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European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015 Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015☆

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Summary of changes since 2010 guidelines

In 2010, post-resuscitation care was incorporated into the Advanced Life Support section of the European Resuscitation Council (ERC) Guidelines.[1] The ERC and the European Society of Intensive Care Medicine (ESICM) have collaborated to produce these post-resuscitation care guidelines, which recognise the importance of high-quality post-resuscitation care as a vital link in the Chain of Survival.[2] These post-resuscitation care guidelines are being co-published in *Resuscitation* and *Intensive Care Medicine*.

The most important changes in post-resuscitation care since 2010 include:

- There is a greater emphasis on the need for urgent coronary catheterisation and percutaneous coronary intervention (PCI) following out-of-hospital cardiac arrest of likely cardiac cause.
- Targeted temperature management remains important but there is now an option to target a temperature of 36 °C instead of the previously recommended 32–34 °C.
- Prognostication is now undertaken using a multimodal strategy and there is emphasis on allowing sufficient time for neurological recovery and to enable sedatives to be cleared.
- A novel section has been added which addresses rehabilitation after survival from a cardiac arrest. Recommendations include the systematic organisation of follow-up care, which should include screening for potential cognitive and emotional impairments and provision of information.

The international consensus on cardiopulmonary resuscitation science and the guidelines process

The International Liaison Committee on Resuscitation (ILCOR, www.ilcor.org) includes representatives from the American Heart Association (AHA), the European Resuscitation Council (ERC), the Heart and Stroke Foundation of Canada (HSFC), the Australian and New Zealand Committee on Resuscitation (ANZCOR), the Resuscitation Council of Southern Africa (RCSA), the Inter-American Heart Foundation (IAHF), and the Resuscitation Council of Asia (RCA). Since 2000, researchers from the ILCOR member councils have evaluated resuscitation science in 5-yearly cycles. The most recent International Consensus Conference was held in Dallas in February 2015 and the published conclusions and recommendations from this process form the basis of the ERC Guidelines 2015 and for these ERC-ESICM post-resuscitation care guidelines. During the three years leading up to this conference, 250 evidence reviewers

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from 39 countries reviewed thousands of relevant, peer-reviewed publications to address 169 specific resuscitation questions, each in the standard PICO (Population, Intervention, Comparison, Outcome) format. To assess the quality of the evidence and the strength of the recommendations, ILCOR adopted the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. Each PICO question was reviewed by at least two evidence reviewers who drafted a science statement based on their interpretation of all relevant data on the specific topic and the relevant ILCOR task force added consensus draft treatment recommendations. Final wording of science statements and treatment recommendations was completed after further review by ILCOR member organisations and by the editorial board, and published in *Resuscitation* and *Circulation* as the 2015 Consensus on Science and Treatment Recommendations (CoSTR). These ERC-ESICM guidelines on post-resuscitation care are based on the 2015 CoSTR document and represent consensus among the writing group, which included representatives of the ERC and the ESICM.

Introduction

Successful return of spontaneous circulation (ROSC) is the first step towards the goal of complete recovery from cardiac arrest. The complex pathophysiological processes that occur following whole body ischaemia during cardiac arrest and the subsequent reperfusion response during CPR and following successful resuscitation have been termed the post-cardiac arrest syndrome.[3] Depending on the cause of the arrest, and the severity of the post-cardiac arrest syndrome, many patients will require multiple organ support and the treatment they receive during this post-resuscitation period influences significantly the overall outcome and particularly the quality of neurological recovery.[4–11] 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., emergency room, cardiac catheterisation laboratory or intensive care unit (ICU)) for continued diagnosis, monitoring and treatment. The post-resuscitation care algorithm (Fig. 1) outlines some of the key interventions required to optimise outcome for these patients.

Some patients do awake rapidly following cardiac arrest – in some reports it is as high as 15–46% of the out-of hospital cardiac arrest patients admitted to hospital.[12–14] Response times, rates of bystander CPR, times to defibrillation and the duration of CPR impact on these numbers.[14] Although we have no data, it is reasonable to recommend that if there is any doubt about the patient's neurological function, the patient's trachea should be intubated and treatment to optimise haemodynamic, respiratory and metabolic variables, together with targeted temperature management started, following the local standardised treatment plan.

Of those comatose patients admitted to ICUs after cardiac arrest, as many as 40–50% survive to be discharged from hospital depending on the cause of arrest, system and quality of care.[7,10,13–20] Of the patients who survive to hospital discharge, the vast majority have a good neurological outcome although many with subtle cognitive impairment.[21–24]

Post-cardiac arrest syndrome

The post-cardiac arrest syndrome comprises post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, the systemic ischaemia/reperfusion response, and the persistent precipitating pathology.[3,25,26] The severity of this syndrome will vary with the duration and cause of cardiac arrest. It may not occur at all if the cardiac arrest is brief. Post-cardiac arrest brain injury manifests as coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction and brain death. Among patients surviving to ICU admission but subsequently dying in-hospital, brain injury is the cause of death in approximately two thirds after out-of hospital cardiac arrest and approximately 25% after in-hospital cardiac arrest.[27–30] Cardiovascular failure accounts for most deaths in the first three days, while brain injury accounts for most of the later deaths.[27,30,31] Withdrawal of life sustaining therapy (WLST) is the most frequent cause of death (approximately 50%) in patients with a prognosticated bad outcome,[14,30] emphasising the importance of the prognostication plan (see below). Post-cardiac arrest brain injury may be exacerbated by microcirculatory failure, impaired autoregulation, hypotension, hypercarbia, hypoxaemia, hyperoxaemia, pyrexia, hypoglycaemia, hyperglycaemia and seizures. Significant myocardial dysfunction is common after cardiac arrest but typically starts to recover by 2–3 days, although full recovery may take significantly longer.[32–34] The whole body ischaemia/reperfusion of cardiac arrest activates immune and coagulation pathways contributing to multiple organ failure and increasing the risk of infection.[35–41] Thus, the post-cardiac arrest syndrome has many features in common with sepsis, including intravascular volume depletion, vasodilation, endothelial injury and abnormalities of the microcirculation.[42–48]

Airway and breathing

Control of oxygenation

Patients who have had a brief period of cardiac arrest responding immediately to appropriate treatment may achieve an immediate return of normal cerebral function. These patients do not require tracheal intubation and ventilation but should be given with oxygen via a facemask if their arterial blood oxygen saturation is less than 94%. Hypoxaemia and hypercarbia both increase the likelihood of a further cardiac arrest and may contribute to secondary brain injury. Several animal studies indicate that hyperoxaemia early after ROSC causes oxidative stress and harms post-ischaemic neurones.[49–53] One animal study showed that adjusting the fractional inspired concentration (FiO_2) to produce an arterial oxygen saturation of 94–96% in the first hour after ROSC (controlled reoxygenation) achieved better neurological outcomes than achieved with the delivery of 100% oxygen.[54] One clinical registry study that included more than 6000 patients supports the animal data and shows post-resuscitation hyperoxaemia in the first 24 h is associated with worse outcome, compared with both normoxaemia and hypoxaemia.[55] A further analysis by the same group showed that the association between hyperoxia and outcome was dose-dependent and that there was not a single threshold for harm.[56] An observational study that included only those patients treated with mild induced hypothermia also showed an association between hyperoxia and poor outcome.[57] In contrast, an observational study of over 12,000 post-cardiac arrest patients showed that after adjustment for the inspired oxygenation concentration and other relevant covariates (including sickness severity), hyperoxia was no longer associated with mortality.[58] A meta-analysis of 14 observational studies showed significant heterogeneity across studies.[59]

The animal studies showing a relationship between hyperoxia and worse neurological outcome after cardiac arrest have generally evaluated the effect of hyperoxia in the first hour after ROSC. There are significant practical challenges with the titration of inspired oxygen concentration immediately after ROSC, particularly in the out-of hospital setting. The only prospective clinical study to

