Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation

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More patients are surviving cardiac arrest than ever before; however, the burden now lies with estimating neurological prognoses in a large number of patients who were initially comatose, in whom the ultimate outcome is unclear. Neurologists, neurointensivists, and clinical neurophysiologists must accurately balance the concern that overly conservative prognostication could leave patients in a severely disabled state, with the possibility that inaccurately pessimistic prognostication could lead to the withdrawal of life-sustaining treatment in patients who might otherwise have a good functional outcome. Prognostic tools have improved greatly, including electrophysiological tests, neuroimaging, and chemical biomarkers. Conclusions about the prognosis should be delayed at least 72 h after arrest to allow for the clearance of sedative drugs. Cognitive impairments, emotional problems, and fatigue are common among patients who have survived cardiac arrest, and often go unrecognised despite being related to caregiver burden and a decreased participation in society. Through simple screening, these problems can be identified, and patients can be provided with adequate information and rehabilitation.

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Introduction

After major improvements in pre-hospital management, patients who are comatose who have been successfully resuscitated from cardiac arrest have become increasingly common in intensive care units. The current recommendations for initial post-resuscitation care from the European Resuscitation Council (ERC) and the European Society for Intensive Care Medicine (ESICM) include artificial ventilation, sedation, and targeted temperature management at 33–36°C for 24 h, initiated within 6 h of cardiac arrest.[1] Neurologists, clinical neurophysiologists, and neurointensivists have a central role prognosticating the neurological outcomes for patients not awakening after sedation clearance. This task can be challenging, and commonly requires multiple tools, including neurological examination, neurophysiological tests, neuroimaging, and chemical biomarkers. Results are preferably evaluated together: relying on any single test is strongly discouraged to avoid false-positive predictions of a poor outcome. A forecasted poor outcome typically leads to the withdrawal of life-sustaining therapy (WLST) and death. Hence the prediction precision, usually reported as specificity, should be maximal.

Different practices of neuroprognostication and WLST most likely explain why only a few patients who have survived long term have a severe neurological disability in most European countries and the USA,[2,3] which conversely represents a common condition in regions where WLST is not practised.[4,5] Patients who survive cardiac arrest generally do well in terms of their health-related quality of life and activities of daily living. However, fatigue, cognitive impairment, and emotional problems are common (panel) and frequently go unrecognised. Although most previous studies crudely classified outcomes as good or poor, methodological advancements in the last decade enable a more detailed assessment of the extent of anoxic brain injury and nuanced neuropsychological outcomes, which is more useful in clinical practice.

The goal of this Review is to provide a practical approach to the prognostication, follow-up, and rehabilitation of post-anoxic brain injury. We refer to a previous review in *The Lancet Neurology*,[6] and focus our systematic literature search on more recent (within the last 5 years) developments. We prioritise discussion of commonly available methods, supported by evidence from multiple sources. Unless stated otherwise, the presented studies are cohort analyses of one or several centres. Throughout this Review, unless indicated otherwise, a poor prognosis means a poor neurological outcome is likely, classified as Cerebral Performance Category (CPC) 3–5, and a good prognosis refers to an expected CPC of 1–2.

Patient assessment in intensive care

Clinical examination

For patients who are comatose after cardiac arrest, neurological assessments should be done serially, ideally without residual sedation. The Glasgow Coma Scale and the Full Outline of UnResponsiveness[7] are the most commonly used clinical scores. Although the Full Outline of UnResponsiveness score is equal to or better than the Glasgow Coma Scale in most conditions, evidence for its use in cardiac arrest is still scarce.[8] The former, especially the verbal subscore,[6] loses accuracy in patients who are intubated; therefore, the Full Outline of UnResponsiveness score is our preferred test.

The bilateral absence of pupillary light reflexes 72 h after cardiac arrest strongly indicates a poor prognosis, including most likely a poor outcome (specificity 99%). The absence of corneal reflexes at 72 h has a similar importance (specificity 95%); however, the sensitivities of the absence of pupillary light reflexes (approximately 20%) and corneal reflexes (approximately 30%) are low.[6] Attention to technique is paramount.[9] Absent pupillary reflexes on admission are also associated with a poor prognosis, but with unacceptably low specificity (at best, 70%).[10] The effect of absent or extensor motor responses on the outcome might be biased by sedatives and a neuromuscular blockade, and

Panel: **Patient perspective by Paul Swindell, a patient who survived cardiac arrest**

"In April, 2014, I was 48 years old, and had a healthy lifestyle with a good diet and regular exercise routine, which meant I was the fittest I'd been for years.

