The Intensive Care Society

Standards for the Management of Patients After Cardiac Arrest

intensive care society
care when it matters

Prepared on behalf of the Council of the Intensive Care Society by:
J Nolan Royal United Hospital Bath NHS Trust

Ratified by ICS Council: October 2008
Review date October 2010

1. Executive Summary

1.1 There are approximately 50,000 treated cardiac arrests each year in the UK and approximately one eighth of these will get admitted to an intensive care unit (ICU). Approximately one third of those admitted to ICU will be discharged from hospital – 80% return to their normal residence. There is considerable variation in the outcome of post cardiac arrest patients admitted to UK ICUs, even when adjustment is made for case mix.

1.2 Consider the post cardiac arrest care bundle for those patients admitted comatose to ICU after cardiac arrest. This comprises: early coronary reperfusion (if appropriate) and haemodynamic optimisation; control of ventilation; blood glucose control; temperature control; and treatment of seizures.

1.3 Consider tracheal intubation, sedation and controlled ventilation in any patient with obtunded cerebral function following resuscitation from cardiac arrest.

1.4 Prior cardiopulmonary resuscitation is not a contraindication to thrombolysis – restoration of coronary perfusion is a priority. If there is evidence of coronary occlusion, consider immediate revascularisation by thrombolysis or percutaneous coronary intervention. If the facilities are available, primary PCI is the preferred technique for revascularisation.

1.5 Prolonged seizure activity may cause cerebral injury, and should be treated promptly and effectively.

1.6 Treat any hyperthermia occurring in the first 72 h after cardiac arrest with antipyretics or active cooling.

1.7 Unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32–34°C. Cooling should be started as soon as possible and continued for at least 12–24 h. Rewarm slowly (0.25–0.5^{o}C/h). Mild hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a non-shockable rhythm, or cardiac arrest in hospital.

1.8 Patients admitted to ICU after cardiac arrest should have their blood glucose monitored frequently and hyperglycaemia treated with an insulin infusion. Recent studies indicate that post cardiac arrest patients may be treated optimally with a target range for blood glucose concentration of up to 8 mmol/L.

1.9 Prognosis cannot be based on the circumstances surrounding cardiac arrest and cardiopulmonary resuscitation. The decision to admit a comatose post cardiac arrest patient to ICU should be based predominantly on the patient's status before the cardiac arrest. Absent pupil or corneal reflexes within days 1 to 3 after CPR, or absent or extensor motor responses 3 days after cardiac arrest reliably predict a poor outcome in the normothermic patient. Myoclonic status epilepticus within the first day after a primary cardiac arrest reliably predicts a poor outcome. Until more data are available, if a patient has been treated with mild hypothermia, prognostication should probably be delayed but the optimal time has yet to be determined.

2. Introduction

2.1 Survival after cardiac arrest

Ischaemic heart disease is the leading cause of death in the world [1] and sudden cardiac arrest is responsible for more than 60% of adult deaths from coronary heart disease. [2] Based on data from Scotland the annual incidence of resuscitation for out-of-hospital cardiac arrest is 60 per 100,000 population – 82% of these are caused by primary cardiac disease. [3] Ventricular fibrillation is the first monitored rhythm in approximately 40% of out-of-hospital primary cardiac arrests.[4] Rates of survival to hospital discharge after out-of-hospital cardiac arrest are 7-10%.[3,5] The incidence of primary cardiac arrest in hospital is approximately 1.5-3.0/1000 admissions[6] and rates of survival to hospital discharge are approximately 17%.[7,8] With the exception of patients resuscitated from a very brief period of cardiac arrest, most of those with a return of spontaneous circulation (ROSC) will initially be comatose and those without extensive comorbidity will generally be admitted to an ICU. Organ injury caused by ischaemia and hypoxia during prolonged cardiac arrest is compounded by reperfusion injury that occurs when a spontaneous circulation is restored. These insults trigger a systemic inflammatory response, similar to that associated with sepsis,[9] which causes multiple organ dysfunction - this is termed the post cardiac arrest syndrome.[10-12] It has been estimated that there are approximately 50,000 treated cardiac arrests each year in the UK and approximately 6350 (12.7%) will get admitted to an intensive care unit (ICU).[13] Based on an analysis of the Intensive

Care National Audit and Research Centre Case Mix Programme Database (ICNARC CMPD), unconscious, mechanically ventilated survivors of cardiac arrest account for 5.8% of all admissions to ICUs in the United Kingdom (UK). Of these 24,132 admissions, 42.9% survived to leave the ICU and 28.6% survived to hospital discharge.[13] Two-thirds of patients dying after admission to ICU following out-of-hospital cardiac arrest die from neurological injury and 25% of patients dying after admission to ICU following in-hospital cardiac arrest die from neurological injury.[14] It is has now been established that interventions in the post-resuscitation period have a significant influence on the ultimate outcome.[15-18] A recent analysis of the ICNARC CMPD indicates that there is considerable variation in the outcome of post cardiac arrest patients admitted to UK ICUs even when adjustment is made for case mix (Harrison D, personal communication).

2.2 The goal of resuscitation

The ultimate goal is to return the patient to a state of normal neurological function with a stable cardiac rhythm and normal haemodynamic function. This will require further resuscitation tailored to the individual needs of each patient. The post-resuscitation phase starts at the location where ROSC is achieved but, once stabilised, the patient is transferred to the most appropriate high-care area (e.g., ICU, coronary care unit) for continued monitoring and treatment.

2.3 Levels of evidence and grades of recommendation

This document provides guidance on the intensive care treatment of patients admitted after resuscitation from cardiac arrest. It is based on systematic reviews of the literature on post resuscitation care. The levels of evidence and treatment recommendations have been graded using the system devised by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk). Most of the relevant studies have already been identified and evaluated by the International Liaison Committee on Resuscitation (ILCOR) during preparation of the 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR).[19] The systematic reviews undertaken for CoSTR can be viewed and downloaded at www.c2005.org. For the purposes of this document, these reviews were updated to include relevant studies published since 2005. The treatment recommendations in this document are consistent with those published in an American Heart Association (AHA)/ILCOR Post-cardiac Arrest Statement of Science.[10]

3. Airway and ventilation

3.1 Science

There are no data supporting precise indications for intubation, ventilation and sedation after cardiac arrest. Although cerebral autoregulation is either absent or altered in a majority of patients in the acute phase after cardiac arrest [2+],[20] cerebrovascular reactivity to changes in arterial carbon dioxide tension seems to be preserved [2+].[21-24] Cerebrovascular resistance may be elevated for at least 24 hours in comatose survivors of cardiac arrest.[25] Studies in brain-injured patients have shown that the cerebral vasoconstriction caused by hyperventilation may produce potentially harmful cerebral ischaemia [1+].[26] There are no data to support the targeting of a specific arterial PCO_2 after resuscitation from cardiac arrest. There are no data to indicate an optimal duration for sedation and positive pressure ventilation after cardiac arrest. The duration will depend on recovery of organ function.

Adequate oxygen delivery is essential, but animal data indicate that too much oxygen during the initial stages of reperfusion can exacerbate neuronal damage through production of free radicals and mitochondrial injury.[27,28] Several animal studies have demonstrated neurological benefits of controlled reoxygenation during the initial phases of resuscitation by ventilating with the minimum FiO_2 required to maintain adequate oxygen saturation of arterial blood.[29] Based on these data, avoid unnecessary arterial hyperoxia, particularly during the initial post-cardiac arrest period. This can be achieved by adjusting the FiO_2 to produce an arterial oxygen saturation of 94-98%.

3.2 Treatment recommendations

3.2.1 Patients who have had a brief period of cardiac arrest responding immediately to appropriate treatment may regain consciousness very quickly. These patients do not require tracheal intubation and ventilation but should be given oxygen via a facemask [D].

3.2.2 Consider tracheal intubation, sedation and controlled ventilation in any patient with obtunded cerebral function [D].

3.2.3 Adjust ventilation to achieve normocarbia and monitor this using the end-tidal PCO_2 and arterial blood gas values [B].