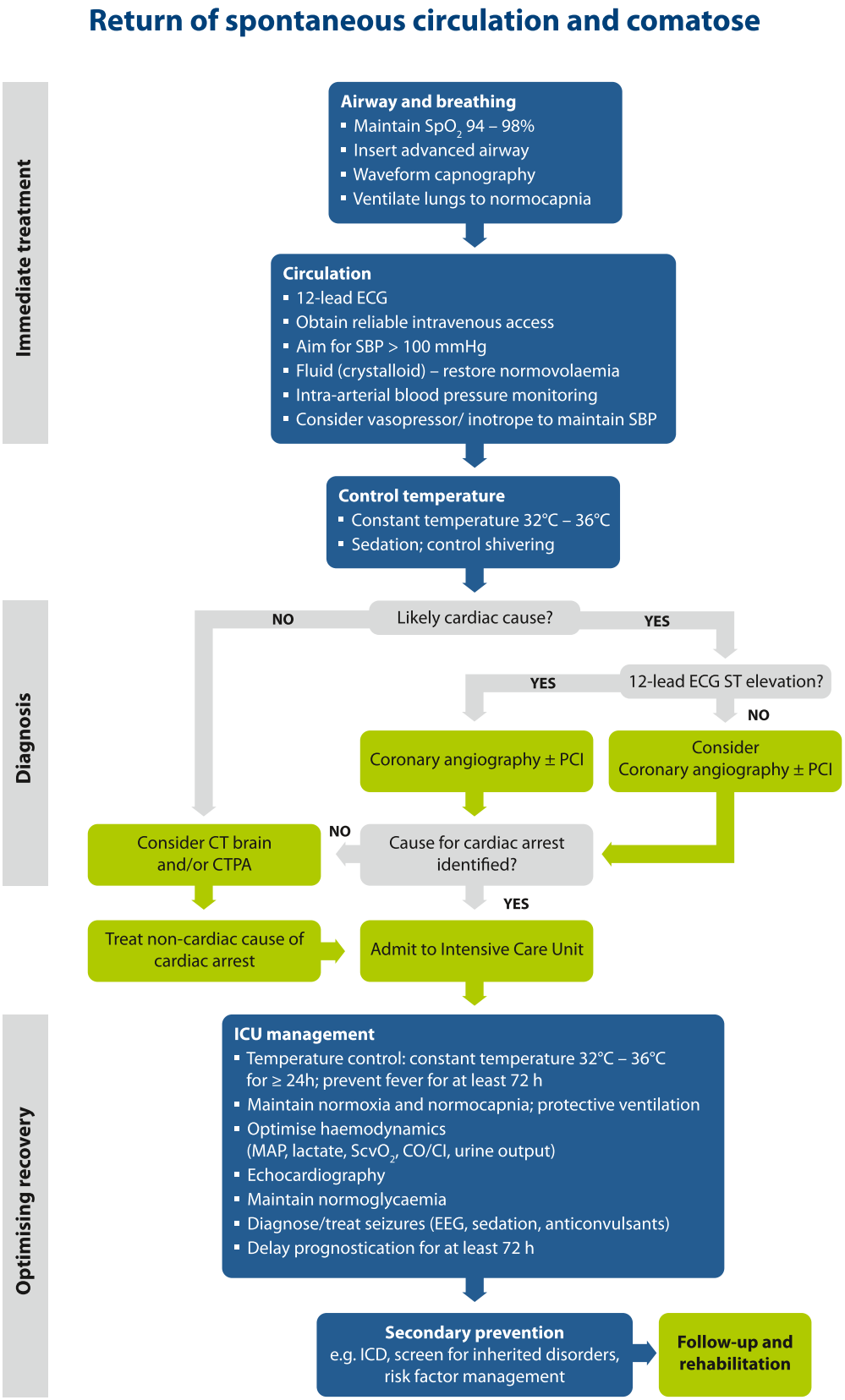

Fig. 5.1. Post-resuscitation care algorithm. SBP: systolic blood pressure; PCI: percutaneous coronary intervention; CTPA: computed tomography pulmonary angiogram; ICU: intensive care unit; MAP: mean arterial pressure; $ScvO_2$: central venous oxygenation; CO/CI: cardiac output/cardiac index; EEG: electroencephalography; ICD: implanted cardioverter defibrillator.

compare oxygen titrated to a target range (in this case 90–94% oxygen saturation) versus giving 100% oxygen after out of hospital cardiac arrest was stopped after enrolling just 19 patients because it proved very difficult to obtain reliable arterial blood oxygen saturation values using pulse oximetry.[60] A recent study of air versus supplemental oxygen in ST-elevation myocardial infarction showed that supplemental oxygen therapy increased myocardial injury, recurrent myocardial infarction and major cardiac arrhythmia and was associated with larger infarct size at 6 months.[61]

Given the evidence of harm after myocardial infarction and the possibility of increased neurological injury after cardiac arrest, as soon as arterial blood oxygen saturation can be monitored reliably (by blood gas analysis and/or pulse oximetry), titrate the inspired oxygen concentration to maintain the arterial blood oxygen saturation in the range of 94–98%. Avoid hypoxaemia, which is also harmful – ensure reliable measurement of arterial oxygen saturation before reducing the inspired oxygen concentration.

Control of ventilation

Consider tracheal intubation, sedation and controlled ventilation in any patient with obtunded cerebral function. Ensure the tracheal tube is positioned correctly, well above the carina. Hypocarbia causes cerebral vasoconstriction and a decreased cerebral blood flow.[62] After cardiac arrest, hypocapnia induced by hyperventilation causes cerebral ischaemia.[63–67] Observational studies using cardiac arrest registries document an association between hypocapnia and poor neurological outcome.[68,69] Two observation studies have documented an association with mild hypercapnia and better neurological outcome among post-cardiac arrest patients in the ICU.[69,70] Until prospective data are available, it is reasonable to adjust ventilation to achieve normocarbia and to monitor this using the end-tidal CO_2 and arterial blood gas values. Lowering the body temperature decreases the metabolism and may increase the risk of hypocapnia during the temperature intervention.[71]

Although protective lung ventilation strategies have not been studied specifically in post-cardiac arrest patients, given that these patients develop a marked inflammatory response, it seems rational to apply protective lung ventilation: tidal volume 6–8 ml kg^{-1} ideal body weight and positive end expiratory pressure 4–8 cm H_2O.[48,72]

Insert a gastric tube to decompress the stomach; gastric distension caused by mouth-to-mouth or bag-mask ventilation will splint the diaphragm and impair ventilation. Give adequate doses of sedative, which will reduce oxygen consumption. A sedation protocol is highly recommended. Bolus doses of a neuromuscular blocking drug may be required, particularly if using targeted temperature management (TTM) (see below). Limited evidence shows that short-term infusion ($\leq$48 h) of short-acting neuromuscular blocking drugs given to reduce patient-ventilator dysynchrony and risk of barotrauma in ARDS patients is not associated with an increased risk of ICU-acquired weakness and may improve outcome in these patients.[73] There are some data suggesting that continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients[74]; however, infusions of neuromuscular blocking drugs interfere with clinical examination and may mask seizures. Continuous electroencephalography (EEG) is recommended to detect seizures in these patients, especially when neuromuscular blockade is used.[75] Obtain a chest radiograph to check the position of the tracheal tube, gastric tube and central venous lines, assess for pulmonary oedema, and detect complications from CPR such as a pneumothorax associated with rib fractures.[76,77]

Circulation

Coronary reperfusion

Acute coronary syndrome (ACS) is a frequent cause of out-of-hospital cardiac arrest (OHCA): in a recent meta-analysis, the prevalence of an acute coronary artery lesion ranged from 59% to 71% in OHCA patients without an obvious non-cardiac aetiology.[78] Since the publication of a pioneering study in 1997,[79] many observational studies have shown that emergent cardiac catheterisation laboratory evaluation, including early percutaneous coronary intervention (PCI), is feasible in patients with ROSC after cardiac arrest.[80,81] The invasive management (i.e., early coronary angiography followed by immediate PCI if deemed necessary) of these patients, particularly those having prolonged resuscitation and nonspecific ECG changes, has been controversial because of the lack of specific evidence and significant implications on use of resources (including transfer of patients to PCI centres).

Percutaneous coronary intervention following ROSC with ST-elevation

In patients with ST segment elevation (STE) or left bundle branch block (LBBB) on the post-ROSC electrocardiogram (ECG) more than 80% will have an acute coronary lesion.[82] There are no randomised studies but given that many observational studies reported increased survival and neurologically favourable outcome, it is highly probable that early invasive management is beneficial in STE patients.[83] Based on available data, emergent cardiac catheterisation laboratory evaluation (and immediate PCI if required) should be performed in adult patients with ROSC after OHCA of suspected cardiac origin with STE on the ECG. This recommendation is based on low quality of evidence from selected populations. Observational studies also indicate that optimal outcomes after OHCA are achieved with a combination of TTM and PCI, which can be included in a standardised post-cardiac arrest protocol as part of an overall strategy to improve neurologically intact survival.[81,84,85]

Percutaneous coronary intervention following ROSC without ST-elevation

In contrast to the usual presentation of ACS in non-cardiac arrest patients, the standard tools to assess coronary ischaemia in cardiac arrest patients are less accurate. The sensitivity and specificity of the usual clinical data, ECG and biomarkers to predict an acute coronary artery occlusion as the cause of OHCA are unclear.[86–89] Several large observational series showed that absence of STE may also be associated with ACS in patients with ROSC following OHCA.[90–93] In these non-STE patients, there are conflicting data from observational studies on the potential benefit of emergent cardiac catheterisation laboratory evaluation.[92,94,95] A recent consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI) has emphasised that in OHCA patients, cardiac catheterisation should be performed immediately in the presence of ST-elevation and considered as soon as possible (less than 2 h) in other patients in the absence of an obvious non-coronary cause, particularly if they are haemodynamically unstable.[96] Currently, this approach in patients without STE remains controversial and is not accepted by all experts. However, it is reasonable to discuss and consider emergent cardiac catheterisation laboratory evaluation after ROSC in patients with the highest risk of a coronary cause for their cardiac arrest. Factors such as patient age, duration of CPR, haemodynamic instability, presenting cardiac rhythm, neurological status upon hospital arrival, and perceived likelihood of cardiac aetiology can influence

the decision to undertake the intervention in the acute phase or to delay it until later on in the hospital stay.

