Post cardiac arrest brain injury

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<h1> Summary

As more people are surviving cardiac arrest, focus need to shift to improving neurological outcomes and quality of life amongst survivors. Post resuscitation brain injury, a common sequalae following cardiac arrest, ranges in severity from mild impairment through to devastating brain injury and brain stem death. Effective strategies to minimise post resuscitation brain injury include early intervention with cardiopulmonary resuscitation and defibrillation, restoration of normal physiology and targeted temperature management. Prognostication plays an important role in identifying those predicted to have a poor outcome, to enable informed choices about continuation or withdrawal of life sustaining treatments. Multi-modal prognostication guidelines seek to avoid premature withdrawal in those who may survive with a good neurological outcome, or prolonging treatment which may result in survival with severe disability. Approximately one in three admitted to intensive care will survive, many of whom will need intensive, tailored rehabilitation after discharge to achieve the best outcomes.

Word count: 150

<h1> Introduction

When cardiac arrest occurs, circulation to the brain ceases and within seconds consciousness is lost. Left untreated, irreversible brain damage and death will rapidly follow. The chance of survival with a favourable neurological outcome declines rapidly the longer someone remains in cardiac arrest.[1] As the heart is more tolerant of ischaemia than the brain, even where initial resuscitation efforts are successful, up to 70% of those admitted to the hospital die from the effects of post-cardiac arrest brain injury.[2-4] The ultimate goal of resuscitation is to restore cardiac and cerebral function to that before the cardiac arrest. Early initiation of high quality cardiopulmonary resuscitation and rapid defibrillation increase the odds of favourable neurological outcome by two to four fold by reducing primary brain injury.[5] Following ROSC, post-cardiac arrest care focuses on minimising secondary brain injury and optimising the chances of recovery. Prognostication tools are used to assess the likelihood of a poor neurological outcome which in some settings may lead to withdrawal of treatment and / or organ donation. After discharge from intensive care, intensive, individualised rehabilitation is required to deliver the best outcomes. The aim of this review is to summarise contemporary knowledge about the epidemiology, pathophysiology, treatment, prognostication, long-term outcome and rehabilitation for post-cardiac arrest brain injury.

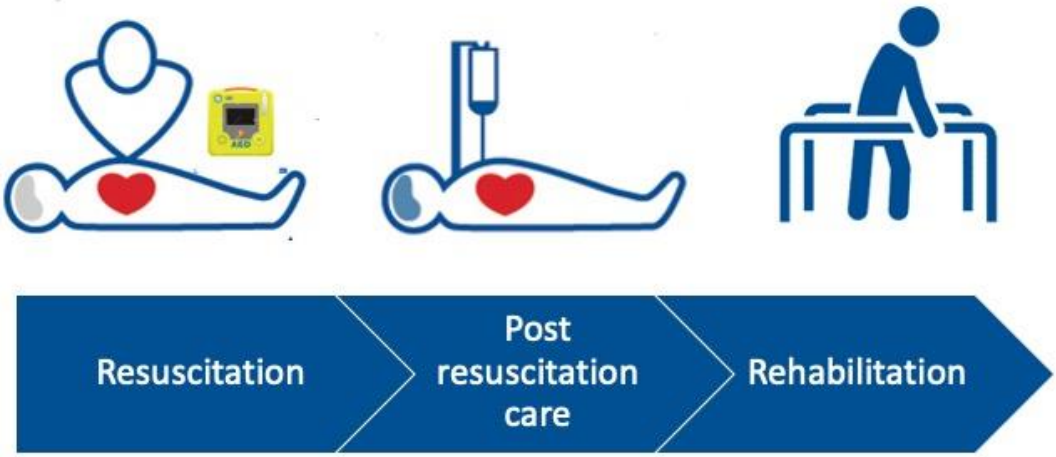


Figure 1: Strategy for reducing post cardiac arrest brain injury. Resuscitation -cardiac arrest recognition, early CPR/defibrillation. Post resuscitation care -targeted temperature management, normalise physiology. Rehabilitation to promote recovery.

Box 1 Search strategy and article selection

We searched Medline (from 2000 to September 2020) using the terms “post cardiac arrest brain injury”; “post cardiac arrest syndrome”, “cardiac arrest” and “brain injury” and relevant section headings (epidemiology, pathophysiology, treatment, rehabilitation). The International Liaison Committee on Resuscitation Consensus on Science and Treatment Recommendations database (costr.ilcor.org) was also searched for relevant systematic reviews. No language restrictions were applied. We prioritised articles published in the last five years but also included key references published outside this period.