3.2.4 Adjust the FiO_2 to achieve an arterial oxygenation of 94-98% [D].

4. Circulation

4.1 Coronary revascularisation

4.1.1 Science

Acute coronary occlusion with myocardial infarction is a common cause of sudden cardiac death and coronary artery disease accounts for two thirds of sudden cardiac deaths [2+].[2,3,30] Acute changes in coronary plaque morphology are found in 40-86% cardiac arrest survivors, and in 15-64% in autopsy studies [3].[31] In a series of 84 consecutive survivors of OHCA who underwent immediate coronary angiography, 40 were found to have coronary artery occlusion [2+].[32] Early post-cardiac arrest coronary angiography with subsequent PCI is well documented [2+].[32-39] In a series of 40 patients treated in Oslo, Norway with primary percutaneous coronary intervention (PCI) after OHCA and ST-elevation myocardial infarction (STEMI), the 2-year mortality was just 27.5%; before PCI, 90% of the patients were unconscious [2+].[33] In another study of 135 cardiac arrest patients who had a STEMI and subsequently underwent coronary angiography, a PCI success rate of 87% and a survival to discharge rate of 67% was reported [2+].[37] Those who were comatose at the time of PCI had a long-term survival of 54%. Similar results were reported in a study of 186 patients who underwent coronary angiography after resuscitation for STEMI [2+]:[36] 54% survived to 6 months and 86% of these survivors had normal cerebral function (Cerebral Performance Category 1). The combination of early angiography/PCI with mild therapeutic hypothermia in 40 comatose patients resuscitated after out-of-hospital cardiac arrest caused by STEMI resulted in a 75% survival-to-discharge rate compared with 44% among patients undergoing PCI but not hypothermia [2+].[39] The patient can be brought to the angiography laboratory while cooling is continued, and the combination of early PCI and mild hypothermia for patients remaining comatose after cardiac arrest caused by STEMI is very promising [2+].[15,38,39]

The safety of thrombolysis after cardiopulmonary resuscitation has been documented [2+].[40,41] In a placebo controlled trial of t-PA given during CPR for asystolic OHCA, the incidence of major haemorrhage was 1.7% (2/117) [1+].[42] The Thrombolysis in Cardiac Arrest (TROICA) Study indicated that the incidence of major bleeding complications was not significantly different between the placebo (7.4%) and thrombolysis (8.9%) groups [1++]. [in press] Symptomatic intracranial haemorrhage occurred in 1% of those given thrombolysis.

The data comparing primary PCI with thrombolysis after acute myocardial infarction are summarised in the 2005 CoSTR [1++].[43] Six randomised studies [1+],[44-49] and three meta-analyses [1++],[50-52] compared primary PCI with thrombolysis in patients with STEMI. These studies documented consistent improvement in the combined end point of death, stroke, and reinfarction when PCI was undertaken by skilled personnel in a high-volume centre (i.e. >75 procedures per operator annually) with minimal delay (balloon inflation ≤90 minutes after first medical contact and within 12 hours after the onset of symptoms). However, there are no randomised controlled trials comparing primary PCI with thrombolysis in post cardiac arrest patients specifically. A meta-analysis of 17 trials concluded that facilitated PCI, in which thrombolysis is given before PCI, is associated with increased intracerebral bleeding risk and mortality, in comparison with PCI alone [1++].[53]

4.1.2 Treatment recommendation

4.1.2.1 Prior cardiopulmonary resuscitation is not a contraindication to thrombolysis – restoration of coronary perfusion is a priority. If there is evidence of coronary occlusion, consider immediate revascularisation by thrombolysis or percutaneous coronary intervention [B].

4.1.2.2 If the facilities are available, primary PCI is the preferred technique for revascularisation [B] – extrapolated from data derived from non-cardiac arrest patients.

4.1.2.3 Management of the ventilated, haemodynamically unstable post cardiac arrest patient in the cardiac catheter laboratory is challenging and requires the presence of an experienced ICU clinician [√].

4.1.2.3. When indicated, cooling can be continued in the angiography laboratory [C].

4.2 Myocardial dysfunction after cardiac arrest

4.2.1 Science

Haemodynamic instability is common after cardiac arrest and manifests as hypotension, low cardiac index, arrhythmias [2++],[54] and impaired contractility on echocardiography [3].[55] This post-resuscitation myocardial dysfunction is usually transient and often reverses within 24–48 h [animal study].[56] The post-resuscitation period is associated with marked elevations in plasma cytokine concentrations, manifesting as a sepsis-like syndrome and multiple organ dysfunction [2++].[57] These patients will commonly require considerable fluid, and inotropes and/or

vasoactive drugs. Mechanical circulatory assistance with an intra-aortic balloon pump (IABP) may be required until myocardial dysfunction has recovered. Several recent studies have documented high long-term survival rates (> 50%) in post cardiac arrest patients despite the need for treatment with an IABP [2+].[15,36,38]

4.2.2 Treatment recommendations

4.2.2.1 Infusion of fluids may be required to increase right heart filling pressures or, conversely, diuretics, vasodilators and inotropes/IABP may be needed to treat myocardial dysfunction [C].

4.2.2.2 In the presence of a significant inflammatory response, noradrenaline may be required to maintain an adequate blood pressure [C].

4.2.2.3 Early echocardiography will enable the extent of myocardial dysfunction to be quantified and may guide therapy [D].

4.3 Blood pressure control after cardiac arrest

4.3.1 Science

There are very few randomised trials evaluating the role of blood pressure on the outcome after cardiac arrest. One randomised study demonstrated no difference in the neurological outcome among patients randomised to a mean arterial pressure of >100 mmHg versus ≤100 mmHg 5 min after ROSC; however, good functional recovery was associated with a higher blood pressure during the first 2 h after ROSC [2+].[58] Good outcomes have been achieved after out-of-hospital cardiac arrest using a MAP target from as low as 65-75 mm Hg to as high as 90-100 mm Hg [2-].[15,59] A patient with an evolving AMI or severe myocardial dysfunction might benefit from the lowest target MAP that will assure adequate cerebral oxygen delivery.

4.3.2 Treatment recommendation

4.3.2.1 In the absence of definitive data, target the mean arterial blood pressure to achieve an adequate urine output, taking into consideration the patient's normal blood pressure [C].

4.4 Prophylactic anti-arrhythmic therapy

4.4.1 Science

No studies have specifically and directly addressed the prophylactic use of antiarrhythmic therapy started immediately after resuscitation from cardiac arrest. Six studies ([2+],[60-64] [3][65]) have shown inconsistent improvement in long-term

survival when prophylactic antiarrhythmics were given to survivors of cardiac arrest from all causes. Six studies ([1++],[66-68] [1+],[69,70] [2++][71]) showed that implantable cardioverter defibrillators (ICDs) improve survival when compared with antiarrhythmics in survivors of cardiac arrest. In comparison with beta-blocker alone, or sotalol, a combination of amiodarone plus beta-blocker reduced the number of shocks from ICDs [1++].[72]

Immediately after cardiac arrest there is often a period of hyperkalaemia, caused by the release of intracellular potassium associated with ischaemia [3].[73] Subsequent endogenous catecholamine release promotes intracellular transportation of potassium, causing hypokalaemia. Hypokalaemia may predispose to ventricular arrhythmias. Dysrhythmias are commonly caused by focal cardiac ischaemia, and early reperfusion treatment is probably the best anti-arrhythmic therapy.

4.4.2 Treatment recommendation

4.4.2.1 Giving prophylactic antiarrhythmics to patients who have survived cardiac arrest, irrespective of aetiology, can neither be recommended nor rejected. It may be reasonable, however, to continue an infusion of an antiarrhythmic drug that restored a stable rhythm successfully during resuscitation [D].

4.4.2.2 Give potassium to maintain the serum potassium concentration between 4.0 and 4.5 mmol/L [D].

4.5 Adrenal function and coagulation

4.5.1 Science

The stress of total body ischemia/reperfusion affects adrenal function. Relative adrenal insufficiency, defined as failure to respond to corticotrophin (i.e. <9 µg/ml increase in cortisol), is common and is associated with increased mortality [2-].[74-78] One small study has demonstrated increased ROSC when patients with out-of-hospital cardiac arrest were treated with hydrocortisone [1-],[79] but the use of steroids has not been studied in the post cardiac arrest phase.

Significant coagulation abnormalities consistent with down-regulation of the thrombomodulin-endothelial protein C pathway have been documented after resuscitation from OHCA [2+].[80] One small study has demonstrated improved six-month survival when high-volume haemofiltration was used after cardiac arrest [1-].[81]

4.5.2 Treatment recommendation

4.5.2.1 Routine steroid treatment after cardiac arrest is not recommended [D].

5. Disability (optimising neurological recovery)

5.1 Cerebral perfusion

5.1.1 Science

The mechanisms of brain damage triggered by cardiac arrest and resuscitation are complex and include excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and activation of cell death signalling pathways [4].[82-84] Many of these processes occur over hours to days following ROSC. Prolonged cardiac arrest can cause failure of cerebral microcirculatory reperfusion, and even small infarctions, despite adequate cerebral perfusion pressures ([4],[85] [animal data][86]).

Immediately after ROSC there is a period of cerebral hyperaemia because of elevated cerebral perfusion pressures and impaired cerebrovascular autoregulation ([2+][20], [3][87], [animal data][88]). After 15–30 min of reperfusion, however, global cerebral blood flow decreases and there is generalised hypoperfusion associated with a decrease in cerebral blood flow to about 50% or less of normal [animal data].[89] The loss of normal cerebral autoregulation leaves cerebral perfusion dependent on mean arterial pressure ([2+][20], [3][87]). Under these circumstances, hypotension will compromise cerebral blood flow severely and will compound any neurological injury. Although transient brain oedema is observed early after ROSC, most commonly after asphyxial cardiac arrest, it is rarely associated with clinically relevant increases in intracranial pressure [3].[90-93]

5.1.2 Treatment recommendation

5.1.2.1 After ROSC, maintain mean arterial pressure at the patient's normal level [D].

5.1.2.2 There is no indication for routine ICP monitoring after cardiac arrest [D].

5.2 Sedation

5.2.1 Science

Although it has been common practice to sedate and ventilate patients for up to 24 h after ROSC, there are no data to support a defined period of ventilation, sedation and neuromuscular blockade after cardiac arrest. The duration of sedation and ventilation

may be influenced by the use of therapeutic hypothermia (see 5.4.2). In comparison with other intubated critically ill patients, post cardiac arrest patients are at particularly high risk of developing pneumonia within the first 48 h of intubation [2+].[94] Mild hypothermia will prolong the clearance of sedative drugs and neuromuscular blockers [2+].[95]

5.2.2 Treatment recommendation

5.2.2.1 There are no data to indicate whether or not the choice of sedation influences outcome, but short-acting drugs (e.g., propofol, alfentanil, remifentanil) will enable earlier neurological assessment [√].