Indications and timing of computed tomography (CT) scanning

Cardiac causes of OHCA have been extensively studied in the last few decades; conversely, little is known on non-cardiac causes. Early identification of a respiratory or neurological cause would enable transfer of the patient to a specialised ICU for optimal care. Improved knowledge of prognosis also enables discussion about the appropriateness of specific therapies, including TTM. Early identification of a respiratory or neurological cause can be achieved by performing a brain and chest CT-scan at hospital admission, before or after coronary angiography. In the absence of signs or symptoms suggesting a neurological or respiratory cause (e.g., headache, seizures or neurological deficits for neurological causes, shortness of breath or documented hypoxia in patients suffering from a known and worsening respiratory disease) or if there is clinical or ECG evidence of myocardial ischaemia, coronary angiography is undertaken first, followed by CT scan in the absence of causative lesions. Several case series showed that this strategy enables diagnosis of non-cardiac causes of arrest in a substantial proportion of patients.[97,98] In those with cardiac arrest associated with trauma or haemorrhage a whole body CT scan may be indicated.[99,100]

Haemodynamic management

Post-resuscitation myocardial dysfunction causes haemodynamic instability, which manifests as hypotension, low cardiac index and arrhythmias.[32,101] Perform early echocardiography in all patients in order to detect and quantify the degree of myocardial dysfunction.[33,102] Post-resuscitation myocardial dysfunction often requires inotropic support, at least transiently. Based on experimental data, dobutamine is the most established treatment in this setting,[103,104] but the systematic inflammatory response that occurs frequently in post-cardiac arrest patients may also cause vasoplegia and severe vasodilation.[32] Thus, noradrenaline, with or without dobutamine, and fluid is usually the most effective treatment. Infusion of relatively large volumes of fluid is tolerated remarkably well by patients with post-cardiac arrest syndrome.[7,8,32] If treatment with fluid resuscitation, inotropes and vasoactive drugs is insufficient to support the circulation, consider insertion of a mechanical circulatory assistance device (e.g., IMPELLA, Abiomed, USA).[7,105]

Treatment may be guided by blood pressure, heart rate, urine output, rate of plasma lactate clearance, and central venous oxygen saturation. Serial echocardiography may also be used, especially in haemodynamically unstable patients. In the ICU an arterial line for continuous blood pressure monitoring is essential. Cardiac output monitoring may help to guide treatment in haemodynamically unstable patients but there is no evidence that its use affects outcome. Some centres still advocate use of an intra aortic balloon pump (IABP) in patients with cardiogenic shock, although the IABP-SHOCK II Trial failed to show that use of the IABP improved 30-day mortality in patients with myocardial infarction and cardiogenic shock.[106,107]

Similarly to the early goal-directed therapy that is recommended in the treatment of sepsis,[108] although challenged by several recent studies,[109–111] a bundle of therapies, including a specific blood pressure target, has been proposed as a treatment strategy after cardiac arrest.[8] However its influence on clinical outcome is not firmly established and optimal targets for mean arterial pressure and/or systolic arterial pressure remain unknown.[7,8,112–114] One observational study of 151 post-cardiac arrest patients identified an association between a time-weighted average mean arterial pressure (measured every 15 min) of greater than 70 mmHg and good neurological outcome.[113] A recent study showed an inverse relationship between mean arterial pressure and mortality.[101] However, whether the use of vasoactive drugs to achieve such a blood pressure target achieves better neurological outcomes remains unknown. In the absence of definitive data, target the mean arterial blood pressure to achieve an adequate urine output (1 ml kg^{-1} h^{-1}) and normal or decreasing plasma lactate values, taking into consideration the patient's normal blood pressure, the cause of the arrest and the severity of any myocardial dysfunction.[3] These targets may vary depending on individual physiology and co-morbid status. Importantly, hypothermia may increase urine output[115] and impair lactate clearance.[101]

Tachycardia was associated with bad outcome in one retrospective study.[116] During mild induced hypothermia the normal physiological response is bradycardia. In animal models this has been shown to reduce the diastolic dysfunction that usually is present early after cardiac arrest.[117] Bradycardia was previously considered to be a side effect, especially below a rate of 40 min^{-1}; however, recent retrospective studies have shown that bradycardia is associated with a good outcome.[118,119] As long as blood pressure, lactate, SvO_2 and urine output are sufficient, a bradycardia of $\leq$40 min^{-1} may be left untreated. Importantly, oxygen requirements during mild induced hypothermia are reduced.

Relative adrenal insufficiency occurs frequently after successful resuscitation from cardiac arrest and it appears to be associated with a poor prognosis when accompanied by post-resuscitation shock.[120,121] Two randomised controlled trials involving 368 patients with IHCA showed improved ROSC with the use of methylprednisolone and vasopressin in addition to adrenaline, compared with the use of placebo and adrenaline alone: combined RR 1.34 (95% CI 1.21–1.43).[122,123] No studies have assessed the effect of adding steroids alone to standard treatment for IHCA. These studies come from a single group of investigators and the population studied had very rapid advanced life support, a high incidence of asystolic cardiac arrest, and low baseline survival compared with other IHCA studies. Further confirmatory studies are awaited but, pending further data, do not give steroids routinely after IHCA. There is no clinical evidence for the routine use of steroids after OHCA.

Immediately after a cardiac arrest there is typically a period of hyperkalaemia. Subsequent endogenous catecholamine release and correction of metabolic and respiratory acidosis promotes intracellular transportation of potassium, causing hypokalaemia. Hypokalaemia may predispose to ventricular arrhythmias. Give potassium to maintain the serum potassium concentration between 4.0 and 4.5 mmol l^{-1}.

Implantable cardioverter defibrillators

Insertion of an implantable cardioverter defibrillator (ICD) should be considered in ischaemic patients with significant left ventricular dysfunction, who have been resuscitated from a ventricular arrhythmia that occurred later than 24–48 h after a primary coronary event.[124–126] ICDs may also reduce mortality in cardiac arrest survivors at risk of sudden death from structural heart diseases or inherited cardiomyopathies.[127,128] In all cases, a specialised electrophysiological evaluation should be performed before discharge for placement of an ICD for secondary prevention of sudden cardiac death.

Disability (optimising neurological recovery)

Cerebral perfusion

Animal studies show that immediately after ROSC there is a short period of multifocal cerebral no-reflow followed by transient

global cerebral hyperaemia lasting 15–30 min.[129–131] This is followed by up to 24 h of cerebral hypoperfusion while the cerebral metabolic rate of oxygen gradually recovers. After asphyxial cardiac arrest, brain oedema may occur transiently after ROSC but it is rarely associated with clinically relevant increases in intracranial pressure.[132,133] In many patients, autoregulation of cerebral blood flow is impaired (absent or right-shifted) for some time after cardiac arrest, which means that cerebral perfusion varies with cerebral perfusion pressure instead of being linked to neuronal activity.[134,135] In a study that used near-infrared spectroscopy to measure regional cerebral oxygenation, autoregulation was disturbed in 35% of post-cardiac arrest patients and the majority of these had been hypertensive before their cardiac arrest[136]; this tends to support the recommendation made in the 2010 ERC Guidelines: after ROSC, maintain mean arterial pressure near the patient's normal level.[1] However, there is a significant gap in the knowledge about how temperature impacts the optimal blood pressure.

Sedation

Although it has been common practice to sedate and ventilate patients for at least 24 h after ROSC, there are no high-level data to support a defined period of ventilation, sedation and neuromuscular blockade after cardiac arrest. Patients need to be sedated adequately during treatment with TTM, and the duration of sedation and ventilation is therefore influenced by this treatment. A meta-analysis of drugs used for sedation during mild induced hypothermia showed considerable variability among 68 ICUs in a variety of countries.[137] There are no data to indicate whether or not the choice of sedation influences outcome, but a combination of opioids and hypnotics is usually used. Short-acting drugs (e.g., propofol, alfentanil, remifentanil) will enable more reliable and earlier neurological assessment and prognostication (see Section 7).[138] Volatile anaesthetics have been used to sedate post cardiac arrest patients[139] but although there are some animal data suggesting myocardial and neurological benefits,[140] there are no clinical data showing an advantage with this strategy. Adequate sedation will reduce oxygen consumption. During hypothermia, optimal sedation can reduce or prevent shivering, which enables the target temperature to be achieved more rapidly. Use of published sedation scales for monitoring these patients (e.g., the Richmond or Ramsay Scales) may be helpful.[141,142]

Control of seizures

Seizures are common after cardiac arrest and occur in approximately one-third of patients who remain comatose after ROSC. Myoclonus is most common and occurs in 18–25%, the remainder having focal or generalised tonic–clonic seizures or a combination of seizure types.[31,143–145] Clinical seizures, including myoclonus may or may not be of epileptic origin. Other motor manifestations could be mistaken for seizures[146] and there are several types of myoclonus[147] the majority being non-epileptic. Use intermittent electroencephalography (EEG) to detect epileptic activity in patients with clinical seizure manifestations. Consider continuous EEG to monitor patients with a diagnosed status epilepticus and effects of treatment.

In comatose cardiac arrest patients, EEG commonly detects epileptiform activity. Unequivocal seizure activity according to strict EEG-terminology[148] is less common but post-anoxic status epilepticus was detected in 23–31% of patients using continuous EEG-monitoring and more inclusive EEG-criteria.[75,149,150] Patients with electrographic status epilepticus may or may not have clinically detectable seizure manifestations that may be masked by sedation. Whether systematic detection and treatment of electrographic epileptic activity improves patient outcome is not known.