<h1> Epidemiology

A review of global cardiac arrest registries identified that over 500,000 people receive treatment for out of hospital cardiac arrests (OHCA) each year with an annual incidence between 30 to 97 per 100,000 people[6] (equivalent to 1/10th the number of myocardial infarctions). Return of spontaneous circulation (ROSC) is achieved by the time of hospital handover in approximately one third of patients.[7] Higher rates of ROSC are seen in North America, Australasia and Europe than in Asia.[7] The majority of cardiac arrests have a cardiac cause.[7] Those who present with an initially shockable rhythm (ventricular fibrillation or ventricular tachycardia) have much better outcomes than those who present with pulseless electrical activity or asystole.[6] The best outcomes from resuscitation occur in those who regain consciousness rapidly after return of ROSC. In a study from Denmark involving 13,953 patients with OHCA, on hospital arrival 776 (5.6%) had ROSC and were conscious, 5205 (37.3%) had ROSC, but were comatose, and 7972 (57.1%) had ongoing CPR at hospital arrival.[8] Most patients who were conscious on arrival were alive 30 days later (89.0% (95% confidence interval [CI] 86.8%–91.2%)) and few developed anoxic brain injury or required nursing home admission (2.4% (95% CI 1.2%–3.6%)).[8] The majority of patients who are comatose on arrival at hospital are admitted to an intensive care unit (ICU) where they spend on average 3-5 days and represent up to 10% of ICU admissions.[9,10] Here, attention is focused on identifying and treating the underlying cause of the cardiac arrest and optimising neurological recovery. Deaths within the first few days of intensive care are usually due to refractory shock, respiratory failure or withdrawal of treatment because of the presence of severe co-morbidities.[11] Patients who wake up in in the first 4 days of ICU care have the best outcomes.[12] In patients who do not wake up quickly, guidelines recommend prognostic assessment no earlier than 72 hours after admission to intensive care. The practice of withdrawal of life sustaining treatment based on prognostication of a poor neurological outcome varies around the world.[13] In centres that withdraw treatment because of a predicted poor outcome, this accounts for approximately 60% of deaths in ICU.[2] In the most severe cases, post-cardiac arrest brain injury progresses to brain death in around 1 in 10 of patients

admitted to an ICU.[14] (Figure 2). Depending on national laws, non-heart beating organ donation and donation after brain stem death may occur in up to 5-10% of non-survivors following cardiac arrest.[10,14] Box 2 highlights a family's story about the devastating consequences of post resuscitation brain injury.

International registry data indicate that amongst those who survive to hospital discharge, on average 19% (range 3% to 47%) have moderate to severe neurological impairments, preventing return to work and activities of daily living.[6] The variation in outcomes may reflect different countries' approaches to ICU admission, therapeutic treatment pathways and approach to withdrawal of life sustaining treatment. Data on neurological outcomes after hospital discharge are sparse and mainly drawn from follow-up data from clinical trials in US and Europe. In systems which practice withdrawal of life sustaining treatment because of predicted poor neurological outcome, by six months approximately 80% of those who are still alive have a favourable neurological outcome.[3,15,16] A prospective, Italian study in a system in which withdrawal of life sustaining treatment was not performed documented a relatively high survival rate (60%), but nearly half (47%) of the survivors were in an unresponsive wakefulness state, 19% had severe disability and only 32% had a favourable neurological outcome.[17]

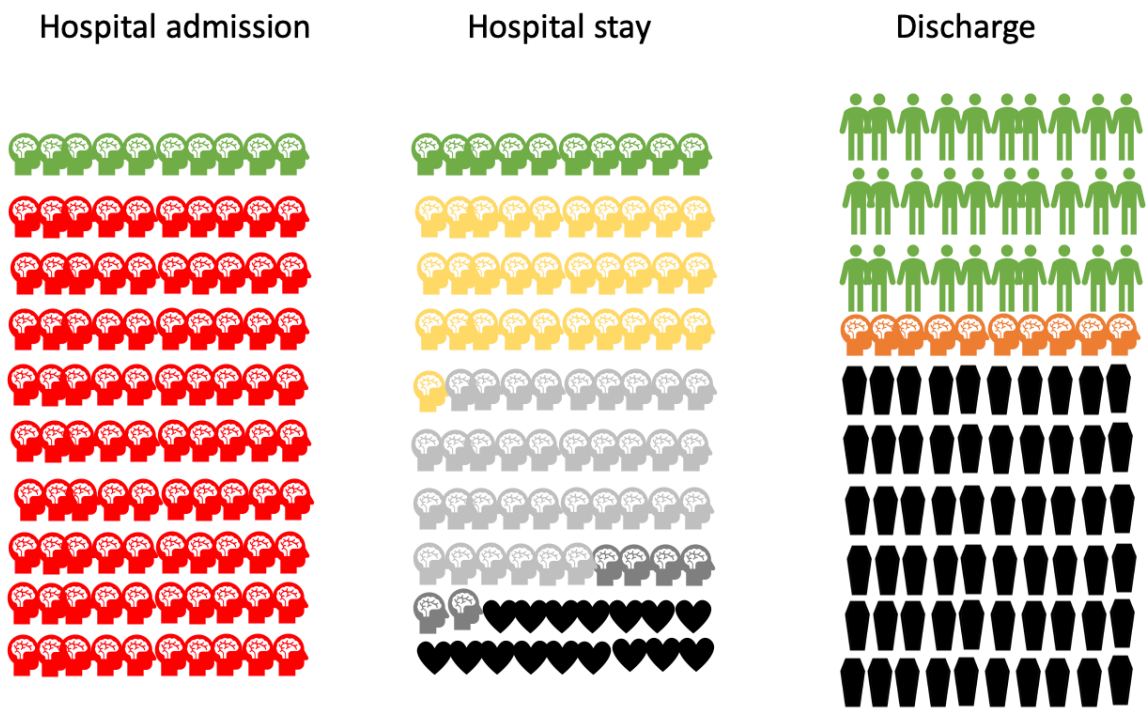


Figure 2: Outcomes following admission for OHCA.

conscious; comatose; neurological improvement; Deaths withdrawal of treatment for predicted adverse neurological outcome; brain death, refractory shock / organ failure); Discharge: favourable neurological outcome poor neurological outcome dead.

Box 2 : Post cardiac arrest brain injury – a family's perspective.

They say life can change in a blink of an eye; it's cliché but it's true! I never in a million years imagined the outcome on the 18th of November 2018… a week earlier I was in Peru when I received the news; my Mam had suffered a major heart attack.