5.3 Prevention and control of seizures

5.3.1 Science

Seizures and/or myoclonus occur in 5%–15% of adult patients who achieve ROSC, and in 10-40% of those who remain comatose ([2++],[96] [2+],[97,98] [3],[99]). Seizures increase cerebral metabolism by up to threefold [animal data].[100] There are no studies that directly addressed the use of prophylactic anticonvulsant drugs after cardiac arrest in adults. Myoclonus can be particularly difficult to treat – phenytoin is often ineffective. Clonazepam is the most effective antimyoclonic drug, but sodium valproate and levetiracetam may also be effective [4].[101] Effective treatment of myoclonus with propofol has been described [3].[102]

Shivering associated with therapeutic hypothermia (see 5.4.2) may require the use of neuromuscular blocking drugs. Because of the relatively high incidence of seizures after cardiac arrest, consider continuous EEG monitoring for patients requiring sustained neuromuscular blockade [3].[103]

5.3.2 Treatment recommendations

5.3.2.1 Prolonged seizure activity may cause cerebral injury, and should be treated promptly and effectively with benzodiazepines, phenytoin, sodium valproate, propofol or a barbiturate [D]. Each of these drugs can cause hypotension, and this must be treated appropriately [√].

5.3.2.2 Clonazepam is the drug of choice for the treatment of myoclonus [D].

5.3.2.3 Maintenance therapy should be started after the first event once potential precipitating causes (e.g. intracranial haemorrhage, electrolyte imbalance, etc) are excluded [√].

5.3.2.4 If continuous infusions of neuromuscular blocking drugs are necessary to control shivering, consider the use of continuous EEG monitoring [D].

5.4 Temperature control

5.4.1 Treatment of hyperthermia

5.4.1.1 Science

A period of hyperthermia is common in the first 48 h after cardiac arrest [2+],[104,105] [animal study].[106]The risk of a poor neurological outcome increases for each degree of body temperature >37°C [2++].[107] Antipyretics and/or physical cooling methods decrease infarct volumes in animal models of global ischaemia.[108,109]

5.4.1.2 Treatment recommendation

Treat any hyperthermia occurring in the first 72 h after cardiac arrest with antipyretics or active cooling [C].

5.4.2 Therapeutic hypothermia

5.4.2.1 Science

Two randomised clinical trials [1+],[110] [1-][111]) and a meta-analysis [1+][112] showed improved outcome in adults who remained comatose after initial resuscitation from out-of-hospital VF cardiac arrest and who were cooled within minutes to hours after ROSC. Patients in these studies were cooled to 33ºC[110] or to the range of 32ºC to 34ºC[111] for 12 to 24 hours. The Hypothermia After Cardiac Arrest (HACA) study included a small subset of patients with in-hospital cardiac arrest.[110]

Three studies with historical control groups showed benefit after therapeutic hypothermia in comatose survivors of OHCA after non-VF arrest [2+][113] and all rhythm arrests [2+][59,114] respectively. Other observational studies also indicate its possible benefit following cardiac arrest in other settings [2-].[115,116] One study documented improved metabolic end points (lactate and O_2 extraction) when comatose adult patients were cooled after ROSC from out-of-hospital cardiac arrest in which the initial rhythm was PEA/asystole[1-].[117] Two studies have indicated favourable outcome from out-of-hospital cardiac arrest associated with STEMI when patients were treated with combination of primary PCI and hypothermia ([2-][39], [3][38]).

External or internal cooling techniques can be used to initiate cooling within minutes to hours ([1+],[110] [1-],[111,117,118] [2+],[59,114] [3][119-123]) An infusion of 30 ml/kg of 4ºC saline achieved a decrease in core temperature of approximately 1.5ºC ([1+][118], [3][119,120,122,124,125]). Ice cold fluids alone cannot be used to maintain hypothermia.[126] One study in patients with cardiac arrest [3][121] and four other studies ([1+],[127] [2+],[128] [3],[129,130]) have documented that intravascular cooling enables more precise control of core temperature than external methods. Studies documenting improved outcome with therapeutic hypothermia after cardiac arrest used continuous temperature monitoring ([1+],[110] [1-],[111,117] [2+],[59,114] [2-],[39] [3],[38]).

Multiple studies in animals indicate the importance of initiating cooling as soon as possible and for adequate duration (e.g.,12 to 24 hours) [animal data];[131-138] this is supported by a recent clinical study [2+].[139] Shivering will necessitate sedation and possibly intermittent or continuous neuromuscular blockade. Use of continuous neuromuscular blockade could mask seizure activity [3].[140]

Other complications of mild therapeutic hypothermia include increased infection, cardiovascular instability, coagulopathy, hyperglycaemia and electrolyte abnormalities such as hypophosphataemia and hypomagnesaemia ([2+],[141] [4], [142]). Particular care must be taken during the cooling and rewarming phases because metabolic rate, plasma electrolyte concentrations and haemodynamics may change rapidly.

The optimum target temperature, rate of cooling, duration of hypothermia and rate of rewarming have yet to be determined; further studies are essential. Although the optimal rate of rewarming is unknown, the consensus is currently about 0.25-0.5 ºC of warming per hour [4].[115]

5.4.2.2 Treatment recommendations

5.4.2.2.1 Unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32–34°C [A].

5.4.2.2.2 Cooling should be started as soon as possible and continued for at least 12–24 h [B]. Most experts recommend cooling for at least 24 h [D].

5.4.2.2.3 Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a non-shockable rhythm, or cardiac arrest in hospital [C].
5.4.2.2.4 Rapid infusion of ice-cold fluid 30 ml/kg is a very effective, simple method for initiating cooling [A].
5.4.2.2.5 Treat shivering by ensuring adequate sedation and giving neuromuscular blocking drugs [D]. Bolus doses of neuromuscular blockers are usually adequate, but infusions are necessary occasionally [D].
5.4.2.2.6 Rewarm the patient slowly (0.25–0.5^{o}C/h) [D].
5.4.2.2.7 Avoid hyperthermia in all comatose post cardiac arrest patients [C].

5.5 Blood glucose control

5.5.1 Science

There is a strong association between high blood glucose after resuscitation from cardiac arrest and poor neurological outcome [2+].[16,143-149] Persistent hyperglycaemia after stroke is associated with a worse neurological outcome ([2++],[150] [2+][151]).

Tight control of blood glucose (4.4–6.1 mmol/L) using insulin reduced hospital mortality in critically ill adults in a surgical ICU [1++],[152] and appeared to protect the central and peripheral nervous system [1+],[153] but this has not been demonstrated in post-cardiac arrest patients specifically. When the same group repeated this study in a medical ICU, the overall mortality was similar in the intensive insulin and control groups [1++].[154] Among the patients with an ICU stay of 3 days or longer, intensive insulin therapy reduced the mortality from 52.5% (control group) to 43% (P=0.009). Sixty-one of the 1200 patients in the medical ICU study had neurological disease – the mortality among these patients was the same in the control and treatment groups (29% versus 30%) [1++].[154] In the UK, the median length of ICU stay for ICU survivors after admission following cardiac arrest is 3.4 days [2+].[13] One rat study has shown that glucose plus insulin improves cerebral outcome after asphyxial cardiac arrest [animal data].[155]

There was no difference in 30-day mortality among 90 unconscious survivors of out-of-hospital VF cardiac arrest who were cooled and randomised between a strict glucose control group (SGC), with a blood glucose target of 4-6 mmol/L, and a moderate glucose control group (MGC), with a blood glucose target of 6-8 mmol/L [1+].[156] Episodes of moderate hypoglycemia (< 3.0 mmol/L) occurred in 18% of the

SGC group and 2% of the MGC group (p 0.008); however, there were no episodes of severe hypoglycemia (< 2.2 mmol/L or 40 mg/dl). The upper glucose value of 8.0 mmol/L, which is significantly higher than the 6.1 mmol/L recommended by van den Berghe [1++],[152] has been suggested by others [2-].[15,157,158] The lower glucose target range may not reduce mortality any further, but instead, may expose patients to the potentially harmful effects of hypoglycemia [1+].[156] The incidence of hypoglycaemia in another recent study of intensive insulin therapy exceeded 18% and some authors have cautioned against its routine use in the critically ill [4].[159,160] Regardless of the chosen glucose target range, blood glucose must be measured frequently ([1+],[156] [2-],[15]) especially when insulin is started and during cooling and rewarming periods.