I arrested unwitnessed at home, and it was serendipitous that my wife chanced upon my motionless body. Controlling her shock and rising panic, she bravely started the chain of survival.

Stabilised by the emergency services then taken to the Essex Cardiothoracic Centre, I was cooled and comatose for 2 days. 2 weeks later, I appeared coherent and relatively ok, and as testing (coronary angiogram and MRI) proved negative, I received an implantable cardioverter-defibrillator and a diagnosis of idiopathic ventricular fibrillation. Discharged with just a device appointment, I was advised to live life as before, and if I had any issues to call the hospital or my general practitioner.

Once home, a short walk left me with the same state of lassitude that I had experienced completing a marathon years earlier. I felt dazed and confused, and had various non-cardiac issues: emotional instability, fatigue, constant headache, sensory sensitivities, lack of focus and concentration, and fragmented communication skills. I felt like a cadaver on autopilot.

Weeks passed with little improvement, and a visit to a general practitioner didn't help as I felt he didn't really understand my predicament, perhaps characterised by the remark, 'what do you expect, you were dead?' Without obvious heart issues, I didn't feel the need to recourse to the hospital and, consequently, my wife and I felt quite abandoned.

Attempting to shake the tiredness and headache, I resumed some activities. Whilst helpful for my mental state, I found it difficult to gauge the optimum levels and regularly found myself exhausted with the need for more recuperation. A lack of guidance and knowledge of what was normal meant I was often in a state of flux.

My wife was also suffering, as she was continually in a state of hypervigilance, checking that I was not going to leave her and our children again. In time, this state abated but later resurfaced, and she was subsequently diagnosed with post-traumatic stress disorder.

Desperate for help I saw a neurologist privately and, although exhausting, it benefited us enormously. He was the first doctor who had really listened and considered the bigger picture.

I also sought help online and found others with a similar experience, and consequently set up Sudden Cardiac Arrest UK, which has benefited not only my family but also many others who have been similarly left wanting after this life-changing event."

are therefore less reliable as indicators of a potentially poor outcome in patients undergoing targeted temperature management (specificity <76%, sensitivity 88%).[6] Localising movements[11] herald a good prognosis, representing one of the few clues in this direction (sensitivity 76%).[6]

Post-anoxic myoclonus (also called status myoclonus if persisting >30 min) has long been considered a reliable indicator of a poor prognosis; however, up to one in ten patients might still have a favourable outcome.[12,13] Post-anoxic myoclonus is observed in about 20% of patients with cardiac arrest; of these patients, 55–89% have a concomitant epileptiform electroencephalogram (EEG).[13,14] In the remaining patients, the myocloni most likely arise from subcortical structures; in fact, the absence of a cortical EEG association is considered a poor prognostic sign,[6] and about two-thirds of patients with an epileptiform EEG have myoclonic twitches.[15] It is paramount to consider myoclonus with a multimodal approach, integrating semiology, timing, and most importantly, EEG findings. It is generally taught that massive, axial jerks might be associated with highly malignant EEG patterns, whereas brief, mostly multifocal jerks do not always herald a poor prognosis; however, the clinical-neurophysiological association of myoclonus appears unreliable.[16,17] EEG showing underlying continuous, reactive patterns suggests a treatable post-anoxic myoclonus, most likely representing early forms of Lance-Adams syndrome.[6,14,18] This syndrome might be incapacitating initially, but responds to treatment and is compatible with a good long-term outcome.[18,19]

Since the clinical examination is commonly tarnished by subjective interpretation and an absence of clearcut threshold values, objective tools are of utmost importance: quantitative pupillometry is associated with neuronal injury, estimated by elevated serum neuron-specific enolase (NSE) concentrations,[20] with 100% specificity and 61% sensitivity for a poor outcome, which is clearly superior to standard pupillary light reflex examination.[20,21] However, the use of different devices and methods limits the generalisability of quantitative pupillometry, preventing routine implementation. Awaiting further data, this quantitative approach might help in addition to standard protocols, especially in situations of unclear prognosis.