People ask how I managed to travel home knowing what had happened. The truth is, I naively never considered the outcome. I knew my Dad had performed CPR and the paramedics had worked tirelessly, with her arresting at home then again in the ambulance. But I knew she was stable enough for the doctors to successfully insert a stent into one of the blood vessels in her heart.

What I didn't think about was the extent of the damage to her brain due to the lack of oxygen. When the doctor took us into a room on the Friday evening and told us there was no chance of survival, it felt surreal like something you see in a movie or as if you're living someone else's life and hearing those words.

I always knew my Mam was as tough as they come; she'd battled through so much in her life. She put up a hell of a fight right to the end, not letting go after the life support was switched off until 2 days later. I guess this was one battle too many for her.

As you can imagine, this has caused massive devastation within our family; Mam was the golden link that held us all together. So as a family, we're trying to raise awareness about post cardiac arrest brain injury and remain positive, as that's what Mam would have done in the same situation.

<h1> Pathophysiology

Whilst the severity and duration of ischaemia during cardiac arrest determines the primary neurological injury (no-flow), secondary damage occurs during CPR (low-flow) and after ROSC (reperfusion). The physiology and molecular consequences associated with post-cardiac arrest brain injury have been described in detail previously[18] and are summarized in Table 1 and figure 3.

Table 1: Mechanisms associated with post cardiac arrest brain injury.

Primary Injury Mechanisms	Secondary Injury Mechanisms
• Impaired oxygen/substrate delivery • Excitotoxicity • Disrupted calcium homeostasis • Oxidative stress • Mitochondrial damage and dysfunction • Pathologic protease activation • Inflammation	• Hypotension • Hypoxaemia • Elevated intracranial pressure (ICP) • Seizures • Dysglycaemia • Hyperthermia

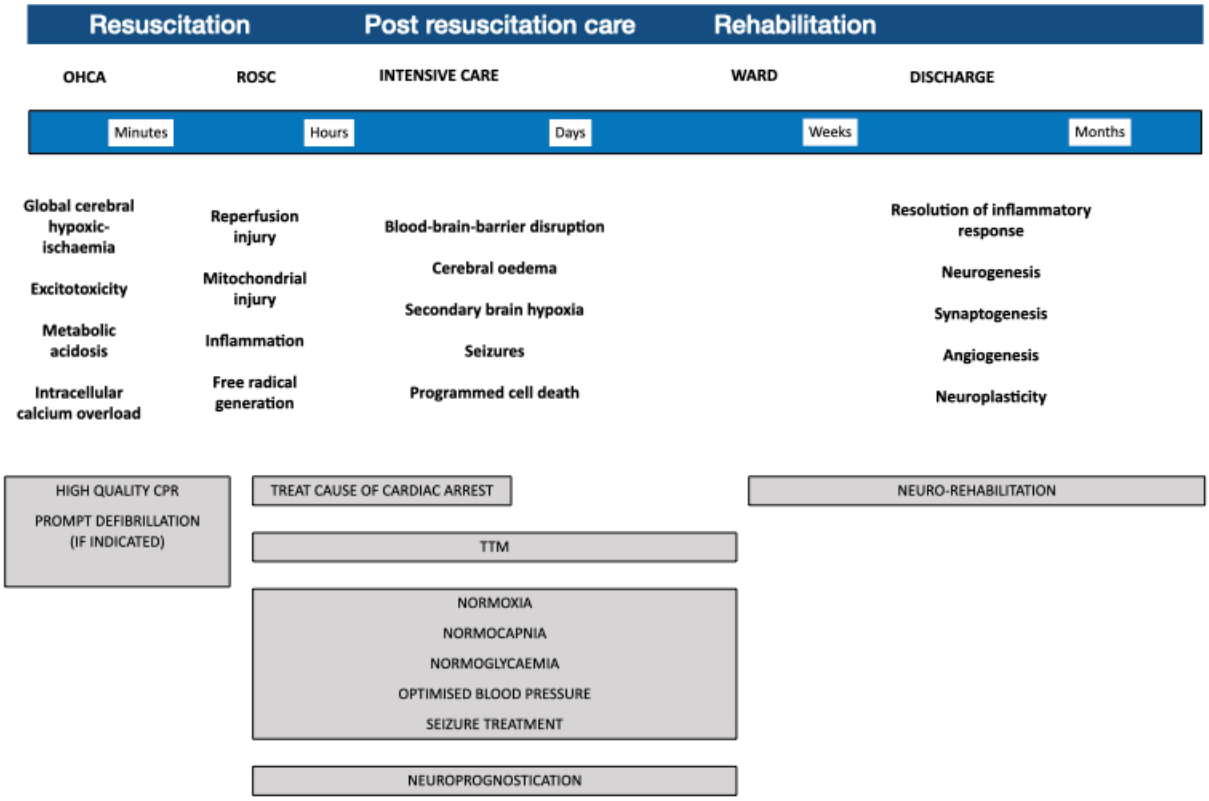


Figure 3: Simplified schematic representation of overlapping phases of post cardiac arrest brain injury and timing of therapeutic interventions.