5.5.2 Treatment recommendations

5.5.2.1 In common with all critically ill patients, patients admitted to a critical care environment after cardiac arrest should have their blood glucose monitored frequently and hyperglycaemia treated with an insulin infusion. The blood glucose concentration that triggers insulin therapy, and the target range of blood glucose concentrations, should be determined by local policy [B].

5.5.2.1 Recent studies indicate that post cardiac arrest patients may be treated optimally with a target range for blood glucose concentration of up to 8 mmol/L [B].

6 Prediction of outcome in comatose survivors after cardiopulmonary resuscitation

6.1 Science

Two thirds of those dying after admission to ICU following out-of-hospital cardiac arrest die from neurological injury [3].[14] A quarter of those dying after admission to ICU following in-hospital cardiac arrest die from neurological injury. Predicting the final outcome of individual patients remaining comatose after resuscitation from cardiac arrest is problematic. The criteria for prognosis must have near to 100% specificity.

The Quality Standards Subcommittee of the American Academy of Neurology has recently completed an evidence-based review of all the studies and on prediction of

outcome in comatose survivors after CPR and has made several recommendations for clinical practice [2++].[161]

6.1.1 Circumstances surrounding cardiopulmonary resuscitation

Numerous studies have documented an association between peri-arrest factors (e.g., first monitored rhythm, no flow time (arrest to start of CPR), duration of CPR, co-morbidity) and outcome. Most studies do not document an association between age and survival after cardiac arrest [2+],[149,162-165] but others show a significantly lower survival in older patients [2+].[166-169] One high-quality study that included only comatose survivors of cardiac arrest documented that increasing age was associated with higher mortality but it was not an independent predictor of poor neurological outcome [2++].[170] This study also showed that no flow time, duration of CPR and first monitored rhythm were all associated with outcome but the false positive rate with these variables ranged from 20-27%. Patients older than 80 years account for 11% of the mechanically ventilated survivors of cardiac arrest in the ICNARC CMPD and approximately 19% of these survive to hospital discharge [2+].[13]

One group has used logistic regression analysis to identify clinical and laboratory variables, which are readily available on admission, to produce a score that will predict outcome (the out-of-hospital cardiac arrest (OHCA) score) [2+].[171] Initial rhythm, estimated no-flow and low-flow intervals, blood lactate and creatinine concentrations were independently associated with poor outcomes and were used to build a continuous severity score. While the performance of this score is good for predicting outcome among cohorts of cardiac arrest patients, it is not appropriate for predicting outcome in individuals.

The lactate concentration in arterial blood at admission is associated weakly with the duration of cardiac arrest and high lactate concentrations are associated with poor neurological outcome [2++].[172] However, arterial lactate concentration has poor prognostic value for estimating the likelihood of a poor neurological outcome in individuals.

6.1.2 Neurological examination

The predictive value of the Glasgow Coma Scale (GCS) score, the motor component of the GCS, brainstem reflexes (pupil light reflexes, corneal reflexes, eye movements), and the presence of convulsions or myoclonic status epilepticus have

been investigated in several studies ([1-],[173] [2++],[96,98,174] [2+],[175-181]). Of these, absence of the pupillary light response, corneal reflex or motor response to painful stimuli at day 3 provides the most reliable predictor of poor outcome (vegetative state or death) [2+].[96,161,182]. Based on a systematic review of the literature, it was reported that absent brainstem reflexes or a Glasgow motor score ≤ 2 (i.e., extensor or absent) at 72 hours had a false positive rate (FPR) of 0% [95% CI 0-3%] for predicting poor outcome [2+].[161] In a recent prospective trial, it was reported that absent pupillary or corneal reflexes at 72 hours had a 0% FPR [95% CI 0-9%] while absent motor response at 72 hours had a 5% FPR [95% CI 2-9%] for poor outcome.[96] Absent pupil light reflexes at 24-72 h after CPR also had a 0% FPR [2++]. [96,98,174] Single convulsions and sporadic focal myoclonus do not predict poor outcome accurately ([2++],[96] [2+][178]). However, myoclonic status epilepticus (spontaneous, repetitive, generalised multifocal clonus involving the face, limbs, and axial musculature in comatose patients) on day 1 predicts a poor outcome with a FPR of 0% [95% CI 0 - 8.8%] ([2++][96,161] [2+][179]). While status myoclonus has been regarded as a reliable predictor of poor outcome, it may be misdiagnosed by non-neurologists. There have been a few case reports of good outcomes despite myoclonic status epilepticus but these have mainly involved patients with primary respiratory arrest [3].[97,183-185]

6.1.3 Electroencephalogram

There have been several studies examining the electroencephalogram (EEG) as a predictor of outcome after cardiac arrest [2+].[178,186-189] Generalised suppression to < 20μV, burst-suppression pattern with generalised epileptiform activity, or generalised period complexes on a flat background are strongly, but not invariably, associated with a poor outcome. The Quality Standards Subcommittee of the American Academy of Neurology meta-analysis of studies reporting malignant EEG patterns documented a FPR for poor outcome of 3% [95% CI 0.9 -11%] [2++].[161]

6.1.4 Somatosensory evoked potentials

Several groups of investigators have studied the use of somatosensory evoked potentials (SSEPs) in response to median nerve stimulation as a means of predicting poor outcome in comatose patients within 3 days after cardiac arrest ([2++][96] [2+][176,178,189-193] [1+],[173,194]). SSEPs are minimally influenced by drugs and metabolic derangements and therefore more useful for prognostication. All but one of these studies[189] had a FPR of 0%. The Quality Standards Subcommittee of the

American Academy of Neurology meta-analysis of studies reporting SSEPs documented a FPR of 0.7% for poor outcome [95% CI 0.1 - 3.7] [2++].[161]

6.1.5 Neurological biochemical markers

Biomarkers that have been studied for their potential for predicting outcome after cardiac arrest include serum neuron-specific enolase (NSE), serum S100, and creatine kinase brain isoenzyme (CKBB). NSE is an isomer of enolase that is located in neurons and neuroectodermal cells; S100 protein is a calcium-binding astroglial protein and CKBB is present in neurons and astrocytes.

In one high-quality study, 231 patients with a NSE > 33 μg/dl at 1-3 days all had a poor outcome: FPR 0% [95% CI 0 - 3%] [2++].[96] Other studies have confirmed the relationship between serum NSE and poor outcome but the cut-off points range from 20 to 65 μg/dl ([2+],[181,195-197] [3],[198]).

Several studies have documented that serum S100 is not as useful as a prognostic indicator ([2++],[96] [2+],[181,195,197,199,200]). Using a cut-off of 0.7 μg/L, the best study reported a FPR of 5% [95% CI 0 - 26] [2+].[96]

In six studies CKBB also proved to be a poor predictor of outcome - the median FPR was 15% [range 0 - 33%] [2+].[201-206]

6.1.6 Radiological studies

Although eight studies have assessed the ability of CT, MRI and nuclear magnetic resonance spectroscopy to predict poor outcome among comatose patients after cardiac arrest ([2+][92,207] [3][208-213]) there is not enough evidence to define lesions that would predict poor outcome with precision [2++].[161] There is some evidence that loss of distinction between grey (GM) and white matter (WM) on CT scan predicts poor outcome in comatose patients after cardiac arrest. In the best of these studies the CT appearances of 25 comatose post cardiac arrest patients were compared with the scans of normal controls [2+].[92] A difference in GM/WM ratio of < 1.18 at the basal ganglia level was 100% predictive of death. This single study is not enough to recommend CT scanning as a means of predicting outcome in individual cases.

6.1.7 Prognostication in hypothermia-treated patients

Therapeutic hypothermia alters the progression of neurological injury and, in comparison with those not subjected to therapeutic hypothermia, alters the evolution of recovery. Therefore, prognostic factors established in patients not treated with hypothermia might not predict accurately the outcome of those treated with hypothermia [4].[10] There are no studies detailing the recovery of key components of the neurologic examination in cooled patients. But some studies have investigated the utility of SSEP and biochemical markers in predicting functional outcome with therapeutic hypothermia after cardiac arrest. One study found that bilateral absence of cortical N20 responses predicted permanent coma similarly with a FPR of 0% (95% CI, 0-8%) [1+].[194] Brainstem auditory evoked potential recordings did not correlate with the outcome in either treatment group. In another study by the same group, patients treated with therapeutic hypothermia had higher baseline concentrations of NSE but more patients in the hypothermia arm had decreases in serum NSE concentrations over the first several days after cardiac arrest than patients assigned to the placebo group [2+].[195] These decreases in NSE were associated with a good outcome. Hypothermia may mask neurologic examination, or delay the clearance of sedative or neuromuscular blocking drugs that may mask neurologic function [2+].[95,161,214]

6.2 Treatment recommendations

6.2.1 Prognosis cannot be based on the circumstances surrounding cardiac arrest and cardiopulmonary resuscitation [B].

6.2.2 The decision to admit a comatose post cardiac arrest patient to ICU should be based predominantly on the patient's status before the cardiac arrest [√].

6.2.3 Absent pupil or corneal reflexes within days 1 to 3 after CPR, or absent or extensor motor responses 3 days after cardiac arrest reliably predict a poor outcome in the normothermic patient [B]. Consider withdrawing therapy.