Seizures may increase the cerebral metabolic rate[151] and have the potential to exacerbate brain injury caused by cardiac arrest: treat with sodium valproate, levetiracetam, phenytoin, benzodiazepines, propofol, or a barbiturate. Myoclonus can be particularly difficult to treat; phenytoin is often ineffective. Propofol is effective to suppress post-anoxic myoclonus.[152] Clonazepam, sodium valproate and levetiracetam are antimyoclonic drugs that may be effective in post-anoxic myoclonus.[147] After the first event, start maintenance therapy once potential precipitating causes (e.g., intracranial haemorrhage, electrolyte imbalance) are excluded.

The use of prophylactic anticonvulsant drugs after cardiac arrest in adults has been insufficiently studied.[153,154] Routine seizure prophylaxis in post-cardiac arrest patients is not recommended because of the risk of adverse effects and the poor response to antiepileptic agents among patients with clinical and electrographic seizures.

Myoclonus and electrographic seizure activity, including status epilepticus, are related to a poor prognosis but individual patients may survive with good outcome (see Section 7).[145,155] Prolonged observation may be necessary after treatment of seizures with sedatives, which will decrease the reliability of a clinical examination.[156]

Glucose control

There is a strong association between high blood glucose after resuscitation from cardiac arrest and poor neurological outcome.[13,15,20,157–163] Although one randomised controlled trial in a cardiac surgical intensive care unit showed that tight control of blood glucose (4.4–6.1 mmol l^{-1} or 80–110 mg dl^{-1}) using insulin reduced hospital mortality in critically ill adults,[164] a second study by the same group in medical ICU patients showed no mortality benefit from tight glucose control.[165] In one randomised trial of patients resuscitated from OHCA with ventricular fibrillation, strict glucose control (72–108 mg dl^{-1}, 4–6 mmol l^{-1}) gave no survival benefit compared with moderate glucose control (108–144 mg dl^{-1}, 6–8 mmol l^{-1}) and there were more episodes of hypoglycaemia in the strict glucose control group.[166] A large randomised trial of intensive glucose control (81 mg dl^{-1} – 108 mg dl^{-1}, 4.5–6.0 mmol l^{-1}) versus conventional glucose control (180 mg dl^{-1}, 10 mmol l^{-1} or less) in general ICU patients reported increased 90-day mortality in patients treated with intensive glucose control.[167,168] Severe hypoglycaemia is associated with increased mortality in critically ill patients,[169] and comatose patients are at particular risk from unrecognised hypoglycaemia. Irrespective of the target range, variability in glucose values is associated with mortality.[170] Compared with normothermia, mild induced hypothermia is associated with higher blood glucose values, increased blood glucose variability and greater insulin requirements.[171] Increased blood glucose variability is associated with increased mortality and unfavourable neurological outcome after cardiac arrest.[157,171]

Based on the available data, following ROSC maintain the blood glucose at $\leq$10 mmol l^{-1} (180 mg dl^{-1}) and avoid hypoglycaemia.[172] Do not implement strict glucose control in adult patients with ROSC after cardiac arrest because it increases the risk of hypoglycaemia.

Temperature control

Treatment of hyperpyrexia

A period of hyperthermia (hyperpyrexia) is common in the first 48 h after cardiac arrest.[13,173–176] Several studies document an association between post-cardiac arrest pyrexia and poor

outcomes.[13,173,175–178] The development of hyperthermia after a period of mild induced hypothermia (rebound hyperthermia) is associated with increased mortality and worse neurological outcome.[179–182] There are no randomised controlled trials evaluating the effect of treatment of pyrexia (defined as ≥37.6 °C) compared to no temperature control in patients after cardiac arrest and the elevated temperature may only be an effect of a more severely injured brain. Although the effect of elevated temperature on outcome is not proven, it seems reasonable to treat hyperthermia occurring after cardiac arrest with antipyretics and to consider active cooling in unconscious patients.

Targeted temperature management

Animal and human data indicate that mild induced hypothermia is neuroprotective and improves outcome after a period of global cerebral hypoxia-ischaemia.[183,184] Cooling suppresses many of the pathways leading to delayed cell death, including apoptosis (programmed cell death). Hypothermia decreases the cerebral metabolic rate for oxygen ($CMRO_2$) by about 6% for each 1 °C reduction in core temperature and this may reduce the release of excitatory amino acids and free radicals.[183,185] Hypothermia blocks the intracellular consequences of excitotoxin exposure (high calcium and glutamate concentrations) and reduces the inflammatory response associated with the post-cardiac arrest syndrome. However, in the temperature range 33–36 °C, there is no difference in the inflammatory cytokine response in adult patients according to a recent study.[186]

All studies of post-cardiac arrest mild induced hypothermia have included only patients in coma. One randomised trial and a pseudo-randomised trial demonstrated improved neurological outcome at hospital discharge or at 6 months in comatose patients after out-of-hospital VF cardiac arrest.[187,188] Cooling was initiated within minutes to hours after ROSC and a temperature range of 32–34 °C was maintained for 12–24 h.

Three cohort studies including a total of 1034 patients, have compared mild induced hypothermia (32–34 °C) to no temperature management in OHCA and found no difference in neurological outcome (adjusted pooled odds ratio (OR), 0.90 [95% CI 0.45–1.82].[189–191] One additional retrospective registry study of 1830 patients documented an increase in poor neurological outcome among those with nonshockable OHCA treated with mild induced hypothermia (adjusted OR 1.44 [95% CI 1.039–2.006]).[192]

There are numerous before and after studies on the implementation of temperature control after in hospital cardiac arrest but these data are extremely difficult to interpret because of other changes in post cardiac arrest care that occurred simultaneously. One retrospective cohort study of 8316 in-hospital cardiac arrest (IHCA) patients of any initial rhythm showed no difference in survival to hospital discharge among those who were treated with mild induced hypothermia compared with no active temperature management (OR 0.9, 95% CI 0.65–1.23) but relatively few patients were treated with mild induced hypothermia.[193]

In the Targeted Temperature Management (TTM) trial, 950 all-rhythm OHCA patients were randomised to 36 h of temperature control (comprising 28 h at the target temperature followed by slow rewarm) at either 33 °C or 36 °C.[31] Strict protocols were followed for assessing prognosis and for withdrawal of life-sustaining treatment (WLST). There was no difference in the primary outcome – all cause mortality, and neurological outcome at 6 months was also similar (hazard ratio (HR) for mortality at end of trial 1.06, 95% CI 0.89–1.28; relative risk (RR) for death or poor neurological outcome at 6 months 1.02, 95% CI 0.88–1.16). Detailed neurological outcome at 6 months was also similar.[22,24] Importantly, patients in both arms of this trial had their temperature well controlled so that fever was prevented in both groups. TTM at 33 °C was associated with decreased heart rate, elevated lactate, the need for increased vasopressor support, and a higher extended cardiovascular SOFA score compared with TTM at 36 °C.[101,194] Bradycardia during mild induced hypothermia may be beneficial – it is associated with good neurological outcome among comatose survivors of OHCA, presumably because autonomic function is preserved.[118,119]

The optimal duration for mild induced hypothermia and TTM is unknown although it is currently most commonly used for 24 h. Previous trials treated patients with 12–28 h of targeted temperature management.[31,187,188] Two observational trials found no difference in mortality or poor neurological outcome with 24 h compared with 72 h of hypothermia.[195,196] The TTM trial provided strict normothermia (<37.5 °C) after hypothermia until 72 h after ROSC.[31]

The term targeted temperature management or temperature control is now preferred over the previous term therapeutic hypothermia. The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation made several treatment recommendations on targeted temperature management[128] and these are reflected in these ERC guidelines:

- Maintain a constant, target temperature between 32 °C and 36 °C for those patients in whom temperature control is used (strong recommendation, moderate-quality evidence).
- Whether certain subpopulations of cardiac arrest patients may benefit from lower (32–34 °C) or higher (36 °C) temperatures remains unknown, and further research may help elucidate this.
- TTM is recommended for adults after OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence).
- TTM is suggested for adults after OHCA with an initial non-shockable rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence).
- TTM is suggested for adults after IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence).
- If targeted temperature management is used, it is suggested that the duration is at least 24 h (as undertaken in the two largest previous RCTs[31,187]) (weak recommendation, very low-quality evidence).

It is clear that the optimal target temperature after cardiac arrest is not known and that more high-quality large trials are needed.[197]

When to control temperature? Whichever target temperature is selected, active temperature control is required to achieve and maintain the temperature in this range. Prior recommendations suggest that cooling should be initiated as soon as possible after ROSC, but this recommendation was based only on preclinical data and rational conjecture.[198] Animal data indicate that earlier cooling after ROSC produces better outcomes.[199,200] Observational studies are confounded by the fact that there is an association between patients who cool faster spontaneously and worse neurological outcome.[201–203] It is hypothesised that those with the most severe neurological injury are more prone to losing their ability to control body temperature.

