962–1970
13. Idris AH, Guffey D, Pepe PE et al (2015) Chest compression rates and survival following out-of-hospital cardiac arrest. Crit Care Med 43:840–848
14. Christenson J, Andrusiek D, Everson-Stewart S et al (2009) Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation 120:1241–1247
15. Vaillancourt C, Everson-Stewart S, Christenson J et al (2011) The impact of increased chest compression fraction on return of spontaneous circulation for out-of-hospital cardiac arrest patients not in ventricular fibrillation. Resuscitation 82:1501–1507
16. Kitamura T, Kiyohara K, Sakai T et al (2016) Public-access defibrillation and out-of-hospital cardiac arrest in Japan. N Engl J Med 375:1649–1659
17. Zijlstra JA, Stieglis R, Riedijk F, Smeekes M, van der Worp WE, Koster RW (2014) Local lay rescuers with AEDs, alerted by text messages, contribute to early defibrillation in a Dutch out-of-hospital cardiac arrest dispatch system. Resuscitation 85:1444–1449
18. Ringh M, Rosenqvist M, Hollenberg J et al (2015) Mobile-phone dispatch of laypersons for CPR in out-of-hospital cardiac arrest. N Engl J Med 372:2316–2325
19. Hansen CM, Wissenberg M, Weeke P et al (2013) Automated external defibrillators inaccessible to more than half of nearby cardiac arrests in public locations during evening, nighttime, and weekends. Circulation 128:2224–2231
20. Finn JC, Bhanji F, Lockey A et al (2015) Part 8: Education, implementation, and teams: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 95:e203–e224
21. Perman SM, Stanton E, Soar J et al (2016) Location of in-hospital cardiac arrest in the United States—variability in event rate and outcomes. J Am Heart Assoc 5:e003638
22. Alam N, Hobbelink EL, van Tienhoven AJ, van de Ven PM, Jansma EP, Nanayakkara PW (2014) The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. Resuscitation 85:587–594
23. Bannard-Smith J, Lighthall GK, Subbe CP et al (2016) Clinical outcomes of patients seen by rapid response teams: a template for benchmarking international teams. Resuscitation 107:7–12
24. Stiell IG, Brown SP, Christenson J et al (2012) What is the role of chest compression depth during out-of-hospital cardiac arrest resuscitation? Crit Care Med 40:1192–1198
25. Meaney PA, Bobrow BJ, Mancini ME et al (2013) Cardiopulmonary resuscitation quality: improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the american heart association. Circulation 128:417–435
26. Nolan JP, Neumar RW, Adrie C et al (2008) Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 79:350–379
27. Sunde K, Pytte M, Jacobsen D et al (2007) Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 73:29–39
28. Stub D, Schmicker RH, Anderson ML et al (2015) Association between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. Resuscitation 92:45–52
29. Gates S, Quinn T, Deakin CD, Blair L, Couper K, Perkins GD (2015) Mechanical chest compression for out of hospital cardiac arrest: systematic review and meta-analysis. Resuscitation 94:91–97
30. Couper K, Yeung J, Nicholson T, Quinn T, Lall R, Perkins GD (2016) Mechanical chest compression devices at in-hospital cardiac arrest: a systematic review and meta-analysis. Resuscitation 103:24–31
31. Sanfilippo F, Corredor C, Santonocito C et al (2016) Amiodarone or lidocaine for cardiac arrest: a systematic review and meta-analysis. Resuscitation 107:31–37
32. Kudenchuk PJ, Brown SP, Daya M et al (2016) Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 374:1711–1722
33. Kudenchuk PJ (2016) Antiarrhythmic drugs in out-of-hospital cardiac arrest: what counts and what doesn't? Resuscitation 109:A5–A7

34. Argaud L, Cour M, Dubien PY et al (2016) Effect of cyclosporine in non-shockable out-of-hospital cardiac arrest: the CYRUS randomized clinical trial. JAMA Cardiol 1:557–565
35. Wiberg S, Hassager C, Thomsen JH et al (2016) GLP-1 analogues for neuroprotection after out-of-hospital cardiac arrest: study protocol for a randomized controlled trial. Trials 17:304
36. Cariou A, Deye N, Vivien B et al (2016) Early high-dose erythropoietin therapy after out-of-hospital cardiac arrest: a multicenter, randomized controlled trial. J Am Coll Cardiol 68:40–49
37. Nielsen N, Wetterslev J, Cronberg T et al (2013) Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 369:2197–2206
38. Nolan JP, Cariou A (2015) Post-resuscitation care: eRC-ESICM guidelines 2015. Intensive Care Med 41:2204–2206
39. Lasa JJ, Rogers RS, Localio R et al (2016) Extracorporeal-cardiopulmonary resuscitation (E-CPR) during pediatric in-hospital cardiopulmonary arrest is associated with improved survival to discharge: a report from the American Heart Association's Get With The Guidelines-Resuscitation (GWTG-R) Registry. Circulation 133:165–176
40. Chen YS, Lin JW, Yu HY et al (2008) Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet 372:554–561
41. Goldberger ZD, Chan PS, Berg RA et al (2012) Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. Lancet 380:1473–1481
42. Lin JW, Wang MJ, Yu HY et al (2010) Comparing the survival between extracorporeal rescue and conventional resuscitation in adult in-hospital cardiac arrests: propensity analysis of three-year data. Resuscitation 81:796–803