6.2.3 Myoclonic status epilepticus within the first day after a primary cardiac arrest reliably predicts a poor outcome [C].

6.2.4 Burst suppression or generalised epileptiform discharges on the EEG predict poor outcome but this is too imprecise for use in individual cases [C]. Timely access to EEG recording and interpretation may be a problem on many ICUs.

6.2.5 Bilateral absence of the N2O component of the SSEP with median nerve stimulation recorded on days 1-3 or later accurately predicts a poor outcome [B]; however, few ICUs will have access to this investigation in a useful time frame.

6.2.6 There are too few data to determine the value of radiological investigations in predicting outcome in comatose post cardiac arrest patients [D].
6.2.7 Until more is known about the impact of therapeutic hypothermia, prognostication should probably be delayed but the optimal time has yet to be determined [D].

7. Information about post resuscitation care for relatives and carers

This section about information for relatives and carers aims to help doctors answer the most likely questions they may be faced with. Unlike other devastating illnesses where a relative's condition may have deteriorated over time, the relative of a cardiac arrest patient may have had normality suddenly shattered. They are consequently often much more afraid. As little medical jargon as possible should be used. A suggested scheme is as follows:

1. What has happened to my relative?
   They have had a period where their heart has stopped beating. Not enough blood and oxygen has gone to their brain and that is why they are not conscious.

2. What has caused it?
   There could be several explanations. One possibility is that an artery supplying the heart with blood and oxygen has become blocked and this has stopped the heart beating. We will need to do more tests.

3. Why are they still asleep?
   There are probably several reasons for this. Sometimes when the heart has stopped beating for a period of time, acids and other substances build up in the blood, which can impair consciousness.

4. Why are they being admitted to an Intensive Care Unit?
   There is some evidence that if your relative has a low level of consciousness after their heart has stopped beating for a period, then they should be looked after in a particular way. This may include lowering their body temperature,

controlling their blood sugar, stopping any fitting, controlling their blood pressure and the amount of oxygen they are receiving.
If the cause is a blocked artery supplying blood to the heart, they may need to get the artery opened up.

5. Will they be brain damaged?
In the first few days, it is difficult to predict this with certainty. We will need to do some tests and allow some time for potential recovery to occur.

6. Will they survive?
This will depend on a lot of factors. Statistically, if you look at all patients in a similar situation admitted to an Intensive Care Unit, they have a just over 40% chance of surviving to discharge from ICU but unfortunately not all of these patients will survive to leave hospital.

8. Implementation, resource issues, and audit

8.1 Local implementation

There is evidence that implementation of mild hypothermia after cardiac arrest has been slow in most of the developed world – several surveys from the last two years suggested that only about 25% of ICUs had ever used this therapy [3].[215-218] However, successful implementation of hypothermia has now been described by many centres [2+].[15,38,39,59,114,219]

A ‘post cardiac arrest care bundle’ has been proposed and comprises [4]:[12]

1. Early coronary reperfusion and haemodynamic optimisation
2. Control of ventilation
3. Blood glucose control
4. Temperature control
5. Treatment of seizures.

Local implementation of the post cardiac arrest care bundle requires collaboration among doctors and nurses across several different specialities, but particularly critical care, emergency medicine and cardiology. Local protocols for the application of the care bundle should be developed jointly by representatives of all these disciplines.

8.2 Resource implications

Many of the interventions applied in the post resuscitation period do not require expensive equipment. The more expensive cooling systems have some advantages but are by no means essential. Maintenance of an adequate mean arterial blood pressure and control of blood glucose are also relatively inexpensive interventions. In some healthcare systems, the lack of 24 hour interventional cardiology systems makes it difficult to implement timely PCI, but in most cases it should still be possible to achieve early reperfusion with thrombolytic therapy. The use of hypothermia should not extend the length of ICU stay significantly but the data to confirm this are awaited.

8.3 Key points for audit

Implementation of the post cardiac arrest care bundle should be the subject of regular audit. The outcome of patients admitted to ICU after cardiac arrest should be the subject of regular and ongoing audit.

8.4 Recommendations for research

The following critical knowledge gaps relating to the post resuscitation period have adapted from those compiled by AHA/ILCOR working groups [4].[10,220] Further research is required on these topics.

8.4.1 Epidemiology

1. What process can be developed to monitor trends in post-cardiac arrest outcomes in the UK?

8.4.2 Pathophysiology

1. Mechanisms and time course of post-cardiac arrest coma
2. Mechanisms and duration of post-cardiac arrest delayed neurodegeneration
3. Mechanisms and duration of post-cardiac arrest myocardial dysfunction
4. Mechanisms and duration of impaired oxygen delivery and utilisation post-cardiac arrest
5. The role of intravascular coagulation in post-cardiac arrest organ dysfunction and failure
6. The mechanism, duration and significance of post-cardiac arrest adrenal insufficiency

8.4.3 Therapy

1. Optimal application of therapeutic hypothermia in the post-cardiac arrest patient.
    a. Which patients benefit?
    b. The optimal target temperature, onset, duration, and rewarming rate
    c. The most effective cooling technique – external versus internal
    d. The indications for neuromuscular blockade
2. Indications for early percutaneous coronary intervention
3. Optimal therapy for post-cardiac arrest myocardial dysfunction
        a. drugs
        b. mechanical
4. The clinical benefit of controlled reoxygenation
5. The clinical benefit of protocolised early hemodynamic optimisation
6. Optimal goals (parameters and target ranges) for early hemodynamic optimization
    a. Mean arterial pressure
    b. Central venous pressure
    c. Central versus mixed venous oxygen saturation
    d. Haemoglobin concentration and transfusion trigger
    e. Lactate concentration
    f. Urine output
    g. Oxygen delivery
    h. Other
7. The clinical benefit of glucose control and the optimal target glucose range?
8. Role of high-volume haemofiltration
9. Role of early glucocorticoid therapy
10. Role of prophylactic anticonvulsants
11. Role of a defined period of sedation and ventilation
12. Role of neuroprotective drugs

8.4.4 Prognosis

1. Optimal decision rule for prognostication of futility
2. The impact of therapeutic hypothermia on the reliability of prognostication of futility

8.4.5 Paediatrics

1. Evidence specific to children for the knowledge gaps listed above
2. Role of ECMO in cardiac arrest in children and post-arrest support?

8.4.5 Barriers

1. The most effective approach to implement therapeutic hypothermia and optimized post-cardiac arrest care
2. The value of regionalisation of post-cardiac arrest care to specialised centres?

9. References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349: 1269-76.
2. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001; 104: 2158-63.
3. Pell JP, Sirel JM, Marsden AK, et al. Presentation, management, and outcome of out of hospital cardiopulmonary arrest: comparison by underlying aetiology. Heart 2003; 89: 839-42.
4. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA 2002; 288: 3008-13.
5. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005; 67: 75-80.
6. Hodgetts TJ, Kenward G, Vlackonikolis I, et al. Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. Resuscitation 2002; 54: 115-23.
7. Gwinnutt CL, Columb M, Harris R. Outcome after cardiac arrest in adults in UK hospitals: effect of the 1997 guidelines. Resuscitation 2000; 47: 125-35.
8. Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation 2003; 58: 297-308.
9. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002; 106: 562-8.
10. Neumar R, Nolan JP. AHA/ILCOR Post-Cardiac Arrest Statement of Science. Circulation 2008; In Press.
11. Soar J, Nolan JP. Mild hypothermia for post cardiac arrest syndrome. BMJ 2007; 335: 459-60.
12. Nolan JP, Soar J. Post resuscitation care – time for a care bundle? Resuscitation 2008; 76.
13. Nolan JP, Laver SR, Welch CA, et al. Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC Case Mix Programme Database. Anaesthesia 2007; 62: 1207-16.
14. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004; 30: 2126-8.
15. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007.
16. Langhelle A, Tyvold SS, Lexow K, et al. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. Resuscitation 2003; 56: 247-63.
17. Langhelle A, Nolan J, Herlitz J, et al. Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: the Utstein style. Resuscitation 2005; 66: 271-83.
18. Herlitz J, Engdahl J, Svensson L, et al. Major differences in 1-month survival between hospitals in Sweden among initial survivors of out-of-hospital cardiac arrest. Resuscitation 2006; 70: 404-9.
19. International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2005; 67: 157-341.
20. Sundgreen C, Larsen FS, Herzog TM, et al. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001; 32: 128-32.

21. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke 1997; 28: 1569-73.
22. Buunk G, van der Hoeven JG, Meinders AE. A comparison of near-infrared spectroscopy and jugular bulb oximetry in comatose patients resuscitated from a cardiac arrest. Anaesthesia 1998; 53: 13-9.
23. Roine RO, Launes J, Nikkinen P, Lindroth L, Kaste M. Regional cerebral blood flow after human cardiac arrest. A hexamethylpropyleneamine oxime single photon emission computed tomographic study. Arch Neurol 1991; 48: 625-9.
24. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. Stroke 1978; 9: 569-73.
25. Buunk G, van der Hoeven JG, Frolich M, Meinders AE. Cerebral vasoconstriction in comatose patients resuscitated from a cardiac arrest? Intensive Care Med 1996; 22: 1191-6.
26. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991; 75: 731-9.
27. Vereczki V, Martin E, Rosenthal RE, et al. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. J Cereb Blood Flow Metab 2006; 26: 821-35.
28. Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. Stroke 2007; 38: 1578-84.
29. Balan IS, Fiskum G, Hazelton J, Cotto-Cumba C, Rosenthal RE. Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest. Stroke 2006; 37: 3008-13.
30. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001; 345: 1473-82.
31. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998; 98: 2334-51.
32. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997; 336: 1629-33.
33. Bendz B, Eritsland J, Nakstad AR, et al. Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous coronary intervention. Resuscitation 2004; 63: 49-53.
34. Keelan PC, Bunch TJ, White RD, Packer DL, Holmes DR, Jr. Early direct coronary angioplasty in survivors of out-of-hospital cardiac arrest. Am J Cardiol 2003; 91: 1461-3, A6.
35. Quintero-Moran B, Moreno R, Villarreal S, et al. Percutaneous coronary intervention for cardiac arrest secondary to ST-elevation acute myocardial infarction. Influence of immediate paramedical/medical assistance on clinical outcome. J Invasive Cardiol 2006; 18: 269-72.
36. Garot P, Lefevre T, Eltchaninoff H, et al. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. Circulation 2007; 115: 1354-62.
37. Gorjup V, Radsel P, Kocjancic ST, Erzen D, Noc M. Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. Resuscitation 2007; 72: 379-85.
38. Hovdenes J, Laake JH, Aaberge L, Haugaa H, Bugge JF. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. Acta Anaesthesiol Scand 2007; 51: 137-42.

39. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. Resuscitation 2007; 74: 227-34.
40. Bottiger BW, Bode C, Kern S, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. Lancet 2001; 357: 1583-5.
41. van Campen LC, van Leeuwen GR, Verheugt FW. Safety and efficacy of thrombolysis for acute myocardial infarction in patients with prolonged out-of-hospital cardiopulmonary resuscitation. Am J Cardiol 1994; 73: 953-5.
42. Abu-Laban RB, Christenson JM, Innes GD, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med 2002; 346: 1522-8.
43. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Part 5: Acute coronary syndromes. Resuscitation 2005; 67: 249-69.
44. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003; 349: 733-42.
45. Berger PB, Ellis SG, Holmes DR, Jr., et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Circulation 1999; 100: 14-20.
46. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. N Engl J Med 1997; 336: 1621-8.
47. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999; 341: 625-34.
48. Widimsky P, Budesinsky T, Vorac D, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial--PRAGUE-2. Eur Heart J 2003; 24: 94-104.
49. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2-4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. Eur Heart J 2002; 23: 550-7.
50. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation 2003; 108: 1809-14.
51. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003; 361: 13-20.
52. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review [published correction appears in *JAMA.* 1998;279:1876]. JAMA 1997; 278: 2093-8.
53. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet 2006; 367: 579-88.

54. Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002; 40: 2110-6.
55. Ruiz-Bailen M, Aguayo de Hoyos E, Ruiz-Navarro S, et al. Reversible myocardial dysfunction after cardiopulmonary resuscitation. Resuscitation 2005; 66: 175-81.
56. Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol 1996; 28: 232-40.
57. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002; 106: 562-8.
58. Mullner M, Sterz F, Binder M, et al. Arterial blood pressure after human cardiac arrest and neurological recovery. Stroke 1996; 27: 59-62.
59. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med 2006; 34: 1865-73.
60. Myerburg RJ, Briese FW, Conde C, et al. Long-term antiarrhythmic therapy in survivors of prehospital cardiac arrest. Initial 18 months' experience. JAMA 1977; 238: 2621-4.
61. Somberg JC, Laux B, Wynn J, Keefe D, Miura DS. Lorcainide therapy in a cardiac arrest population. Am Heart J 1986; 111: 648-53.
62. Moosvi AR, Goldstein S, VanderBrug Medendorp S, et al. Effect of empiric antiarrhythmic therapy in resuscitated out-of-hospital cardiac arrest victims with coronary artery disease. Am J Cardiol 1990; 65: 1192-7.
63. Haverkamp W, Martinez-Rubio A, Hief C, et al. Efficacy and safety of d,l-sotalol in patients with ventricular tachycardia and in survivors of cardiac arrest. J Am Coll Cardiol 1997; 30: 487-95.
64. Hallstrom AP, Cobb LA, Yu BH, Weaver WD, Fahrenbruch CE. An antiarrhythmic drug experience in 941 patients resuscitated from an initial cardiac arrest between 1970 and 1985. Am J Cardiol 1991; 68: 1025-31.
65. Peter T, Hamer A, Weiss D, Mandel WJ. Prognosis after sudden cardiac death without associated myocardial infarction: one year follow-up of empiric therapy with amiodarone. Am Heart J 1984; 107: 209-13.
66. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). The CASCADE Investigators. Am J Cardiol 1993; 72: 280-7.
67. Wever EFD, Hauer RNW, Van Capelle FJL, et al. Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. Circulation 1995; 91: 2195-203.
68. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 1997; 337: 1576-83.
69. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000; 101: 1297-302.
70. Connolly SJ, Hallstrom AP, Cappato R, et al. Metal-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J 2000; 21: 2071-8.
71. Hennersdorf MG, Niebch V, Vester EG, et al. Long-term follow-up of sudden cardiac arrest survivors and electrophysiologically guided antiarrhythmic therapy. Cardiology 2003; 99: 190-7.
72. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from

implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. Jama 2006; 295: 165-71.
73. Martin GB, Nowak RM, Cisek JE, Carden DL, Tomlanovich MC. Hyperkalemia during human cardiopulmonary resuscitation: incidence and ramifications. J Emerg Med 1989; 7: 109-13.
74. Hekimian G, Baugnon T, Thuong M, et al. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. Shock 2004; 22: 116-9.
75. Schultz CH, Rivers EP, Feldkamp CS, et al. A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest. Crit Care Med 1993; 21: 1339-47.
76. Pene F, Hyvernat H, Mallet V, et al. Prognostic value of relative adrenal insufficiency after out-of-hospital cardiac arrest. Intensive Care Med 2005; 31: 627-33.
77. Kim JJ, Lim YS, Shin JH, et al. Relative adrenal insufficiency after cardiac arrest: impact on postresuscitation disease outcome. Am J Emerg Med 2006; 24: 684-8.
78. Miller JB, Donnino MW, Rogan M, Goyal N. Relative adrenal insufficiency in post-cardiac arrest shock is under-recognized. Resuscitation 2007.
79. Tsai MS, Huang CH, Chang WT, et al. The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 2007; 25: 318-25.
80. Adrie C, Monchi M, Laurent I, et al. Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: implication of the protein C anticoagulant pathway. J Am Coll Cardiol 2005; 46: 21-8.
81. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005; 46: 432-7.
82. Neumar RW. Molecular mechanisms of ischemic neuronal injury. Ann Emerg Med 2000; 36: 483-506.
83. Lipton P. Ischemic cell death in brain neurons. Physiol Rev 1999; 79: 1431-568.
84. Bano D, Nicotera P. Ca2+ signals and neuronal death in brain ischemia. Stroke 2007; 38: 674-6.
85. Ames A, 3rd, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia. II. The no-reflow phenomenon. Am J Pathol 1968; 52: 437-53.
86. Wolfson SK, Jr., Safar P, Reich H, et al. Dynamic heterogeneity of cerebral hypoperfusion after prolonged cardiac arrest in dogs measured by the stable xenon/CT technique: a preliminary study. Resuscitation 1992; 23: 1-20.
87. Nishizawa H, Kudoh I. Cerebral autoregulation is impaired in patients resuscitated after cardiac arrest. Acta Anaesthesiol Scand 1996; 40: 1149-53.
88. Angelos MG, Ward KR, Hobson J, Beckley PD. Organ blood flow following cardiac arrest in a swine low-flow cardiopulmonary bypass model. Resuscitation 1994; 27: 245-54.
89. Buunk G, van der Hoeven JG, Meinders AE. Cerebral blood flow after cardiac arrest. Neth J Med 2000; 57: 106-12.
90. Sakabe T, Tateishi A, Miyauchi Y, et al. Intracranial pressure following cardiopulmonary resuscitation. Intensive Care Med 1987; 13: 256-9.
91. Morimoto Y, Kemmotsu O, Kitami K, Matsubara I, Tedo I. Acute brain swelling after out-of-hospital cardiac arrest: pathogenesis and outcome. Crit Care Med 1993; 21: 104-10.
92. Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest. Stroke 2000; 31: 2163-7.