Five randomised controlled trials used cold intravenous fluids after ROSC to induce hypothermia,[204–207] one trial used cold intravenous fluid during resuscitation,[208] and one trial used intra-arrest intranasal cooling.[209] The volume of cold fluid ranged from 20 to 30 ml kg^{-1} and up to 2 l, although some patients did not receive the full amount before arrival at hospital. All seven trials suffered from the unavoidable lack of blinding of the clinical team, and three also failed to blind the outcomes assessors. These trials showed no overall difference in mortality for patients treated with prehospital cooling (RR, 0.98; 95% CI 0.92–1.04) compared with

those who did not receive prehospital cooling. No individual trial found an effect on either poor neurological outcome or mortality.

Four RCTs provided low quality evidence for an increased risk of re-arrest among subjects who received prehospital induced hypothermia (RR, 1.22; 95% CI 1.01–1.46),[204,205,207] although this result was driven by data from the largest trial.[207] Three trials reported no pulmonary oedema in any group, two small pilot trials found no difference in the incidence of pulmonary oedema between groups,[204,208] and one trial showed an increase in pulmonary oedema in patients who received prehospital cooling (RR, 1.34; 95% CI 1.15–1.57).[207]

Based on this evidence, prehospital cooling using a rapid infusion of large volumes of cold intravenous fluid immediately after ROSC is not recommended. It may still be reasonable to infuse cold intravenous fluid where patients are well monitored and a lower target temperature (e.g., 33 °C) is the goal. Early cooling strategies, other than rapid infusion of large volumes of cold intravenous fluid, and cooling during cardiopulmonary resuscitation in the prehospital setting have not been studied adequately. Whether certain patient populations (e.g., patients for whom transport time to a hospital is longer than average) might benefit from early cooling strategies remains unknown.

How to control temperature? The practical application of TTM is divided into three phases: induction, maintenance and rewarming.[210] External and/or internal cooling techniques can be used to initiate and maintain TTM. If a target temperature of 36 °C is chosen, for the many post cardiac arrest patients who arrive in hospital with a temperature less than 36 °C, a practical approach is to let them rewarm spontaneously and to activate a TTM-device when they have reached 36 °C. The maintenance phase at 36 °C is the same as for other target temperatures; shivering, for example, does not differ between patients treated at 33 °C and 36 °C.[31] When using a target of 36 °C, the rewarming phase will be shorter.

If a lower target temperature, e.g., 33 °C is chosen, an infusion of 30 ml kg^{-1} of 4 °C saline or Hartmann's solution will decrease core temperature by approximately 1.0–1.5 °C.[206,207,211] However, in one prehospital randomised controlled trial this intervention was associated with increased pulmonary oedema (diagnosed on the initial chest radiograph) and an increased rate of re-arrest during transport to hospital.[207]

Methods of inducing and/or maintaining TTM include:

- Simple ice packs and/or wet towels are inexpensive; however, these methods may be more time consuming for nursing staff, may result in greater temperature fluctuations, and do not enable controlled rewarming.[11,19,188,212–219] Ice cold fluids alone cannot be used to maintain hypothermia,[220] but even the addition of simple ice packs may control the temperature adequately.[218]
- Cooling blankets or pads.[221–227]
- Water or air circulating blankets.[7,8,10,182,226,228–234]
- Water circulating gel-coated pads.[7,224,226,233,235–238]
- Transnasal evaporative cooling[209] – this technique enables cooling before ROSC and is undergoing further investigation in a large multicentre randomised controlled trial.[239]
- Intravascular heat exchanger, placed usually in the femoral or subclavian veins.[7,8,215,216,226,228,232,240–245]
- Extracorporeal circulation (e.g., cardiopulmonary bypass, ECMO).[246,247]

In most cases, it is easy to cool patients initially after ROSC because the temperature normally decreases within this first hour.[13,176] Admission temperature after OHCA is usually between 35 °C and 36 °C and in a recent large trial the median temperature was 35.3 °C.[31] If a target temperature of 36 °C is chosen allow a slow passive rewarm to 36 °C. If a target temperature of 33 °C is chosen, initial cooling is facilitated by neuromuscular blockade and sedation, which will prevent shivering.[248] Magnesium sulphate, a naturally occurring NMDA receptor antagonist, that reduces the shivering threshold slightly, can also be given to reduce the shivering threshold.[210,249]

In the maintenance phase, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferred. This is best achieved with external or internal cooling devices that include continuous temperature feedback to achieve a set target temperature.[250] The temperature is typically monitored from a thermistor placed in the bladder and/or oesophagus.[210,251,252] As yet, there are no data indicating that any specific cooling technique increases survival when compared with any other cooling technique; however, internal devices enable more precise temperature control compared with external techniques.[226,250]

Plasma electrolyte concentrations, effective intravascular volume and metabolic rate can change rapidly during rewarming, as they do during cooling. Rebound hyperthermia is associated with worse neurological outcome.[179,180] Thus, rewarming should be achieved slowly: the optimal rate is not known, but the consensus is currently about 0.25–0.5 °C of rewarming per hour.[228] Choosing a strategy of 36 °C will reduce this risk.[31]

Physiological effects and side effects of hypothermia. The well-recognised physiological effects of hypothermia need to be managed carefully[210]:

- Shivering will increase metabolic and heat production, thus reducing cooling rates – strategies to reduce shivering are discussed above. The occurrence of shivering in cardiac arrest survivors who undergo mild induced hypothermia is associated with a good neurological outcome[253,254]; it is a sign of a normal physiological response. Occurrence of shivering was similar at a target temperature of 33 °C and 36 °C.[31] A sedation protocol is required.
- Mild induced hypothermia increases systemic vascular resistance and causes arrhythmias (usually bradycardia).[241] Importantly, the bradycardia caused by mild induced hypothermia may be beneficial (similar to the effect achieved by beta-blockers); it reduces diastolic dysfunction[117] and its occurrence has been associated with good neurological outcome.[118,119]
- Mild induced hypothermia causes a diuresis and electrolyte abnormalities such as hypophosphataemia, hypokalaemia, hypomagnesaemia and hypocalcaemia.[31,210,255]
- Hypothermia decreases insulin sensitivity and insulin secretion, and causes hyperglycaemia,[188] which will need treatment with insulin (see glucose control).
- Mild induced hypothermia impairs coagulation and may increase bleeding, although this effect seems to be negligible[256] and has not been confirmed in clinical studies.[7,31,187] In one registry study, an increased rate of minor bleeding occurred with the combination of coronary angiography and mild induced hypothermia, but this combination of interventions was the also the best predictor of good outcome.[20]
- Hypothermia can impair the immune system and increase infection rates.[210,217,222] Mild induced hypothermia is associated with an increased incidence of pneumonia[257,258]; however, this seems to have no impact on outcome. Although prophylactic antibiotic treatment has not been studied prospectively, in an observational study, use of prophylactic antibiotics was associated with a reduced incidence of pneumonia.[259] In another observational study of 138 patients admitted to ICU after OHCA, early use of antibiotics was associated with improved survival.[260]

- The serum amylase concentration is commonly increased during hypothermia but the significance of this unclear.
- The clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a core temperature of 34 °C.[261] Clearance of sedative and other drugs will be closer to normal at a temperature closer to 37.0 °C.

Contraindications to targeted temperature management. Generally recognised contraindications to TTM at 33 °C, but which are not applied universally, include: severe systemic infection and pre-existing medical coagulopathy (fibrinolytic therapy is not a contraindication to mild induced hypothermia). Two observational studies documented a positive inotropic effect from mild induced hypothermia in patients in cardiogenic shock,[262,263] but in the TTM study there was no difference in mortality among patients with mild shock on admission who were treated with a target temperature of 33 °C compared with 36 °C.[194] Animal data also indicate improved contractile function with mild induced hypothermia probably because of increased Ca^{2+} sensititvity.[264]

Other therapies

Neuroprotective drugs (Coenzyme Q10,[223] thiopental,[153] glucocorticoids,[123,265] nimodipine,[266,267] lidoflazine[268] or diazepam[154]) used alone, or as an adjunct to mild induced hypothermia, have not been shown to increase neurologically intact survival when included in the post arrest treatment of cardiac arrest. The combination of xenon and mild induced hypothermia has been studied in a feasibility trial and is undergoing further clinical evaluation.[269]

Prognostication

This section has been adapted from the Advisory Statement on Neurological Prognostication in comatose survivors of cardiac arrest,[270] written by members of the ERC ALS Working Group and of the Trauma and Emergency Medicine (TEM) Section of the European Society of Intensive Care Medicine (ESICM), in anticipation of the 2015 Guidelines.