43. Soar J, Nolan JP (2013) Airway management in cardiopulmonary resuscitation. Curr Opin Crit Care 19:181–187
44. Kurz MC, Prince DK, Christenson J et al (2016) Association of advanced airway device with chest compression fraction during out-of-hospital cardiopulmonary arrest. Resuscitation 98:35–40
45. Wang HE, Prince DK, Stephens SW et al (2016) Design and implementation of the resuscitation outcomes consortium pragmatic airway resuscitation trial (PART). Resuscitation 101:57–64
46. Taylor J, Black S, Brett SJ et al (2016) Design and implementation of the AIRWAYS-2 trial: a multi-centre cluster randomised controlled trial of the clinical and cost effectiveness of the i-gel supraglottic airway device versus tracheal intubation in the initial airway management of out of hospital cardiac arrest. Resuscitation 109:25–32
47. Nichol G, Leroux B, Wang H et al (2015) Trial of continuous or interrupted chest compressions during CPR. N Engl J Med 373:2203–2214
48. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL (2011) Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. Resuscitation 82:1138–1143
49. Loomba RS, Nijhawan K, Aggarwal S, Arora RR (2015) Increased return of spontaneous circulation at the expense of neurologic outcomes: is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? J Crit Care 30:1376–1381
50. Perkins GD, Quinn T, Deakin CD et al (2016) Pre-hospital assessment of the role of adrenaline: measuring the effectiveness of drug administration in cardiac arrest (PARAMEDIC-2): trial protocol. Resuscitation 108:75–81
51. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R (2012) The effect of hyperoxia following cardiac arrest—a systematic review and meta-analysis of animal trials. Resuscitation 83:417–422
52. Stub D, Smith K, Bernard S et al (2015) Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 131:2143–2150
53. Kilgannon JH, Jones AE, Shapiro NI et al (2010) Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 303:2165–2171
54. Bellomo R, Bailey M, Eastwood GM et al (2011) Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care 15:R90
55. Kuisma M, Boyd J, Voipio V, Alaspaa A, Roine RO, Rosenberg P (2006) Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. Resuscitation 69:199–206
56. Young P, Bailey M, Bellomo R et al (2014) HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): a randomised controlled feasibility trial. Resuscitation 85:1686–1691
57. Bouzat P, Suys T, Sala N, Oddo M (2013) Effect of moderate hyperventilation and induced hypertension on cerebral tissue oxygenation after cardiac arrest and therapeutic hypothermia. Resuscitation 84:1540–1545
58. Eastwood GM, Schneider AG, Suzuki S et al (2016) Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). Resuscitation 104:83–90
59. Kim F, Nichol G, Maynard C et al (2014) Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA 311:45–52
60. Millin MG, Comer AC, Nable JV et al (2016) Patients without ST elevation after return of spontaneous circulation may benefit from emergent percutaneous intervention: a systematic review and meta-analysis. Resuscitation 108:54–60
61. Dankiewicz J, Nielsen N, Annborn M et al (2015) Survival in patients without acute ST elevation after cardiac arrest and association with early coronary angiography: a post hoc analysis from the TTM trial. Intensive Care Med 41:856–864
62. Dumas F, Bougouin W, Geri G et al (2016) Emergency percutaneous coronary intervention in post-cardiac arrest patients without st-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv 9:1011–1018
63. Shah N, Chaudhary R, Mehta K et al (2016) Therapeutic hypothermia and stent thrombosis: a nationwide analysis. JACC Cardiovasc Interv 9:1801–1811
64. Laitio R, Hynninen M, Arola O et al (2016) Effect of inhaled xenon on cerebral white matter damage in comatose survivors of out-of-hospital cardiac arrest: a randomized clinical trial. JAMA 315:1120–1128
65. Sandroni C, Cariou A, Cavallaro F et al (2014) Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med 40:1816–1831
66. Seder DB, Sunde K, Rubertsson S et al (2015) Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. Crit Care Med 43:965–972
67. Westhall E, Rosen I, Rossetti AO et al (2015) Interrater variability of EEG interpretation in comatose cardiac arrest patients. Clin Neurophysiol 126:2397–2404
68. Hirsch LJ, LaRoche SM, Gaspard N et al (2013) American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. J Clin Neurophysiol 30:1–27
69. Paul M, Bougouin W, Geri G et al (2016) Delayed awakening after cardiac arrest: prevalence and risk factors in the Parisian registry. Intensive Care Med 42:1128–1136
70. Moulaert VR, van Heugten CM, Winkens B et al (2015) Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: a randomised controlled trial. Int J Cardiol 193:8–16
71. Lilja G, Nielsen N, Friberg H et al (2015) Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33 degrees C versus 36 degrees C. Circulation 131:1340–1349
72. Andersson AE, Rosen H, Sunnerhagen KS (2015) Life after cardiac arrest: a very long term follow up. Resuscitation 91:99–103
73. Weisfeldt ML (2016) Stop randomizing all cardiac arrests. Circulation 134:2035–2036