Somatosensory-evoked potentials

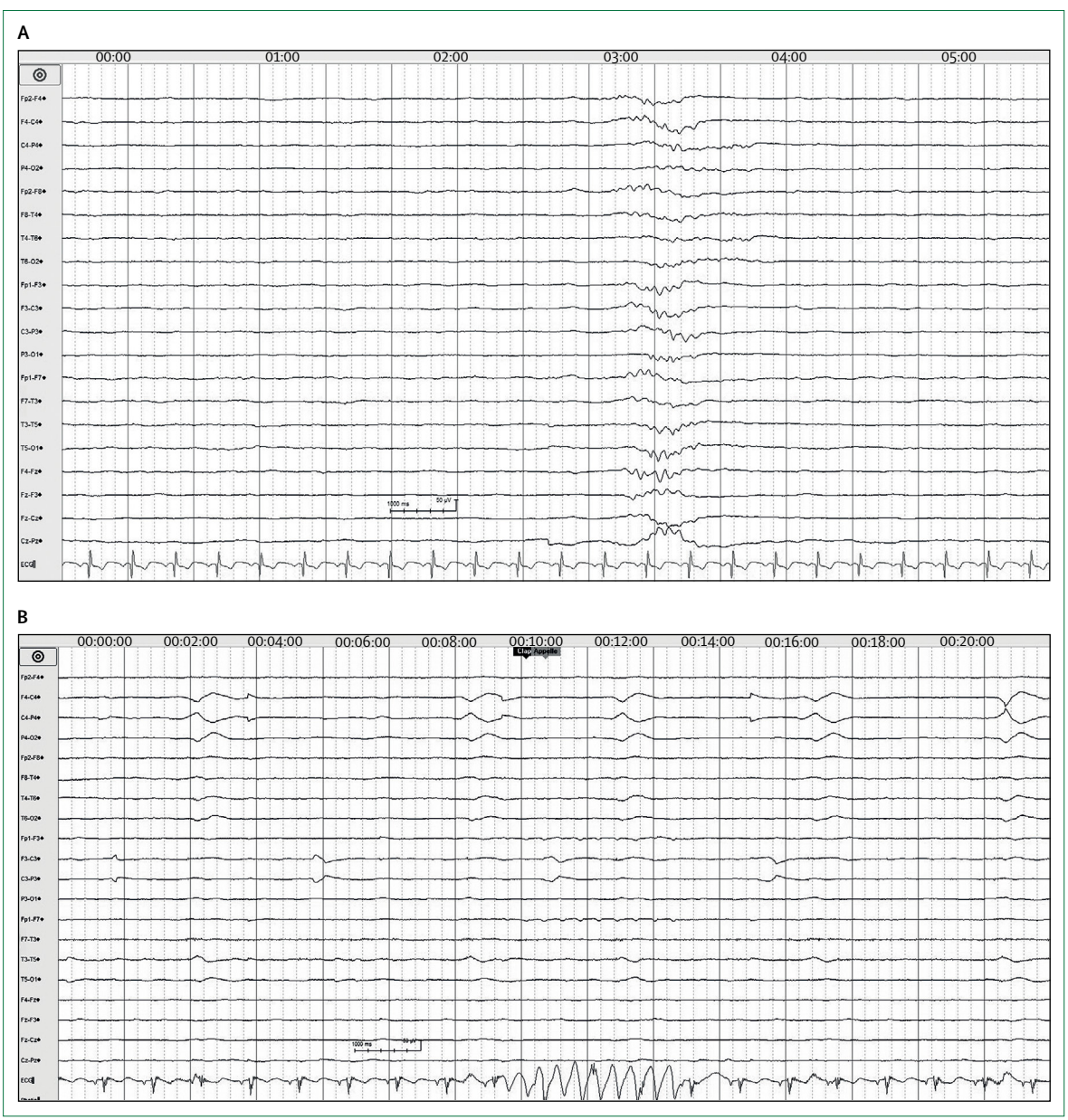
The bilateral absence of cortical somatosensory-evoked potentials (SSEPs) after median nerve stimulation (so-called N20 responses) robustly predicts a poor outcome (specificity >99%), but with little sensitivity (43–49%).[6,15] Although an analysis of 35 studies including 3816 patients suggested that the specificity might be only 93% (considering WLST triggered by SSEP results[22]), a non-systematic review of patients surviving despite the absence of cortical SSEPs underscored that the specificity approaches 100% if technical and other issues influencing the results are considered.[23] Regardless, widespread SSEP availability is suboptimal because of not enough recording software and trained personnel, and a redundancy with EEG findings has been noted.[24] Consideration of N20 amplitudes might improve the sensitivity for a favourable outcome; studies have identified a range of less than 0·62–0·65 μV for a poor prognosis (specificity 100%, sensitivity 57–71%), suggesting that patients with amplitudes greater than 2·5 μV do not have severe brain damage.[25,26] However, validation is required before routine implementation.