Hypoxic-ischaemic brain injury is common after resuscitation from cardiac arrest.[271] Two thirds of those dying after admission to ICU following out-of-hospital cardiac arrest die from neurological injury; this has been shown both before[28] and after[27,30,31] the implementation of target temperature management (TTM) for post-resuscitation care. Most of these deaths are due to active withdrawal of life sustaining treatment (WLST) based on prognostication of a poor neurological outcome.[27,30] For this reason, when dealing with patients who are comatose after resuscitation from cardiac arrest minimising the risk of a falsely pessimistic prediction is essential. Ideally, when predicting a poor outcome the false positive rate (FPR) should be zero with the narrowest possible confidence interval (CI). However, most prognostication studies include so few patients that even if the FPR is 0%, the upper limit of the 95% CI is often high.[272,273] Moreover, many studies are confounded by self-fulfilling prophecy, which is a bias occurring when the treating physicians are not blinded to the results of the outcome predictor and use it to make a decision on WLST.[272,274] Finally, both TTM itself and sedatives or neuromuscular blocking drugs used to maintain it may potentially interfere with prognostication indices, especially those based on clinical examination.[156]

Clinical examination

Bilateral absence of pupillary light reflex at 72 h from ROSC predicts poor outcome with close to 0% FPR, both in TTM-treated and in non-TTM-treated patients (FPR 1 [0–3] and 0 [0–8], respectively)[156,275–284] and a relatively low sensitivity (19% and 18%, respectively). Similar performance has been documented for bilaterally absent corneal reflex.[272,273]

In non-TTM-treated patients[276,285] an absent or extensor motor response to pain at 72 h from ROSC has a high (74 [68–79]%) sensitivity for prediction of poor outcome, but the FPR is also high (27 [12–48]%). Similar results were observed in TTM-treated patients.[156,277–280,282–284,286–288] Nevertheless, the high sensitivity of this sign may enable it to be used to identify the population with poor neurological status needing prognostication. Like the corneal reflex, the motor response can be suppressed by sedatives or neuromuscular blocking drugs.[156] When interference from residual sedation or paralysis is suspected, prolonging observation of these clinical signs beyond 72 h from ROSC is recommended, in order to minimise the risk of obtaining false positive results.

Myoclonus is a clinical phenomenon consisting of sudden, brief, involuntary jerks caused by muscular contractions or inhibitions. A prolonged period of continuous and generalised myoclonic jerks is commonly described as status myoclonus. Although there is no definitive consensus on the duration or frequency of myoclonic jerks required to qualify as status myoclonus, in prognostication studies in comatose survivors of cardiac arrest the minimum reported duration is 30 min. The names and definitions used for status myoclonus vary among those studies.

While the presence of myoclonic jerks in comatose survivors of cardiac arrest is not consistently associated with poor outcome (FPR 9%),[145,272] a status myoclonus starting within 48 h from ROSC was consistently associated with a poor outcome (FPR 0 [0–5]%; sensitivity 8%) in prognostication studies made in non-TTM-treated patients,[276,289,290] and is also highly predictive (FPR 0% [0–4]; sensitivity 16%) in TTM-treated patients.[144,156,291] However, several case reports of good neurological recovery despite an early-onset, prolonged and generalised myoclonus have been published. In some of these cases myoclonus persisted after awakening and evolved into a chronic action myoclonus (Lance–Adams syndrome).[292–297] In others it disappeared with recovery of consciousness.[298,299] The exact time when recovery of consciousness occurred in these cases may have been masked by the myoclonus itself and by ongoing sedation. Patients with post-arrest status myoclonus should be evaluated off sedation whenever possible; in those patients, EEG recording can be useful to identify EEG signs of awareness and reactivity and to reveal a coexistent epileptiform activity.

While predictors of poor outcome based on clinical examination are inexpensive and easy to use, they cannot be concealed from the treating team and therefore their results may potentially influence clinical management and cause a self-fulfilling prophecy. Clinical studies are needed to evaluate the reproducibility of clinical signs used to predict outcome in comatose post-arrest patients.

Electrophysiology

Short-latency somatosensory evoked potentials (SSEPs)

In non-TTM-treated post-arrest comatose patients, bilateral absence of the N20 SSEP wave predicts death or vegetative state (CPC 4–5) with 0 [0–3]% FPR as early as 24 h from ROSC,[276,300,301] and it remains predictive during the following 48 h with a consistent sensitivity (45–46%).[276,300,302–304] Among a total of 287 patients with absent N20 SSEP wave at ≤72 h from ROSC, there was only one false positive result (positive predictive value 99.7 [98–100]%).[305]

In TTM-treated patients, bilateral absence of the N20 SSEP wave is also very accurate in predicting poor outcome both during mild induced hypothermia[278,279,301,306] (FPR 2 [0–4]%) and after rewarming[277,278,286,288,304] (FPR 1 [0–3]%). The few cases of false reports observed in large patient cohorts were due mainly

to artefacts.[279,284] SSEP recording requires appropriate skills and experience, and utmost care should be taken to avoid electrical interference from muscle artefacts or from the ICU environment. Interobserver agreement for SSEPs in anoxic–ischaemic coma is moderate to good but is influenced by noise.[307,308]

In most prognostication studies bilateral absence of N20 SSEP has been used as a criterion for deciding on withdrawal of life-sustaining treatment (WLST), with a consequent risk of self-fulfilling prophecy.[272] SSEP results are more likely to influence physicians' and families' WLST decisions than those of clinical examination or EEG.[309]

Electroencephalography

Absence of EEG reactivity. In TTM-treated patients, absence of EEG background reactivity predicts poor outcome with 2 [1–7]% FPR[288,310,311] during TH and with 0 [0–3]% FPR[286,288,310] after rewarming at 48–72 h from ROSC. However, in one prognostication study in posthypoxic myoclonus three patients with no EEG reactivity after TTM had a good outcome.[144] Most of the prognostication studies on absent EEG reactivity after cardiac arrest are from the same group of investigators. Limitations of EEG reactivity include lack of standardisation as concerns the stimulation modality and modest interrater agreement.[312]

Status epilepticus. In TTM-treated patients, the presence of status epilepticus (SE), i.e., a prolonged epileptiform activity, during TH or immediately after rewarming[150,291,313] is almost invariably – but not always – followed by poor outcome (FPR from 0% to 6%), especially in presence of an unreactive[150,314] or discontinuous EEG background.[75] All studies on SE included only a few patients. Definitions of SE were inconsistent among those studies.

Burst-suppression. Burst-suppression has recently been defined as more than 50% of the EEG record consisting of periods of EEG voltage <10 μV, with alternating bursts.[148] However, most of prognostication studies do not comply with this definition.

In comatose survivors of cardiac arrest, either TTM-treated or non-TH-treated, burst-suppression is usually a transient finding. During the first 24–48 h after ROSC[305] in non-TTM-treated patients or during hypothermia in TTM-treated patients[288,306,315] burst-suppression may be compatible with neurological recovery while at ≥72 h from ROSC[75,276,316] a persisting burst-suppression pattern is consistently associated with poor outcome. Limited data suggest that specific patterns like a pattern of identical bursts[317] or association with status epilepticus[75] have very high specificity for prediction of poor outcome.

Apart from its prognostic significance, recording of EEG – either continuous or intermittent – in comatose survivors of cardiac arrest both during TH and after rewarming is helpful to assess the level of consciousness – which may be masked by prolonged sedation, neuromuscular dysfunction or myoclonus – and to detect and treat non-convulsive seizures[318] which may occur in about one quarter of comatose survivors of cardiac arrest.[75,149,291]

Biomarkers

NSE and S-100B are protein biomarkers that are released following injury to neurons and glial cells, respectively. Their blood values after cardiac arrest are likely to correlate with the extent of anoxic–ischaemic neurological injury and, therefore, with the severity of neurological outcome. S-100B is less well documented than is NSE.[319] Advantages of biomarkers over both EEG and clinical examination include quantitative results and likely independence from the effects of sedatives. Their main limitation as prognosticators is that it is difficult to find a consistent threshold for identifying patients destined to a poor outcome with a high degree of certainty. In fact, serum concentrations of biomarkers are per se continuous variables, which limits their applicability for predicting a dichotomous outcome, especially when a threshold for 0% FPR is desirable.

Neuron-specific enolase (NSE)

In non-TTM-treated patients the NSE threshold for prediction of poor outcome with 0% FPR at days 24–72 from ROSC was 33 mcg l^{-1} or less in some studies.[276,320,321] However, in other studies this threshold was 47.6 mcg l^{-1} at 24 h, 65.0 mcg l^{-1} at 48 h and 90.9 mcg l^{-1} at 72 h.[302]

In TTM-treated patients the threshold for 0% FPR varied between 49.6 mcg l^{-1} and 151.4 mcg l^{-1} at 24 h,[313,322–326] between 25 mcg l^{-1} and 151.5 mcg l^{-1} at 48 h,[279,313,322–329] and between 57.2 mcg l^{-1} and 78.9 mcg l^{-1} at 72 h.[321,324,327]

The main reasons for the observed variability in NSE thresholds include the use of heterogeneous measurement techniques (variation between different analysers),[330–332] the presence of extra-neuronal sources of biomarkers (haemolysis and neuroendocrine tumours),[333] and the incomplete knowledge of the kinetics of its blood concentrations in the first few days after ROSC. Limited evidence suggests that the discriminative value of NSE levels at 48–72 h is higher than at 24 h.[323,325,334] Increasing NSE levels over time may have an additional value in predicting poor outcome.[323,324,334] In a secondary analysis of the TTM trial, NSE values were measured at 24, 48 and 72 h in 686 patients; an increase in NSE values between any two points was associated with a poor outcome.[335]

Imaging

Brain CT

The main CT finding of global anoxic–ischaemic cerebral insult following cardiac arrest is cerebral oedema,[133] which appears as a reduction in the depth of cerebral sulci (sulcal effacement) and an attenuation of the grey matter/white matter (GM/WM) interface, due to a decreased density of the GM, which has been quantitatively measured as the ratio (GWR) between the GM and the WM densities. The GWR threshold for prediction of poor outcome with 0% FPR in prognostication studies ranged between 1.10 and 1.22.[281,325,336] The methods for GWR calculation were inconsistent among studies.