<h2> Primary injury (minutes–hours)

Neuronal injury is rapidly triggered in the brain when the severity and duration of ischaemia is sufficient to cause sustained depolarisation of the neuronal plasma membrane - defined as “ischaemic depolarisation”. This occurs within minutes of cardiac arrest, due to cessation of cerebral blood flow and subsequent oxygen, glucose and adenosine triphosphate (ATP) depletion and loss of mitochondrial inner-membrane potential. Energy dependent ion pumps fail and loss of plasma membrane potential triggers opening of voltage-gated ion channels followed by excitatory neurotransmitter release opening ligand-gated ion channels. The resultant equalisation of ionic gradients causes pathological cellular oedema, intracellular

calcium overload and activation of pathological proteases. With ROSC, restoration of oxygen oxidative phosphorylation and mitochondrial membrane potential is necessary to resume ATP synthesis, but also contributes to free radical generation, which damages DNA, proteins, and lipids. Excessive mitochondrial buffering of elevated cytosolic calcium can also damage mitochondria and lead to mitochondrial permeability transition triggering programmed cell death. Within minutes of reperfusion, there are significant changes in the gene expression in post-ischaemic neurons and glial cells that may contribute to or mitigate ongoing injury mechanisms or programmed cell death pathways.[18]

<h2> Secondary injury (hours-days)

Following partial or complete restoration of blood flow, persistent or recurrent inadequate brain oxygen delivery can cause secondary brain injury. Contributing factors include hypoxaemia, inadequate cerebral perfusion pressure due to refractory hypotension or disrupted cerebrovascular autoregulation, or elevated ICP caused by brain oedema. Clinical or subclinical seizures, hyperglycaemia, and hyperthermia can also increase brain metabolic demand, further contributing to secondary brain injury. The systemic inflammatory response in patients after cardiac arrest is associated with multiple organ dysfunction and death.[19] In addition to the systemic inflammatory response, activation of neuronal immune and inflammatory cascades likely to be detrimental to neuronal survival occurring in the hours immediately after the onset of ischaemia. Transient ischaemia results in the release of primary proinflammatory cytokines IL-1b and TNF-alpha from activated microglia, endothelial cells and neurons.[20] Cerebral oedema after ischaemia/reperfusion results primarily from cellular swelling over the first days after ischemia as water shifts intracellularly, as disruption of the blood–brain barrier is brief and transient.[21] Oedema can develop quickly, raise ICP, and compromise local and global cerebral perfusion.

It remains difficult to synthesise a unifying pathophysiological framework underpinning poor neurological outcomes after OHCA because of the multiple molecular and physiological pathways, the complexity of their interactions and the different phenotypes of brain injury dependent on the aetiology.[22] Nevertheless, it is clear that post-ischaemic neuronal death continues to occur in the hours and days after ROSC, instead of occurring within a single, narrowly defined temporal window. This raises the possibility that there exists a window for therapeutic intervention to improve cognitive outcomes.

<h1> Interventions to reduce post-cardiac arrest brain injury

European Resuscitation Council and European Society for Intensive Care Medicine Guidelines provide comprehensive information on the care of patients following return of spontaneous.[23] Those specifically targeting post cardiac arrest brain injury include targeted temperature management, treatment of seizures and maintenance of normal physiology.

<h2> Primary injury

Reducing the duration of no-flow with bystander CPR and public access defibrillation is one of the most effective strategies to reduce post cardiac arrest brain injury.[5] Other intra-arrest interventions, including the use of drugs[24] and cooling,[25,26] have so far been unsuccessful at improving neurological outcomes. Where initial resuscitation efforts are unsuccessful, the early initiation of extracorporeal CPR has shown promise in some studies,[27] but larger trials are needed to confirm the generalisability of these findings.

<h2> Secondary injury

<h3> Pre-hospital interventions

Immediately following ROSC, guidelines recommend avoidance of hypoxaemia and hypotension, based on their association with poor outcomes.[23] Despite experimental data

supporting benefits from initiating targeted temperature management immediately after ROSC,[28] these findings have not been replicated in clinical trials.[29,30] Transfer to a cardiac arrest centre which has access to 24/7 on-site coronary angiography, critical care and diagnostic imaging will help facilitate co-ordinated post resuscitation care.[31]

<h3> Interventions after arrival in hospital

<h4> Targeted temperature management

A large randomised controlled trial demonstrated that targeted temperature management (TTM) at 32-34ºC versus no TTM increased the proportion of good neurological outcomes by 16% in comatose patients presenting in cardiac arrest with ventricular fibrillation.[32] A more recent trial reported that TTM at 33ºC versus TTM at 37ºC increased the proportion of good neurological outcomes from 4.5% to 10% in patients presenting with non-shockable rhythms. Interpretation is however limited by a fragility index of 1 which is lower than the number of patients who withdrew or were lost to follow-up.[33] The optimal depth of hypothermia for TTM is less certain, because the largest multicentre trial to date detected no difference in outcomes of comatose post-cardiac arrest survivors between TTM at 33ºC versus TTM at 36ºC treatment.[9] The duration of TTM in practice is typically 24 hours as in the original trials, though a smaller multi-centre trial observed a non-significant 4.9% increase in the proportion of good neurological outcomes with TTM for 48 hours versus TTM for 24 hours.[34] Current consensus is that care for post-cardiac arrest patients with coma should include TTM. A large 1900 patient trial comparing 33º versus active fever prevention has finished randomization and follow-up and will be published in spring 2021. Guidelines, based on low certainty evidence, suggest following the completion of TTM, fever should be actively treated.[23]

<h4> Oxygenation and ventilation

Blood content of oxygen and carbon dioxide also influence cerebral blood flow and oxygen delivery. Current recommendations are to maintain normoxia and normocapnia following