Seizures and EEG

EEG is a cornerstone of prognostication and is able to identify patients destined for poor or good outcomes.[6] A standard EEG assessment adhering to the validated American Clinical Neurophysiology Society (ACNS) terminology[27] is encouraged, not only to optimise generalisability but also to facilitate comprehensive description of the so-called ictal-interictal continuum, a spectrum of

alterations with prognostic and therapeutic implications. Identification of highly malignant patterns (suppressed or burst-suppressed EEG, with or without superimposed epileptiform discharges) has a reported specificity of 100% (but sensitivity as low as 5–50%) after targeted temperature management (figure 1).[28] This scoring strongly relates to other clinical, biochemical, and neurophysiological prognostic variables, highlighting the central role of EEG in multimodal prognostication.[29] The discriminative performance seems more robust at 12–24 h after cardiac arrest;[15,30] furthermore, routine targeted temperature management and sedation do not substantially alter the prognostic value of EEG.[31]

The return of continuous baseline activity is a favourable sign, with the sensitivity for a good outcome being between 63% (at 12 h), 80% (at 30 h), and 98% (within 120 h),[15,30] but with one important caution: α coma (frontally predominant, monotonous, and unreactive activity in the low α range) is strongly linked to poor outcome.[6] Also, early background discontinuity during targeted temperature management is still compatible with a good outcome.[15] Background reactivity to stimulation heralds a good outcome, with sensitivity up to 93%,[6] but its use is limited by a variable inter-rater agreement:[32,33] a Dutch multicentre study of 160 patients reported a specificity for a poor outcome of only 82% with absent reactivity[32] (which



(Figure 1 continues on next page)