93. Iida K, Satoh H, Arita K, et al. Delayed hyperemia causing intracranial hypertension after cardiopulmonary resuscitation. Crit Care Med 1997; 25: 971-6.
94. Rello J, Diaz E, Roque M, Valles J. Risk factors for developing pneumonia within 48 hours of intubation. Am J Respir Crit Care Med 1999; 159: 1742-6.
95. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007; 35: 2196-204.
96. Zandbergen EG, Hijdra A, Koelman JH, et al. Prediction of poor outcome within the first 3 days of postanoxic coma. Neurology 2006; 66: 62-8.
97. Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. Neurology 1988; 38: 401-5.
98. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. JAMA 1985; 253: 1420-6.
99. Snyder BD, Hauser WA, Loewenson RB, et al. Neurologic prognosis after cardiopulmonary arrest, III: seizure activity. Neurology 1980; 30: 1292-7.
100. Ingvar M. Cerebral blood flow and metabolic rate during seizures. Relationship to epileptic brain damage. Ann N Y Acad Sci 1986; 462: 194-206.
101. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol 2004; 3: 598-607.
102. Wijdicks EF. Propofol in myoclonus status epilepticus in comatose patients following cardiac resuscitation. J Neurol Neurosurg Psychiatry 2002; 73: 94-5.
103. Rundgren M, Rosen I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med 2006; 32: 836-42.
104. Takino M, Okada Y. Hyperthermia following cardiopulmonary resuscitation. Intensive Care Med 1991; 17: 419-20.
105. Takasu A, Saitoh D, Kaneko N, Sakamoto T, Okada Y. Hyperthermia: is it an ominous sign after cardiac arrest? Resuscitation 2001; 49: 273-7.
106. Hickey RW, Kochanek PM, Ferimer H, et al. Induced hyperthermia exacerbates neurologic neuronal histologic damage after asphyxial cardiac arrest in rats. Crit Care Med 2003; 31: 531-5.
107. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001; 161: 2007-12.
108. Coimbra C, Boris-Moller F, Drake M, Wieloch T. Diminished neuronal damage in the rat brain by late treatment with the antipyretic drug dipyrone or cooling following cerebral ischemia. Acta Neuropathol (Berl) 1996; 92: 447-53.
109. Coimbra C, Drake M, Boris-Moller F, Wieloch T. Long-lasting neuroprotective effect of postischemic hypothermia and treatment with an anti-inflammatory/antipyretic drug: evidence for chronic encephalopathic processes following ischemia. Stroke 1996; 27: 1578-85.
110. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346: 549-56.
111. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346: 557-63.
112. Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med 2005; 33: 414-8.

113. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 1997; 30: 146-53.
114. Busch M, Soreide E, Lossius HM, Lexow K, Dickstein K. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. Acta Anaesthesiol Scand 2006; 50: 1277-83.
115. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007; 35: 1041-7.
116. Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. Stroke 2006; 37: 1792-7.
117. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation 2001; 51: 275-81.
118. Kim F, Olsufka M, Longstreth WT, Jr., et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation 2007; 115: 3064-70.
119. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 2003; 56: 9-13.
120. Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation 2004; 62: 299-302.
121. Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. Resuscitation 2004; 62: 143-50.
122. Kliegel A, Losert H, Sterz F, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest--a feasibility study. Resuscitation 2005; 64: 347-51.
123. Haugk M, Sterz F, Grassberger M, et al. Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. Resuscitation 2007.
124. Kim F, Olsufka M, Carlbom D, et al. Pilot study of rapid infusion of 2 L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. Circulation 2005; 112: 715-9.
125. Polderman KH, Rijnsburger ER, Peerdeman SM, Girbes AR. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. Crit Care Med 2005; 33: 2744-51.
126. Kliegel A, Janata A, Wandaller C, et al. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation 2007; 73: 46-53.
127. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med 2004; 32: 1489-95.
128. Keller E, Imhof HG, Gasser S, Terzic A, Yonekawa Y. Endovascular cooling with heat exchange catheters: a new method to induce and maintain hypothermia. Intensive Care Med 2003; 29: 939-43.
129. Schmutzhard E, Engelhardt K, Beer R, et al. Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients: a prospective pilot study. Crit Care Med 2002; 30: 2481-8.

130. Guluma KZ, Hemmen TM, Olsen SE, Rapp KS, Lyden PD. A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. Acad Emerg Med 2006; 13: 820-7.
131. Agnew DM, Koehler RC, Guerguerian AM, et al. Hypothermia for 24 hours after asphyxic cardiac arrest in piglets provides striatal neuroprotection that is sustained 10 days after rewarming. Pediatr Res 2003; 54: 253-62.
132. Hicks SD, DeFranco DB, Callaway CW. Hypothermia during reperfusion after asphyxial cardiac arrest improves functional recovery and selectively alters stress-induced protein expression. J Cereb Blood Flow Metab 2000; 20: 520-30.
133. Sterz F, Safar P, Tisherman S, et al. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 1991; 19: 379-89.
134. Xiao F, Safar P, Radovsky A. Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats. Am J Emerg Med 1998; 16: 17-25.
135. Katz LM, Young AS, Frank JE, Wang Y, Park K. Regulated hypothermia reduces brain oxidative stress after hypoxic-ischemia. Brain Res 2004; 1017: 85-91.
136. Abella BS, Zhao D, Alvarado J, et al. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. Circulation 2004; 109: 2786-91.
137. Lawrence EJ, Dentcheva E, Curtis KM, et al. Neuroprotection with delayed initiation of prolonged hypothermia after in vitro transient global brain ischemia. Resuscitation 2005; 64: 383-8.
138. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993; 21: 1348-58.
139. Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol 2008.
140. Hovland A, Nielsen EW, Kluver J, Salvesen R. EEG should be performed during induced hypothermia. Resuscitation 2006; 68: 143-6.
141. Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurg 2001; 94: 697-705.
142. Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality--Part 2: Practical aspects and side effects. Intensive Care Med 2004; 30: 757-69.
143. Calle PA, Buylaert WA, Vanhaute OA. Glycemia in the post-resuscitation period. The Cerebral Resuscitation Study Group. Resuscitation 1989; 17 Suppl: S181-8; discussion S99-206.
144. Longstreth WT, Jr., Diehr P, Inui TS. Prediction of awakening after out-of-hospital cardiac arrest. N Engl J Med 1983; 308: 1378-82.
145. Longstreth WT, Jr., Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. Ann Neurol 1984; 15: 59-63.
146. Longstreth WT, Jr., Copass MK, Dennis LK, et al. Intravenous glucose after out-of-hospital cardiopulmonary arrest: a community-based randomized trial. Neurology 1993; 43: 2534-41.
147. Mackenzie CF. A review of 100 cases of cardiac arrest and the relation of potassium, glucose, and haemoglobin levels to survival. West Indian Med J 1975; 24: 39-45.
148. Mullner M, Sterz F, Binder M, et al. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. J Cereb Blood Flow Metab 1997; 17: 430-6.

149. Skrifvars MB, Pettila V, Rosenberg PH, Castren M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. Resuscitation 2003; 59: 319-28.
150. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001; 32: 2426-32.
151. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke 2003; 34: 2208-14.
152. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345: 1359-67.
153. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005; 64: 1348-53.
154. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354: 449-61.
155. Katz LM, Wang Y, Ebmeyer U, Radovsky A, Safar P. Glucose plus insulin infusion improves cerebral outcome after asphyxial cardiac arrest. Neuroreport 1998; 9: 3363-7.
156. Oksanen T, Skrifvars MB, Varpula T, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med 2007.
157. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA 2003; 290: 2041-7.
158. Losert H, Sterz F, Roine RO, et al. Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12h after cardiac arrest might not be necessary. Resuscitation 2007.
159. Marik PE, Varon J. Intensive insulin therapy in the ICU: is it now time to jump off the bandwagon? Resuscitation 2007; 74: 191-3.
160. Watkinson P, Barber VS, Young JD. Strict glucose control in the critically ill. BMJ 2006; 332: 865-6.
161. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 67: 203-10.
162. Skogvoll E, Isern E, Sangolt GK, Gisvold SE. In-hospital cardiopulmonary resuscitation. 5 years' incidence and survival according to the Utstein template. Acta Anaesthesiol Scand 1999; 43: 177-84.
163. Di Bari M, Chiarlone M, Fumagalli S, et al. Cardiopulmonary resuscitation of older, inhospital patients: immediate efficacy and long-term outcome. Crit Care Med 2000; 28: 2320-5.
164. Schwenzer KJ, Smith WT, Durbin CG, Jr. Selective application of cardiopulmonary resuscitation improves survival rates. Anesth Analg 1993; 76: 478-84.
165. Ballew KA, Philbrick JT, Caven DE, Schorling JB. Predictors of survival following in-hospital cardiopulmonary resuscitation. A moving target. Arch Intern Med 1994; 154: 2426-32.
166. Tunstall-Pedoe H, Bailey L, Chamberlain DA, et al. Survey of 3765 cardiopulmonary resuscitations in British hospitals (the BRESUS Study): methods and overall results. BMJ 1992; 304: 1347-51.
167. Cooper S, Janghorbani M, Cooper G. A decade of in-hospital resuscitation: outcomes and prediction of survival? Resuscitation 2006; 68: 231-7.