ROSC.[23,35] However, unintentional hyperoxia occurs following inadvertent and prolonged use of 100% oxygen.[36] Sub-group analyses from the ICU-ROX trial suggested improved outcomes with tightly controlled compared with more liberal oxygen use in patients at risk of brain injury after OHCA,[37] however this was not significantly different when corrected for baseline differences between groups.[38] On the other hand a sub-group analysis of 332 patients at risk of cardiac arrest related brain injury included in the multi-centre HOT-ICU trial, did not show any difference in outcome with an oxygen target of 60 mmHg (8 kPa) compared to 90 mmHg (12 kPa).[39] Given the absence of conclusive evidence, it is prudent to target normoxia (PaO_2 10-12 kPa) but to carefully avoid hypoxia (PaO_2 < 8 kPa), as multiple studies have shown association between hypoxia and poor functional outcome.[40] A slightly elevated carbon dioxide may act as a vasodilator and has been shown to increase cerebral oxygenation when measured with near infrared spectroscopy.[41] However, the potential vasodilatory benefits of hypercarbia cannot be realised if cerebral perfusion pressure is inadequate. Some experimental studies have shown anti-convulsive and anti-inflammatory effects with mild hypercapnia.[42] Whether this results in better outcome is unclear and a large multicentre trial is underway (NCT03114033). Until then normocapnia should be targeted, taking care to avoid hypocapnia which causes vasoconstriction leading to cerebral ischaemia.[23]

<h4> Blood pressure

Higher mean arterial pressure goals (80-100 mmHg) are required in some patients to achieve adequate brain tissue oxygenation,[43] perhaps because of swelling in perivascular cells or cerebral capillary collapse. Studies of cerebral autoregulation using near infrared spectroscopy (NIRS) show that following ischaemia-reperfusion, patients with chronic hypertension may have a right shift in their autoregulation curve and may warrant a higher MAP.[44] The benefits of routinely targeting a higher MAP have yet to be answered definitively but in two recent pilot trials a higher MAP goal compared to standard MAP goal did not reduce biomarkers of neuronal injury after the arrest.[41,45] Ongoing research seeks to identify whether individualised MAP goals are achievable.[18] Until such data are available, avoid MAP less than

65 mmHg and target a MAP that is sufficient to achieve adequate urine output (>0.5 mL kg^{-1} hr^{-1}) and normal or decreasing lactate.[23]

<h4> Other interventions

Seizures occur in 20-30% of cardiac arrest patients in ICU and are usually a sign of severe post cardiac arrest brain injury and should be treated with levetiracetam or sodium valproate as first-line antiepileptic drugs in addition to sedative drugs.[23] Hyperglycaemia is common after cardiac arrest. Although there is no definitive evidence of benefit, most clinicians would treat hyperglycaemia with a continuous insulin infusion, aiming for a blood glucose of 7.8-10.0 mmol L^{-1}.[23]

<h2> Ongoing trials

Trials investigating pharmaceutical interventions (e.g. calcium channel blockers, thiopental, magnesium, steroids, erythropoietin, xenon, glucagon) have not identified any effective interventions to date, although few had adequate power to detect a realistic difference in patient-centred outcomes.[46] A search of clinical trials.gov (September 2020) identified 23 randomised controlled trials with neurological outcomes as a primary or secondary end-point. Key trials are summarised in Table 2.

Table 2: On-going trials of therapies to reduce post resuscitation brain injury.

Timing	**Intervention**	**Primary Outcome**	**Planned Enrollment**
Intra-arrest	Ketamine / Morphine	Pre-hospital, blinded, randomized, placebo-controlled trial to determine in adults if intra-arrest ketamine or morphine improves survival and neurological outcome following out of hospital cardiac arrest. (NCT04009759)	2100
Immediately post ROSC	Optimised PaO_2	Multi-centre, randomised, controlled trial (RCT) to determine whether reducing oxygen administration to target an oxygen saturation of 90-94%, compared to 98-100%, as soon as possible following successful resuscitation from OHCA improves outcome at hospital discharge. (NCT03138005).	
Post ROSC ICU	Optimising TTM	Targeted Hypothermia Versus Targeted Normothermia After Out-of-hospital Cardiac Arrest (TTM2). Multi-centre randomised controlled trial	1900