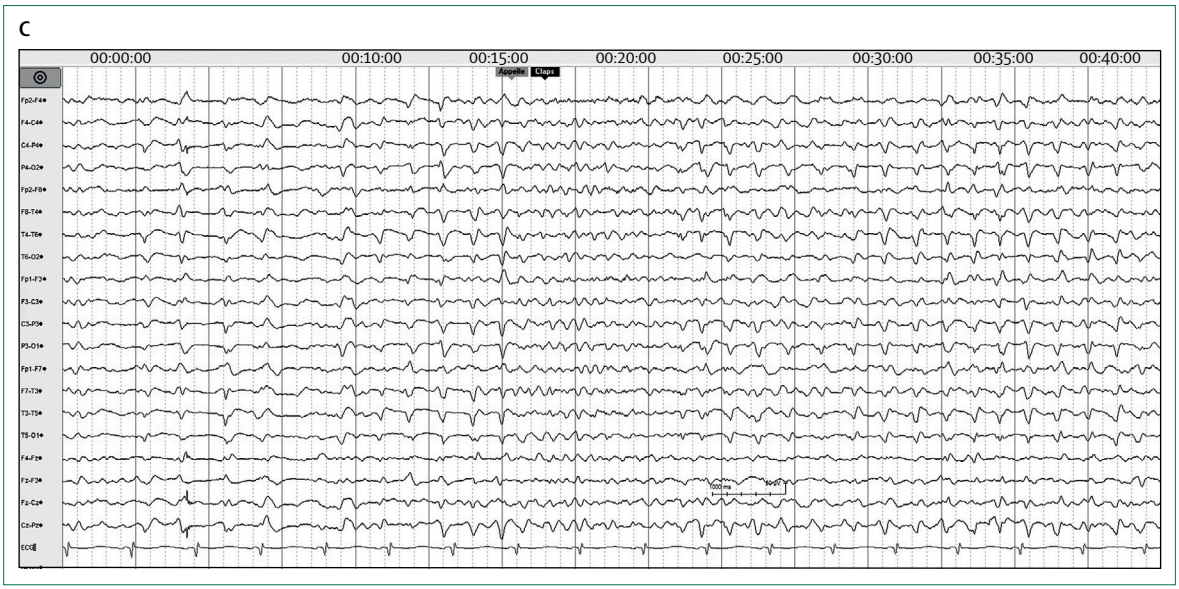


Figure 1: **Examples of highly malignant EEG patterns**
(A) EEG of a 58-year-old man 48 h after cardiac arrest (pulseless electrical activity, cardiac cause, and time to return of spontaneous circulation 35 min), after targeted temperature management (36°C, propofol weaning), with the EEG showing burst-suppression with non-epileptiform bursts (diffuse, irregular, θ), unreactive to stimuli. He only triggered respiration on examination. SSEP-N20 potentials were bilaterally absent, and peak serum NSE at 48 h was 83 ng/mL. He died after the withdrawal of life-sustaining therapy 4 days after cardiac arrest. (B) EEG of a 51-year-old man 59 h after cardiac arrest (ventricular fibrillation, cardiac cause, and time to return of spontaneous circulation 25 min), who was normothermic, off sedation, with a diffusely suppressed background, and not reactive to auditory stimulation (marks at the top of the figure; note also electrocardiogram artefacts of clapping hands, and periodic EEG respiration artefacts). Clinically, he only triggered respirations; SSEP-N20 potentials were bilaterally absent, and peak serum NSE at 24 h was 197 ng/mL. He died after the withdrawal of life-sustaining therapy 4 days after cardiac arrest. (C) Example of epileptiform EEG patterns compatible with awakening. EEG of a 77-year-old man 48 h after cardiac arrest (ventricular fibrillation, cardiac cause, and time to return of spontaneous circulation 17 min), after propofol weaning, showing a continuous θ-δ activity with superimposed, diffuse low-medium voltage periodic discharges; the background acelerated upon auditory stimulation (marks at the top of the figure), and the epileptiform elements disappear transiently. SSEP-N20 potentials were bilaterally present, and peak serum NSE at 24 h was 21 ng/mL. After receiving clonazepam, levetiracetam, and valproate intravenously, he awoke on day 5 and reached a Cerebral Performance Category of 2 at 3 months. EEG=electroencephalogram. NSE=neuron-specific enolase. SSEP=somatosensory-evoked potentials.

is concerning, but possibly underestimated).[34] Video-EEG association and standard stimulations should always be applied to optimise accuracy.

Similar to overt clinical seizures, an epileptiform EEG is often associated with a poor outcome; however, important exceptions are identifiable with the use of multimodal prognostication. Of note, clinical-neurophysiological associations are variable; therefore, we advise the use of ACNS EEG terminology,[27] especially in the absence of clearcut electrographic seizures (which are rare in this setting). There is no evidence supporting the use of prophylactic treatment with antiepileptic agents. A current study is evaluating post-cardiac arrest aggressive antiseizure management in an intended 172 patients (TELSTAR).[35] Repetitive electrographic epileptiform discharges, including seizures or status epilepticus, occur in 20–30% of patients who survive cardiac arrest,[36,37] historically associating with a poor outcome. However, at least 10% of these patients might awaken with appropriate treatment.[6,37] A continuous, reactive EEG background with peri-midline epileptiform discharges,[18] after targeted temperature management, and with preserved brainstem reflexes,[15,36,38] might identify patients with a better prognosis. Conversely, absent bilateral cortical SSEPs identify patients in whom treatment seems futile.[6] In patients with a potentially favourable prognosis, we recommend antiepileptic agents such as benzodiazepines, valproate, and levetiracetam;[39] without solid evidence, this recommendation is based on our experience. Pharmacological coma with midazolam or propofol, or both, might be indicated in refractory cases; additional options include perampanel, zonisamide, or topiramate.[18,19] The optimal treatment duration is also unknown, but in our experience, a reasonable trial is 2–3 weeks, with an extension in select patients (eg, patients without severe premorbid conditions, or younger than 60 years, or both, with NSE concentrations that are not high and an otherwise favourable multimodal assessment). There is still no solid evidence that such treatment, beyond decreasing EEG epileptiform activity,[39] leads to improved outcomes. Long-lasting intensive care might be indicated; one study described three patients, aged 50, 51, and 71 years, with extended EEG burst-suppression and epileptiform discharges but an otherwise favourable multimodal assessment, who started recovering several weeks after cardiac arrest; all had θ frequency within their bursts.[40]