168. de Vos R, Koster RW, De Haan RJ, et al. In-hospital cardiopulmonary resuscitation: prearrest morbidity and outcome. Arch Intern Med 1999; 159: 845-50.
169. Cooper S, Cade J. Predicting survival, in-hospital cardiac arrests: resuscitation survival variables and training effectiveness. Resuscitation 1997; 35: 17-22.
170. Rogove HJ, Safar P, Sutton-Tyrrell K, Abramson NS. Old age does not negate good cerebral outcome after cardiopulmonary resuscitation: analyses from the brain resuscitation clinical trials. The Brain Resuscitation Clinical Trial I and II Study Groups. Crit Care Med 1995; 23: 18-25.
171. Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J 2006; 27: 2840-5.
172. Mullner M, Sterz F, Domanovits H, et al. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. Intensive Care Med 1997; 23: 1138-43.
173. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA 2004; 291: 870-9.
174. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 1994; 343: 1055-9.
175. Madl C, Grimm G, Kramer L, et al. Early prediction of individual outcome after cardiopulmonary resuscitation. Lancet 1993; 341: 855-8.
176. Chen R, Bolton CF, Young B. Prediction of outcome in patients with anoxic coma: a clinical and electrophysiologic study. Crit Care Med 1996; 24: 672-8.
177. Johkura K, Komiyama A, Kuroiwa Y. Vertical conjugate eye deviation in postresuscitation coma. Ann Neurol 2004; 56: 878-81.
178. Bassetti C, Bomio F, Mathis J, Hess CW. Early prognosis in coma after cardiac arrest: a prospective clinical, electrophysiological, and biochemical study of 60 patients. J Neurol Neurosurg Psychiatry 1996; 61: 610-5.
179. Wijdicks EF, Parisi JE, Sharbrough FW. Prognostic value of myoclonus status in comatose survivors of cardiac arrest. Ann Neurol 1994; 35: 239-43.
180. Cheliout-Heraut F, Durand MC, Clair B, Gajdos P, Raphael JC. [Importance of evoked potentials in the evolutive prognosis of coma during cerebral anoxia in adults]. Neurophysiol Clin 1992; 22: 269-80.
181. Pfeifer R, Borner A, Krack A, et al. Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation 2005; 65: 49-55.
182. Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 1998; 352: 1808-12.
183. Arnoldus EP, Lammers GJ. Postanoxic coma: good recovery despite myoclonus status. Ann Neurol 1995; 38: 697-8.
184. Harper SJ, Wilkes RG. Posthypoxic myoclonus (the Lance-Adams syndrome) in the intensive care unit. Anaesthesia 1991; 46: 199-201.
185. Morris HR, Howard RS, Brown P. Early myoclonic status and outcome after cardiorespiratory arrest. J Neurol Neurosurg Psychiatry 1998; 64: 267-8.
186. Edgren E, Hedstrand U, Nordin M, Rydin E, Ronquist G. Prediction of outcome after cardiac arrest. Crit Care Med 1987; 15: 820-5.
187. Hockaday JM, Potts F, Epstein E, Bonazzi A, Schwab RS. Electroencephalographic Changes in Acute Cerebral Anoxia from Cardiac or Respiratory Arrest. Electroencephalogr Clin Neurophysiol 1965; 18: 575-86.

188. Lemmi H, Hubbert CH, Faris AA. The electroencephalogram after resuscitation of cardiocirculatory arrest. J Neurol Neurosurg Psychiatry 1973; 36: 997-1002.
189. Young GB, Doig G, Ragazzoni A. Anoxic-ischemic encephalopathy: clinical and electrophysiological associations with outcome. Neurocrit Care 2005; 2: 159-64.
190. Berek K, Lechleitner P, Luef G, et al. Early determination of neurological outcome after prehospital cardiopulmonary resuscitation. Stroke 1995; 26: 543-9.
191. Madl C, Kramer L, Domanovits H, et al. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. Crit Care Med 2000; 28: 721-6.
192. Gendo A, Kramer L, Hafner M, et al. Time-dependency of sensory evoked potentials in comatose cardiac arrest survivors. Intensive Care Med 2001; 27: 1305-11.
193. Logi F, Fischer C, Murri L, Mauguiere F. The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol 2003; 114: 1615-27.
194. Tiainen M, Kovala TT, Takkunen OS, Roine RO. Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. Crit Care Med 2005; 33: 1736-40.
195. Tiainen M, Roine RO, Pettila V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003; 34: 2881-6.
196. Fogel W, Krieger D, Veith M, et al. Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. Crit Care Med 1997; 25: 1133-8.
197. Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. Stroke 1998; 29: 2363-6.
198. Dauberschmidt R, Zinsmeyer J, Mrochen H, Meyer M. Changes of neuron-specific enolase concentration in plasma after cardiac arrest and resuscitation. Mol Chem Neuropathol 1991; 14: 237-45.
199. Rosen H, Rosengren L, Herlitz J, Blomstrand C. Increased serum levels of the S-100 protein are associated with hypoxic brain damage after cardiac arrest. Stroke 1998; 29: 473-7.
200. Bottiger BW, Mobes S, Glatzer R, et al. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. Circulation 2001; 103: 2694-8.
201. Longstreth WT, Jr., Clayson KJ, Sumi SM. Cerebrospinal fluid and serum creatine kinase BB activity after out-of-hospital cardiac arrest. Neurology 1981; 31: 455-8.
202. Clemmensen P, Strandgaard S, Rasmussen S, Grande P. Cerebrospinal fluid creatine kinase isoenzyme BB levels do not predict the clinical outcome in patients unconscious following cardiac resuscitation. Clin Cardiol 1987; 10: 235-6.
203. Roine RO, Somer H, Kaste M, Viinikka L, Karonen SL. Neurological outcome after out-of-hospital cardiac arrest. Prediction by cerebrospinal fluid enzyme analysis. Arch Neurol 1989; 46: 753-6.
204. Tirschwell DL, Longstreth WT, Jr., Rauch-Matthews ME, et al. Cerebrospinal fluid creatine kinase BB isoenzyme activity and neurologic prognosis after cardiac arrest. Neurology 1997; 48: 352-7.
205. Rothstein TL, Thomas EM, Sumi SM. Predicting outcome in hypoxic-ischemic coma. A prospective clinical and electrophysiologic study. Electroencephalogr Clin Neurophysiol 1991; 79: 101-7.

206. Sherman AL, Tirschwell DL, Micklesen PJ, Longstreth WT, Jr., Robinson LR. Somatosensory potentials, CSF creatine kinase BB activity, and awakening after cardiac arrest. Neurology 2000; 54: 889-94.
207. Torbey MT, Geocadin R, Bhardwaj A. Brain arrest neurological outcome scale (BrANOS): predicting mortality and severe disability following cardiac arrest. Resuscitation 2004; 63: 55-63.
208. Schaafsma A, de Jong BM, Bams JL, et al. Cerebral perfusion and metabolism in resuscitated patients with severe post-hypoxic encephalopathy. J Neurol Sci 2003; 210: 23-30.
209. Wijdicks EF, Campeau NG, Miller GM. MR imaging in comatose survivors of cardiac resuscitation. AJNR Am J Neuroradiol 2001; 22: 1561-5.
210. Edgren E, Enblad P, Grenvik A, et al. Cerebral blood flow and metabolism after cardiopulmonary resuscitation. A pathophysiologic and prognostic positron emission tomography pilot study. Resuscitation 2003; 57: 161-70.
211. Martin GB, Paradis NA, Helpern JA, Nowak RM, Welch KM. Nuclear magnetic resonance spectroscopy study of human brain after cardiac resuscitation. Stroke 1991; 22: 462-8.
212. Arbelaez A, Castillo M, Mukherji SK. Diffusion-weighted MR imaging of global cerebral anoxia. AJNR Am J Neuroradiol 1999; 20: 999-1007.
213. Els T, Kassubek J, Kubalek R, Klisch J. Diffusion-weighted MRI during early global cerebral hypoxia: a predictor for clinical outcome? Acta Neurol Scand 2004; 110: 361-7.
214. Fukuoka N, Aibiki M, Tsukamoto T, Seki K, Morita S. Biphasic concentration change during continuous midazolam administration in brain-injured patients undergoing therapeutic moderate hypothermia. Resuscitation 2004; 60: 225-30.
215. Laver SR, Padkin A, Atalla A, Nolan JP. Therapeutic hypothermia aftre cardiac arrest. A survey of practice in intensive care units in the United Kingdom. Anaesthesia 2006; 61: 873-7.
216. Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. JAMA 2005; 293: 305-10.
217. Merchant RM, Soar J, Skrifvars MB, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. Crit Care Med 2006; 34: 1935-40.
218. Wolfrum S, Radke PW, Pischon T, et al. Mild therapeutic hypothermia after cardiac arrest - a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. Resuscitation 2007; 72: 207-13.
219. Scott BD, Hogue T, Fixley MS, Adamson PB. Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. Clin Cardiol 2006; 29: 525-9.
220. Gazmuri RJ, Nolan JP, Nadkarni VM, et al. Scientific knowledge gaps and clinical research priorities for cardiopulmonary resuscitation and emergency cardiovascular care identified during the 2005 International Consensus Conference on ECC and CPR Science with Treatment Recommendations A Consensus Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Stroke Council; and the Cardiovascular Nursing Council. Resuscitation 2007; 75: 400-11.

We would welcome comments on this document and suggestions for other standards in intensive care.
Please send any comments to: admin@ics.ac.uk