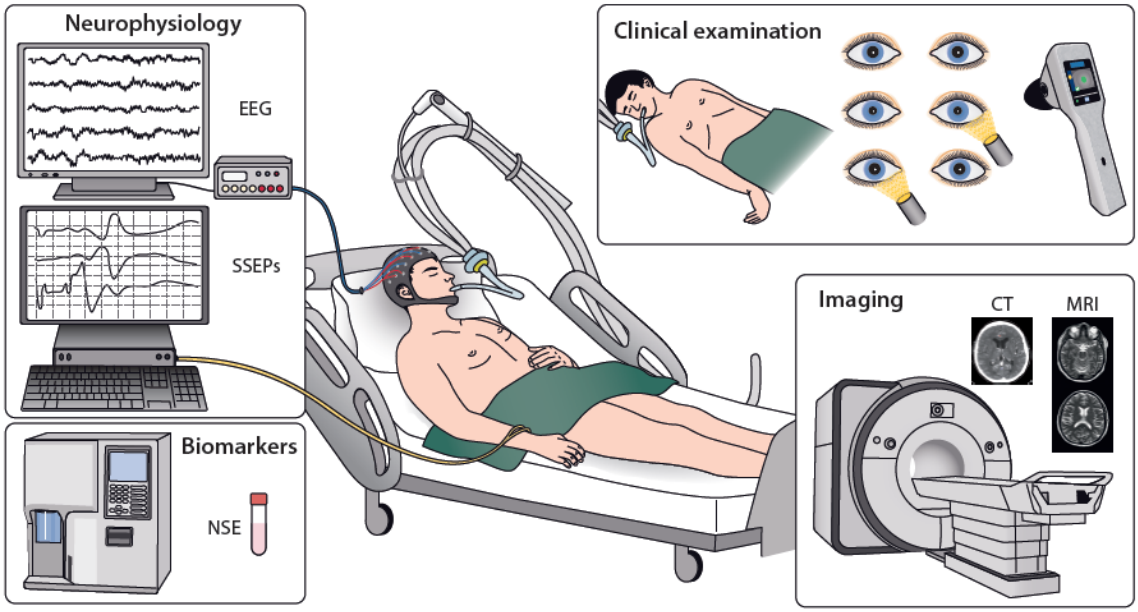
		comparing standard care with early treatment of fever with targeted temperature management to 33°C for up to 28 hours. (NCT02908308)	
Post ROSC ICU	Optimising TTM	Multicenter, randomized, adaptive allocation clinical trial to determine if increasing durations of induced hypothermia are associated with an increasing rate of good neurological outcomes and to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of cardiac arrest. (NCT04217551)	1800
Post ROSC ICU	Xenon	To evaluate whether there is a difference in functional outcome with xenon 50% and oxygen during TTM compared with similar oxygen content in air during TTM in comatose subjects with sustained restoration of spontaneous circulation (ROSC) within 30 minutes after out-of-hospital cardiac arrest (NCT03176186)	1436
Post ROSC ICU	Optimised PaO_2 and blood pressure	Multicenter, randomized trial in 2x2 factorial design allocating comatose OHCA patients to one of two target blood pressures (double blind) and restrictive vs. liberal oxygenation (open label) with blinded outcome evaluation. (NCT03141099)	800
Post ROSC ICU	Optimised $PaCO_2$	Multi-centre randomised controlled trial in resuscitated cardiac arrest patients. This trial will	1700

		determine whether targeted therapeutic mild hypercapnia applied during the first 24 hours of mechanical ventilation in the intensive care unit improves neurological outcome at 6 months compared to standard care (targeted normocapnia (NCT03114033).	
Rehabilitation	Computer-assisted self training.	Randomised, open label trial comparing Computer-Assisted Self-Training Versus Unspecific Training in Patients After Stroke, Cardiac Arrest or in Parkinson's Disease to Improve Executive Function. (NCT04229056).	600

<h1> Prognostication

Prediction of either a favourable or unfavourable outcome among comatose post-cardiac arrest patients improves communication with patient's families who usually seek some indication of the likelihood of a good recovery. Where a favourable outcome is predicted it provides justification for continuation of multi-organ support. Where an unfavourable neurological outcome (survival with severe disability requiring on-going care from others, unresponsive wakefulness syndrome or death) is predicted, some healthcare systems allow withdrawal of life sustaining treatment to prevent support of patients under conditions that are not consistent with their values. Where local practices permit, recognising that further organ support will not result in patient recovery may enable relatives to consider organ donation.

To date, most prognostication studies have focused on tests aimed at predicting a poor outcome. The challenge is to identify tests that have both high sensitivity (the ability to detect most of those destined to have a poor outcome) and high specificity (very low false positive rate). Of these, the very low false positive rate is particularly important because the risk of self-fulfilling prophecy is very high in this patient population (withdrawal of life sustaining treatment is likely to result in death even if a patient might have had delayed awakening). Self-fulfilling prophecy can create a false sense of accuracy among clinicians, because the true outcomes of patients are never observed.[47] Current evidence emphasises the importance of multimodal prognostication.[48] The main prognostic test modalities are summarised in Figure 4 and Table 3.



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380 **Figure 4: Key tests used to assess prognosis after cardiac arrest. Figure reproduced**

381 **with permission from the European Resuscitation Council.**

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383 **Table 3. Tests used for prognostication in post-cardiac arrest patients.**

Test modality	Explanatory notes
Clinical examination • Pupillary light reflex (standard or automated pupillometry) • Corneal reflex • Glasgow motor score • Myoclonus	• Pupillary light reflex and corneal reflex are often absent in the hours shortly after arrest, but these reflexes recover in survivors. Persistent absence of brainstem reflexes for days after removal of sedatives is associated with unfavourable outcome. Quantitative pupillometry appears more reliable than visual inspection.[49] • Improving Glasgow motor score represents clinical signs of recovering cortical function. However, motor exam alone is not reliable for predicting poor outcome.[50] • Myoclonus occurring in the early days after cardiac arrest may be malignant myoclonus which is associated with poor outcome or Lance-Adams syndrome which may have a favourable outcome.[51,52] Electrophysiological investigations are required to distinguish these syndromes.[51]
Blood markers of brain injury • Neuron specific enolase (NSE) • S-100B protein • Glial fibrillary acidic protein (GFAP) • Serum neurofilament light chain (NFL)	• NSE is released from neurons and rises over at least 72 hours after severe brain injury. Higher peak values are associated with unfavourable outcome. NSE may not be specific for brain injury, because it is also released from extracerebral sites.[53] • S-100B and GFAP are released from glia and peak shortly after cardiac arrest. Prognostic significance of specific values is less clear.[53] • NFL is released from axons. Higher NFL values correlate with unfavourable outcome more accurately than NSE in some cohorts, but experience with NFL is more limited.[53]
Electrophysiology • Bilaterally absent N20 somatosensory evoked potential (SSEP) wave • Electroencephalogram (EEG)	• SSEP measures the presence or absence of cortical response to electrical stimulation of the median nerve. The test can be performed at the bedside. Absent cortical response from a technically adequate study in the absence of sedative or other confounders is very specific for unfavourable outcome.[35,48] • EEG can demonstrate highly malignant patterns at various times after cardiac arrest that are associated with unfavourable outcome.[54] Unequivocal seizures on the EEG increases the likelihood of unfavourable outcome. Return of reactive, continuous EEG is associated with awakening. Reliable interpretation of EEG requires special expertise.[35,48]
Imaging • Brain computed tomography (CT) grey matter/white matter ratio (GWR) • Brian magnetic resonance imaging (MRI) diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC)	• CT can demonstrate early, severe cerebral oedema (low GWR at < 24 hours after arrest) that is associated with unfavourable outcome, including risk of progressive oedema leading to brain death.[1,35,48] • After 72 hours, areas of brain injury are visible as areas of restricted diffusion on MRI. Widespread cortical damage is associated with unfavourable outcome, but the significance of focal lesions and subcortical lesions is less clear.[35,55]