Although in some centres continuous EEG is done for up to 48–72 h, repeated standard (20 min) EEG might represent an alternative for hospitals with few resources, without any discernable influence on the outcome.[41]

Because the EEG typically evolves over time, also reflecting changes in the concentration of sedatives,[30] continuous or repeated assessments are recommended in the first 48–72 h. Reduced electrode montages seem suited for background assessment, but might be less sensitive for seizure detection.[36,42]

The ACNS EEG terminology does not prevent the subjective assessment of reactivity or so-called modifiers, such as superimposed rhythmic or sharp activity. To further improve objectivity, automated EEG interpretation seems promising, especially with machine learning (area under the curve for good outcome prediction is 0·80 *vs* 0·69 for expert reading),[43] or with the attempted identification of machine-used variables to prognosticate (which are strikingly similar to the human eye).[44] Agreement with expert reading seems good (κ=0·71).[45] The principal limitation of these techniques is their generalisability, because each group that studied this technique developed their own procedure; furthermore, the number of possible mathematical approaches is virtually endless. Prospective, multicentre efforts are urgently needed.

Neuroimaging

Imaging represents an adjunct tool in neuroprognostication and is the only modality providing a visual picture of structural brain injury. The degree of imaging can be quantified and followed through repeated examinations. Furthermore, advanced tools, such as diffusion tensor imaging of whole-brain white matter, can give deeper insight to functional recovery, especially in patients with long-term disorders of consciousness.[46]

The two most common modalities used in the initial post-cardiac arrest period are CT and MRI. Both are widely available, non-invasive, and safe, even in patients who are intubated in an intensive care unit. The choice of modality and timing should consider patient factors, such as respiratory or haemodynamic stability. CT might be normal initially, even in patients with an ultimately poor prognosis, but might be useful to identify severe early oedema (poor grey-white matter differentiation, sulcal effacement, and cisternal compression), which is highly likely to herald a poor outcome and possibly progression to brain death.[47] If the CT is unrevealing, an MRI at 3–5 days after cardiac arrest might be appropriate, because this timepoint appears to be the most sensitive to indicate the degree of injury.[48,49]

A systematic review and meta-analysis of 44 studies, including 4008 patients, evaluated CT and MRI predictive accuracies.[50] Decreased CT grey-white matter ratio (20 studies) predicted a poor outcome with a specificity of 97%, but a sensitivity of 44%; similarly, diffusion-weighted imaging abnormalities on MRI had 92% specificity (improving to 95% when combining fluid-attenuated inversion recovery sequences with diffusion-weighted imaging) and 77% sensitivity. However, there was a marked heterogeneity in the timing of the imaging and neurological assessments, and MRI abnormality quantification was scarce or absent. Figure 2 shows examples of the spectrum of MRI abnormalities after cardiac arrest. Importantly, global mild MRI changes might be compatible with a good outcome.[46,51]

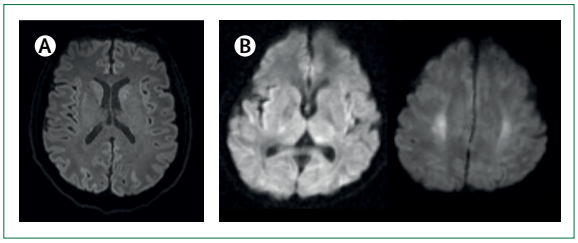


Figure 2: **Spectrum of an MRI-detected global ischaemic injury after cardiac arrest**
(A) MRI of a 56-year-old patient with a 30 min pulseless electrical activity arrest. Diffusion-weighted imaging (left) shows diffuse and severe injury throughout the basal ganglia and cortex. The patient remained comatose and died after the withdrawal of life-sustaining therapy on day 9 after arrest. (B) MRI of a 27-year-old woman with cardiac arrest because of ventricular fibrillation and 8–15 min of resuscitation. Initial Glasgow Coma Scale motor score was 4 (flexion to painful stimuli), and she developed eye opening by day 7. Her MRI on day 7 post-cardiac arrest showed diffusion-weighted changes in the thalami (left) and white matter (right) bilaterally. She recovered to have a modified Rankin Scale score of 2 at 6 months, and continues to receive rehabilitation, including cognitive training.