MRI

MRI changes after global anoxic–ischaemic brain injury due to cardiac arrest appear as a hyperintensity in cortical areas or basal ganglia on diffusion weighted imaging (DWI) sequences. In two small studies,[337,338] the presence of large multilobar changes on DWI or FLAIR MRI sequences performed within five days from ROSC was consistently associated with poor outcome while focal or small volume lesions were not.[329]

Apparent diffusion coefficient (ADC) is a quantitative measure of ischaemic DWI changes. ADC values between 700 and 800×10^{-6} mm^2 s^{-1} are considered to be normal.[339] Brain ADC measurements used for prognostication include whole-brain ADC,[340] the proportion of brain volume with low ADC[341] and the lowest ADC value in specific brain areas, such as the cortical occipital area and the putamen.[322,342] The ADC thresholds associated with 0% FPR vary among studies. These methods depend partly on subjective human decision in identifying the region of interest to be studied and in the interpretation of results, although automated analysis has recently been proposed.[343]

Advantages of MRI over brain CT include a better spatial definition and a high sensitivity for identifying ischaemic brain injury; however, its use can be problematic in the most clinically unstable patients.[339] MRI can reveal extensive changes when results of other predictors such as SSEP or ocular reflexes are normal.[329,339]

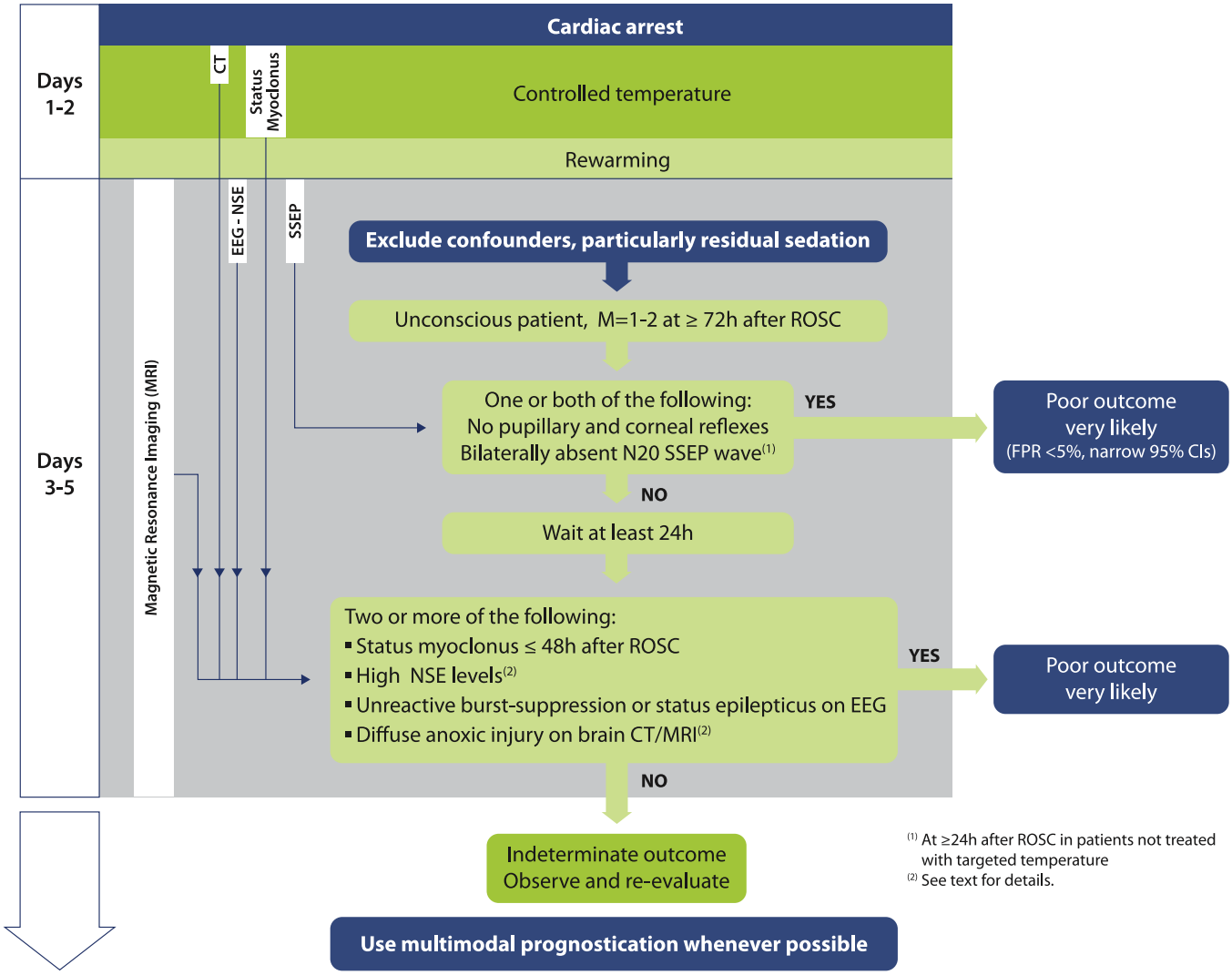

Fig. 5.2. Prognostication strategy algorithm. EEG: electroencephalography; NSE: neuron-specific enolase; SSEP: somatosensory evoked potentials; ROSC: return of spontaneous circulation; FPR: false positive rate; CI: confidence interval.

All studies on prognostication after cardiac arrest using imaging have a small sample size with a consequent low precision, and a very low quality of evidence. Most of those studies are retrospective, and brain CT or MRI had been requested at the discretion of the treating physician, which may have caused a selection bias and overestimated their performance.

Suggested prognostication strategy

A careful clinical neurological examination remains the foundation for prognostication of the comatose patient after cardiac arrest.[344] Perform a thorough clinical examination daily to detect signs of neurological recovery such as purposeful movements or to identify a clinical picture suggesting that brain death has occurred.

The process of brain recovery following global post-anoxic injury is completed within 72 h from arrest in most patients.[290,345] However, in patients who have received sedatives ≤12 h before the 72 h post ROSC neurological assessment, the reliability of clinical examination may be reduced.[156] Before decisive assessment is performed, major confounders must be excluded[346,347]; apart from sedation and neuromuscular blockade, these include hypothermia, severe hypotension, hypoglycaemia, and metabolic and respiratory derangements. Suspend sedatives and neuromuscular blocking drugs for long enough to avoid interference with clinical examination. Short-acting drugs are preferred whenever possible. When residual sedation/paralysis is suspected, consider using antidotes to reverse the effects of these drugs.

The prognostication strategy algorithm (Fig. 2) is applicable to all patients who remain comatose with an absent or extensor motor response to pain at ≥72 h from ROSC. Results of earlier prognostic tests are also considered at this time point.

Evaluate the most robust predictors first. These predictors have the highest specificity and precision (FPR <5% with 95% CIs <5% in patients treated with controlled temperature) and have been documented in >5 studies from at least three different groups of investigators. They include bilaterally absent pupillary reflexes at ≥72 h from ROSC and bilaterally absent SSEP N20 wave after rewarming (this last sign can be evaluated at ≥24 h from ROSC in patients who have not been treated with controlled temperature). Based on expert opinion, we suggest combining the absence of pupillary reflexes with those of corneal reflexes for predicting poor outcome at this time point. Ocular reflexes and SSEPs maintain their predictive value irrespective of target temperature.[283,284]

If none of the signs above is present to predict a poor outcome, a group of less accurate predictors can be evaluated, but the degree of confidence in their prediction will be lower. These have FPR <5% but wider 95% CIs than the previous predictors, and/or their definition/

threshold is inconsistent in prognostication studies. These predictors include the presence of early status myoclonus (within 48 h from ROSC), high values of serum NSE at 48–72 h after ROSC, an unreactive malignant EEG pattern (burst-suppression, status epilepticus) after rewarming, the presence of a marked reduction of the GM/WM ratio or sulcal effacement on brain CT within 24 h after ROSC or the presence of diffuse ischaemic changes on brain MRI at 2–5 days after ROSC. Based on expert opinion, we suggest waiting at least 24 h after the first prognostication assessment and confirming unconsciousness with a Glasgow motor score of 1–2 before using this second set of predictors. We also suggest combining at least *two* of these predictors for prognostication.

No specific NSE threshold for prediction of poor outcome with 0% FPR can be recommended at present. Ideally, every hospital laboratory assessing NSE should create its own normal values and cut-off levels based on the test kit used. Sampling at multiple timepoints is recommended to detect trends in NSE levels and to reduce the risk of false positive results.[335] Care should be taken to avoid haemolysis when sampling NSE.

Although the most robust predictors showed no false positives in most studies, none of them singularly predicts poor outcome with absolute certainty when the relevant comprehensive evidence is considered. Moreover, those predictors have often been used for WLST decisions, with the risk of a self-fulfilling prophecy. For this reason, we recommend that prognostication should be multimodal whenever possible, even in presence of one of these predictors. Apart from increasing safety, limited evidence also suggests that multimodal prognostication increases sensitivity.[286,311,325,348]

When prolonged sedation and/or paralysis is necessary, for example, because of the need to treat severe respiratory insufficiency, we recommend postponing prognostication until a reliable clinical examination can be performed. Biomarkers, SSEP and imaging studies may play a role in this context, since they are insensitive to drug interference.