While data to support a favourable or unfavourable prognosis accumulate from the first moments after ROSC, changes in life-sustaining treatments or resuscitation based on prediction of neurological outcome should not occur until at least 72 h after cardiac arrest, as most patients who wake up will do so within that window. Assessment for an adverse neurological outcome should be considered in any patient who at 72 hours after cardiac arrest has a Glasgow Coma Scale Motor Score (GCS-M) of ≤ 3 (extending or no response to a noxious stimulus) at this time point.[56] Other testing modalities are then used to refine estimates of prognosis. One challenge of multimodal approaches is that the results of the various tests often do not align. About half the patients will be classified as indeterminate (about 14% of these will have a good outcome).[56] Current research seeks to better classify this group of patients.

Ultimately, the only way to reliably determine the performance of prognostic tests is to remove any element of self-fulfilling prophecy by continuing to support patients for a prolonged period regardless of the test results. The ability of a 30-minute EEG, SSEPs and brain CT within 24 h of the event to predict poor neurological outcome at 6 months (defined as dead or unresponsive wakefulness syndrome) was evaluated in 346 comatose cardiac arrest survivors who had no withdrawal of life sustaining treatment unless brain death was diagnosed.[57] Bilaterally absent or abnormal SSEPs, a gray matter:white matter ratio < 1.21 on brain CT and isoelectric/burst suppression EEG patterns predicted poor outcome with 0% falst positive rate (95% CI 0–3%). Another study examined the prognostic performance of SSEPs for 262 patients in a health care setting where withdrawal of life sustaining treatment is not practiced.[58] Bilaterally absent cortical responses predicted poor outcome with 0% false positive rate (95% CI 0.0-4.3%). Despite the need for more data such as these, the many patients surviving with unresponsive wakefulness syndrome in these studies presents an ethical challenge to conducting similar cohort studies in many systems.

<h1> Clinical and patient focused outcomes

Patients and the public involved in developing a Core Outcome Set for Cardiac Arrest highlighted the importance of outcomes beyond survival and gross assessments of neurological function.[59] Common sequalae of post cardiac arrest brain injury include impairments in cognition, emotional wellbeing, physical function, pain and fatigue, participation and return to work, which reduce health related quality of life.[59]

<h2> Cognition

Mild to severe cognitive impairment occurs in 25-55% of survivors.[60-63] Even mild cognitive impairment may be associated with reduced emotional status, exercise tolerance, quality of life, and social autonomy.[61,62,64] Most cognitive recovery occurs within the first three to six-months.[60,61,63,65] Further changes up to 12-months post-arrest are reported.[60,61] Some however report increased problems over time, potentially due to increased awareness of cognitive limitations as survivors return to activities with higher demands on their mental capacity.[64,65] Routine screening for impairments that are amenable to post-hospital rehabilitative interventions is recommended before hospital discharge, with re-assessment at 1-3-months, and up to a year.[60,61] The association between objective cognitive assessments and survivor-reported complaints is weak, and screening should measure both patient performance and patient-reported symptoms. The Montreal Cognitive Assessment is one potential screening assessment before more intense objective assessment.[64] The IQ-CODE-CA is an observer-reported questionnaire which explores the caregiver's perspective of deficits.[66]

<h2> Emotional wellbeing

Up to one third of survivors report symptoms of anxiety at 3-6-months (15-36%), with similar levels reported at 12-months (15-34%).[60,65] High levels of depression are similarly reported at 3-6-months (13-32%), with some reduction by 12-months (7-15%).[60,65] Post-traumatic stress is reported in approximately 25% of survivors at 6-12 months.[65] Up to one third of caregivers report high levels of post-traumatic stress at 1-2-years post-event, especially those who witnessed resuscitation.[67] Symptoms of anxiety and depression are more common in female and younger survivors and are strongly associated with health-related quality of life (health related quality of life) and cognition.[60]

<h2> Physical function and activities of daily life

When compared with the general population, survivors have reduced physical function at 3-months, 6-months, 12-months and 3-years.[68,69] At 6-months, physical limitations are reported in almost one half of survivors,[68] with 19-47% reporting mobility restrictions[63,65,69] and limitations in usual activities at 12-months.[65,70] Such complaints are more common in cognitively impaired, older survivors and females.[63,68]

<h2> Fatigue

Reports of physical and cognitive fatigue remain high throughout the first year of survival (25-71% at 6-months; 50% at 12-months)[61,62,65,68] and may be associated with emotional problems, sleep, stress, physical and cognitive impairment.[60]

<h2> Pain

Problems with pain are reported in 61% of survivors at 3-6 months,[70] 21% at 6-months,[68] and 23%-39% at 12-months.[63,65,69] Pain may be the result of CPR, in-hospital procedures, or other factors but so far such evaluations are limited.