Study findings have called into question the accuracy of grey-white abnormalities on early CT after targeted temperature management,[52] and technical differences might lead to discrepant results.[53] The overall quality of evidence for neuroimaging appears low.[54] Nonetheless, the use of this method has been included in prognostication guidelines.[1] Given the data quality, however, recommendations have suggested the use of "diffuse anoxic injury on brain CT or MRI" as a lower-tier prognostic factor, again without quantification or a clear definition of what diffuse denotes.

Blood biomarkers

Breakdown products from neurons and astrocytes measured in the serum after cardiac arrest constitute a rapidly developing field. NSE and glial S100 protein have been clinically available for several years. High NSE serum concentrations within the first 48–72 h are recommended for prognostication,[1,55] and seem superior to S100; there was no added value in combining these two markers.[56] NSE has a reasonable prognostic performance (sensitivity 52–63%, specificity 95–100%),[57] is available on standard analytical instruments, and was used as a surrogate for brain injury in clinical trials for cardiac arrest.[58,59] Ease of sampling and interpretation, little effect from sedation, and quantitative measurement of brain injury represent advantages compared with other methods. The major limitations are the absence of calibration standards between laboratories and analytical methods, no consensus on cutoff values, and possible contamination by haemolysis, because NSE is also present in erythrocytes.[60–62] Low NSE provides evidence against severe hypoxic-ischaemic brain injury.[63] Among the many new serum biomarkers, neurofilament light chain appears most promising. In a large study of 782 patients, it

	Timing	Notes
Neurological examination: Full Outline of UnResponsiveness score	Daily; base prognostication on results ≥72 h after arrest, off sedation	Poor motor examination no longer considered highly specific for a poor prognosis
EEG	Continuous monitoring until awakening; or routine EEG at 12–24 h and repeated after sedation weaning (48–72 h) for patients still comatose	Highly malignant EEG patterns might evolve over time and follow a trend. Reactivity should be assessed; its presence might portend a better outcome
Chemical biomarkers neuron-specific enolase	Daily for the first 3 days. Omit or interrupt if patient wakes up	Trend over 3 days (of neuron-specific enolase) might be helpful to exclude contamination; rising values over 24–48 h suggest a brain origin
CT	For patients still comatose at 48–72 h	CT on admission helps exclude a CNS cardiac arrest cause (eg, intracranial haemorrhage) in some patients
Somatosensory-evoked potentials	Triage by EEG results. For patients still comatose at 48–72 h	Bilateral, technically optimal assessment in patients without cortical responses is mandatory
MRI	Day 3–5 after arrest	Necessary only if initial CT not already showing severe anoxic injury. Advanced techniques (diffusion tensor imaging, functional MRI) might be considered in specialised centres

EEG=electroencephalogram.

Table 1: **Proposed algorithm for the timing of neuroprognostic tests**

outperformed S100, NSE, and S-Tau, as well as EEG, SSEP, and brain CT.[64]

Multimodal prognostication

An approach in which multiple methods are combined is recommended by guidelines[1,55] and experts,[6] but any supporting evidence is still scarce. Two fundamentally different strategies exist. In a stepwise approach, additional investigations might be added until a hypothesis is supported, typically predicting a poor prognosis. Another approach is to routinely gather and balance as much evidence as possible for and against a poor (or good) prognosis. Although the stepwise approach is prone to confirmation bias, the parallel approach is more complex, costly, and possibly less efficient. Combining SSEP with CT and EEG in a stepwise approach with a specificity set at 100% led to a sensitivity of 74·4%. However, if a positive finding in two-thirds of all tests was required, the sensitivity declined to 49·7%.[5] The currently most widely used multimodal algorithm is from the ERC ESICM guidelines,[1] requiring evidence from two or more methods to reliably forecast poor prognosis. A validation study reported a 100% specificity of this algorithm, but only 28% sensitivity:[51] there is apparently a consequence to safe predictions, highlighting an urgent need for novel methods with high sensitivity.