When dealing with an uncertain outcome, clinicians should consider prolonged observation. Absence of clinical improvement over time suggests a worse outcome. Although awakening has been described as late as 25 days after arrest,[291,298,349] most survivors will recover consciousness within one week.[31,329,350–352] In a recent observational study,[351] 94% of patients awoke within 4.5 days from rewarming and the remaining 6% awoke within ten days. Even those awakening late, can still have a good neurological outcome.[351]

Rehabilitation

Although neurological outcome is considered to be good for the majority of cardiac arrest survivors, cognitive and emotional problems and fatigue are common.[23,24,279,353–356] Long-term cognitive impairments are present in half of survivors.[22,357,358] Memory is most frequently affected, followed by problems in attention and executive functioning (planning and organisation).[23,359] The cognitive impairments can be severe, but are mostly mild.[22] In one study, of 796 OHCA survivors who had been employed before their cardiac arrest, 76.6% returned to work.[360] Mild cognitive problems are often not recognised by health care professionals and cannot be detected with standard outcome scales such as the Cerebral Performance Categories (CPC) or the Mini-Mental State Examination (MMSE).[24,361] Emotional problems, including depression, anxiety and posttraumatic stress are also common.[362,363] Depression is present in 14–45% of the survivors, anxiety in 13–61% and symptoms of posttraumatic stress occur in 19–27%.[355] Fatigue is also a complaint that is often reported after cardiac arrest. Even several years after a cardiac arrest, 56% of the survivors suffer severe fatigue.[356]

It is not only the patients who experience problems; their partners and caregivers can feel highly burdened and often have emotional problems, including symptoms of posttraumatic stress.[356,364] After hospital discharge both survivors and caregivers frequently experience a lack of information on important topics including physical and emotional challenges, implantable cardioverter defibrillators (ICD), regaining daily activities, partner relationships and dealing with health care providers.[365] A systematic review on coronary heart disease patients also showed the importance of active information supply and patient education.[366]

Both cognitive and emotional problems have significant impact and can affect a patient's daily functioning, return to work and quality of life.[356,367,368] Therefore, follow-up care after hospital discharge is necessary. Although the evidence on the rehabilitation phase appears scarce, three randomised controlled trials have shown that the outcome after cardiac arrest can be improved.[369–371] First, an eleven-session nursing intervention reduced cardiovascular mortality and depressive symptoms. It did so by focussing on physiological relaxation, self-management, coping strategies and health education.[369] Another nursing intervention was found to improve physical symptoms, anxiety, self-confidence and disease knowledge.[370,371] This intervention consisted of eight telephone sessions, a 24/7 nurse pager system and an information booklet and was directed at improving self-efficacy, outcome efficacy expectations and enhancing self-management behavioural skills.[372] A third intervention called 'Stand still. . ., and move on', improved overall emotional state, anxiety and quality of life, and also resulted in a faster return to work.[373] This intervention aimed to screen early for cognitive and emotional problems, to provide information and support, to promote self-management and to refer to specialised care, if needed.[374,375] It generally consisted of only one or two consultations with a specialised nurse and included supply of a special information booklet.

The organisation of follow-up after cardiac arrest varies widely between hospitals and countries in Europe. Follow-up care should be organised systematically and can be provided by a physician or specialised nurse. It includes at least the following aspects:

Screening for cognitive impairments. There is currently no gold standard on how to perform such screening. A good first step would be to ask the patient and a relative or caregiver about cognitive complaints (for example problems with memory, attention, planning). If feasible, administer a structured interview or checklist, such as the Checklist Cognition and Emotion,[376] or a short cognitive screening instrument, such as the Montreal Cognitive Assessment (MoCA) (freely available in many languages at http://www.mocatest.org). In cases where there are signs of cognitive impairments, refer to a neuropsychologist for neuropsychological assessment or to a specialist in rehabilitation medicine for a rehabilitation programme.[377]

Screening for emotional problems. Ask whether the patient experiences any emotional problems, such as symptoms of depression, anxiety or posttraumatic stress. General measures that can be used include the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale.[378,379] In case of emotional problems refer to a psychologist or psychiatrist for further examination and treatment.[355]

Provision of information. Give active information on the potential non-cardiac consequences of a cardiac arrest including cognitive impairment, emotional problems and fatigue. Other topics that can be addressed include heart disease, ICDs, regaining daily activities, partner relationships and sexuality, dealing with health care providers and caregiver strain.[365] It is best to combine written information with the possibility for personal consultation. An example of an information booklet is available (in Dutch and English).[373,374]

Organ donation

Organ donation should be considered in those who have achieved ROSC and who fulfil criteria for death using neurological criteria.[380] In those comatose patients in whom a decision is made to withdraw life-sustaining therapy, organ donation should be considered after circulatory death occurs. Organ donation can also be considered in individuals where CPR is not successful in achieving ROSC. All decisions concerning organ donation must follow local legal and ethical requirements, as these vary in different settings.

Non-randomised studies have shown that graft survival at one year is similar from donors who have had CPR compared with donors who have not had CPR: adult hearts (3230 organs[381–387]), adult lungs (1031 organs[383,385,388]), adult kidneys (5000 organs[381,383]), adult livers (2911 organs[381,383]), and adult intestines (25 organs[383]).

Non-randomised studies have also shown that graft survival at one year was similar when organs recovered from donors with ongoing CPR were compared to other types of donors for adult kidneys (199 organs[389–391]) or adult livers (60 organs[390,392,393]).

Solid organs have been successfully transplanted after circulatory death. This group of patients offers an opportunity to increase the organ donor pool. Organ retrieval from donation after circulatory death (DCD) donors is classified as controlled or uncontrolled.[394,395] Controlled donation occurs after planned withdrawal of treatment following non-survivable injuries and illnesses. Uncontrolled donation describes donation from patients with unsuccessful CPR in whom a decision has been made that CPR should be stopped. Once death has been diagnosed, the assessment of which includes a pre-defined period of observation to ensure a spontaneous circulation does not return,[396] organ preservation and retrieval takes place. Aspects or uncontrolled organ donation are complex and controversial as some of the same techniques used during CPR to attempt to achieve ROSC are also used for organ preservation after death has been confirmed, e.g., mechanical chest compression and extracorporeal circulation. Locally agreed protocols must therefore be followed.

Screening for inherited disorders

Many sudden death victims have silent structural heart disease, most often coronary artery disease, but also primary arrhythmia syndromes, cardiomyopathies, familial hypercholesterolaemia and premature ischaemic heart disease. Screening for inherited disorders is crucial for primary prevention in relatives as it may enable preventive antiarrhythmic treatment and medical follow-up.[397–399] This screening should be performed using clinical examination, electrophysiology and cardiac imaging. In selected cases, genetic mutations associated with inherited cardiac diseases should also be searched.[400]

Cardiac arrest centres

There is wide variability in survival among hospitals caring for patients after resuscitation from cardiac arrest.[9,13,16,17,401–403] Many studies have reported an association between survival to hospital discharge and transport to a cardiac arrest centre but there is inconsistency in the hospital factors that are most related to patient outcome.[4,5,9,17,401,404–416] There is also inconsistency in the services that together define a cardiac arrest centre. Most experts agree that such a centre must have a cardiac catheterisation laboratory that is immediately accessible 24/7 and the facility to provide targeted temperature management. The availability of a neurology service that can provide neuroelectrophysiological monitoring (electroencephalography (EEG)) and investigations (e.g., EEG and somatosensory evoked potentials (SSEPs)) is also essential.

There is some low-level evidence that ICUs admitting more than 50 post-cardiac arrest patients per year produce better survival rates than those admitting less than 20 cases per year[17]; however, differences in case mix could account for these differences. An observational study showed that unadjusted survival to discharge was greater in hospitals that received ≥40 cardiac arrest patients/year compared with those that received <40 per year, but this difference disappeared after adjustment for patient factors.[417]

Several studies with historic control groups have shown improved survival after implementation of a comprehensive package of post-resuscitation care that includes mild induced hypothermia and percutaneous coronary intervention.[7,10,11,418] There is also evidence of improved survival after out-of-hospital cardiac arrest in large hospitals with cardiac catheter facilities compared with smaller hospitals with no cardiac catheter facilities.[9] In a study of 3981 patients arriving with a sustained pulse at one of 151 hospitals, the Resuscitation Outcome Consortium (ROC) investigators have shown that early coronary intervention and mild induced hypothermia were associated with a favourable outcome.[84] These interventions were more frequent in hospitals that treated higher number of OHCA patients per year.

Several studies of OHCA arrest failed to demonstrate any effect of transport interval from the scene to the receiving hospital on survival to hospital discharge if ROSC was achieved at the scene and transport intervals were short (3–11 min).[406,412,413] This implies that it may be safe to bypass local hospitals and transport the post-cardiac arrest patient to a regional cardiac arrest centre. There is indirect evidence that regional cardiac resuscitation systems of care improve outcome after ST elevation myocardial infarction (STEMI).[407,419–442]

The implication from all these data is that specialist cardiac arrest centres and systems of care may be effective.[443–446] Despite the lack of high quality data to support implementation of cardiac arrest centres, it seems likely that regionalisation of post-cardiac arrest care will be adopted in most countries.

Conflicts of interest

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