<h2> Social participation, return to work and health related quality of life

Most survivors (90%) are discharged to home and living independently at 12-months.[60,65] However, reduced social participation in half of survivors at 6-months is strongly associated with depression, fatigue, cognition and mobility restrictions.[60,62] Limitations in usual activities may be due to physical and, to a lesser extent, emotional problems.[68] For survivors who were working pre-arrest, half return to work by 6-months,[62] with most (62-85%) returning by 12-months.[69] However, cognitive impairment and fatigue may impede any return, with reduced hours (50%) or other adaptations necessary.[60,62,65,69] Survivor health related quality of life is often reported to approximate that of the general population.[61,65,68,69] However, the limitations of such broad, generic assessments should be recognised.[61]

<h1> Rehabilitation

There are currently no widely accepted rehabilitation care pathways for post cardiac arrest brain injury, unlike for stroke, traumatic brain injury,[71] or myocardial infarction patients.[72] Depending on the cause of cardiac arrest, patients may be included in rehabilitation pathways designed for other patient groups such as post-myocardial infarction or brain injury rehabilitation. However, many patients receive limited or no rehabilitation.

<h2> Early rehabilitation

Early rehabilitation interventions described for critically ill patients are assumed to be suitable those with post cardiac arrest brain injury. These include early mobilisation and activation,

delirium management[73] and ICU diaries. Although there have been positive results in individual trials, there is only limited evidence for such interventions for long-term outcomes. ICU diaries are effective in decreasing emotional problems.[74]

<h2> In-hospital brain-injury rehabilitation

For patients with severe post cardiac arrest brain injury, further in-hospital brain-injury rehabilitation is recommended. Rehabilitation interventions are the same as those used for patients with acquired brain injury (see braininuryguidelines.org). The first step is an interdisciplinary assessment of common impairments (e.g. motor, pain, bulbar function, sensory dysfunction, bladder / bowel function, cognition and behavioural problems) to enable to development of individualised care plan. Goals include increasing independency in basic activities of daily living, supporting quality of life, and decreasing caregiver burden.[60] When baseline function and cognitive impairments are equivalent, outcomes following in-hospital rehabilitation are similar for post cardiac arrest brain injury (n=40) and traumatic brain injury (n=40).[75] For individuals with prolonged disorders of consciousness after cardiac arrest, rehabilitation potential is low.[61]

<h2> At hospital discharge

Systematic discharge planning is not routinely provided routinely for cardiac arrest survivors, which may lead to decreased access to, or priority for, patient-centered care and rehabilitation.[60,61] A standard multidisciplinary discharge checklist may be useful.[61]

<h2> Follow-up programs/services

Subtle symptoms, such as fatigue, cognitive impairment and emotional problems, may not be captured during the hospital course. These may become evident only upon return to more

demanding activities and roles.[60] In a randomised controlled trial, cardiac arrest survivors provided with an early structured follow-up by a trained nurse (n=79; mean time from cardiac arrest 90 days; mean number of follow up consultations 1.8, range 1-5) had earlier return to work (50% vs. 21% at 3 months) and better emotional well-being at 12 months compared to the control group (estimated mean differences 9-43%). The intervention included cognitive and emotional screening, provision of support and information, promotion of self-management strategies, and referral to specialised care (18%).[76]

<h2> Further referral/support

Rehabilitation may include physical-, cognitive-, cardiac-rehabilitation and/or psychosocial support.[60,61] Rehabilitative interventions focusing on adaptation to impairments can reduce these symptoms.[77] Individual rehabilitation plans should include both short- and long-term rehabilitation goals, such as return to hobbies and work, driving ability, ability to perform activities of daily living and participation. An individualised fatigue management telephone intervention (median 4 sessions, range 3-5) based on energy conservation and problem-solving techniques was specifically tested for patients with moderate to severe fatigue (>3 months post cardiac arrest) in a small feasibility study (n=18). Results suggested small improvements in both physical and cognitive fatigue (effect sizes r=0.23-0.25).[77,78]

<h1> Conclusion

Post-cardiac arrest brain injury remains a substantial cause of morbidity and mortality. Early recognition and response to cardiac arrest which includes high quality bystander CPR and rapid defibrillation, can mitigate the devastating consequences of post-cardiac arrest brain injury. Most people admitted to hospital have impaired consciousness and require admission to intensive care where best supportive care comprises targeted temperature management,

normalising physiology and allowing sufficient time for neurological recovery. Assessment for withdrawal of life sustaining treatments should be deferred until at least 72 hours after ROSC and should involve a multi-modal evaluation. Survivors of cardiac arrest may have sustained cognitive, emotional and physical impairment which can reduce social participation, return to work and adversely affect health-related quality of life. Post-cardiac arrest follow-up and rehabilitation may help accelerate recovery, but the evidence supporting one intervention over the other is sparse and warrants ongoing studies.

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<h1> Conflicts of interest

GDP reports grants from National Institute for Health Research, British Heart Foundation, Resuscitation Council UK, CWC reports grants from National Institute for Health, and a US patent (6,174,875 B1); MBS reports personal fees from BARD Medical. JPN reports grants from National Institute for Health Research, MR reports grants from National Institute for Health Research and a UK Patent (1062957.7). No conflicts to declare: RWN, KH, GL, KS. All authors have or previously held volunteer roles with one or more professional organisations associated with resuscitation including International Liaison Committee on Resuscitation, American Heart Association, European Resuscitation Council (ERC), ERC Research net and national resuscitation councils.

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