A practical approach to prognostication and related decisions

A daily neurological examination, including the formal testing of brainstem reflexes, appears effective to monitor functional recovery; the occurrence and distribution of myoclonus should be noted. We recommend continuous or routine EEG in all patients within the first 24 h, and serial daily serum NSE sampling. Although only a small group of patients die during the first 1–2 days, mainly because of cardiac or multiorgan failure, a large proportion wakes up after sedation is discontinued at 24–36 h.[65] Short-acting sedatives allow earlier awakening,[66] and most patients with an early awakening have a favourable trajectory and require no further testing.[55] For those remaining unconscious, additional NSE sampling at 48 h and possibly 72 h, another EEG at 48–72 h and brain imaging (preferably MRI) is recommended (table 1). On the basis of EEG results, patients might be stratified for SSEP.[24]

To reliably predict a prognosis, we recommend the use of the ERC ESICM algorithm,[1] which is currently undergoing an update. This algorithm supports a multimodal approach (rather than relying on any single test), taking into account sedation effects and advocating for patience and delayed prognostication in cases of uncertainty. Accordingly, prognostication should start at 72 h after cardiac arrest (or later if confounders are present). If the patient does not fulfil the criteria for a most likely poor prognosis, continued observation is recommended, since a delayed awakening with a reasonable outcome is common.[67] Patients aggressively treated for electrographic seizures with antiseizure and sedative agents need more time to recover: brain MRI, repeated clinical examinations, and EEG are helpful. Test results indicating a poor outcome should be balanced against those indicating the opposite (table 2). However, indicators of a good prognosis are considerably less investigated and, although sensitive, they are usually less specific.

One of the most challenging, but also most common, situations for patients after cardiac arrest is decision making around WLST.[68] The timing can be tricky, because there is a temptation, including desires from the family or caregivers, to establish a prognosis early.[69] Premature determination of a poor prognosis might be quite common.[70] If acted upon, it can lead to death in patients who might otherwise have done well (self-fulfilling prophecy).[69] Decision making should take into account not only neurological injuries but also the patients' preferences and systemic and premorbid factors: a patient with pre-existing dementia or an advanced malignancy might warrant less aggressive treatment than a younger patient with no comorbidities. Furthermore, patients might sustain severe and sometimes irreversible systemic injuries from their cardiac arrest, which certainly should factor into decision making.

Death by neurological criteria (ie, clinical brain death) represents 10–15% of patients with cardiac arrest dying before hospital discharge.[71] The timing and means for diagnosis might be challenging. Firstly, a clinical brain death determination requires proving the permanent, irreversible, and complete absence of all brain function. Given that patients can have little to no brain function early after cardiac arrest but later recover some brainstem function, it is recommended to wait at least 24 h after

arrest and with complete rewarming, in contrast to brain death associated with other cerebral injuries.[72] Secondly, brain death determination in a patient after cardiac arrest can be confounded by targeted temperature management, along with concomitant sedation and paralytics. It is therefore advisable to wait and eliminate confounding factors whenever possible. Neuroimaging can be helpful in this situation, and signs suggesting cerebral circulatory arrest, such as severe cerebral oedema with herniation, should be present before other ancillary tests are considered accurate.

Long-term outcome of survivors

Outcomes after cardiac arrest are commonly reported by the use of crude ordinal scales, such as the CPC or the modified Rankin Scale,[73] typically dichotomised into good or poor categories. The poor category usually includes those dead, unresponsive, or awake but dependent for basic activities of daily living (ie, CPC 3–5, modified Rankin Scale 4–6). In countries where WLST is uncommon, a poor outcome because of hypoxic-ischaemic brain injury is seen in more than 50% of patients.[4,5] In this context, all patients with unresponsive wakefulness more than 1 month after cardiac arrest were still severely impaired or dead at 2-year follow-up,[4,74] and only 4% of patients who had survived with a poor outcome at 30 days had a meaningful improvement.[4]

When WLST is routinely practised, most patients who survived cardiac arrest (>90%) have a good outcome (CPC or modified Rankin Scale).[2,3] However, as shown by the patient story (panel), a seemingly good outcome might still include long-term consequences, such as cognitive impairment, especially decreased processing speed or attention, or both;[75–77] memory deficits;[76–79] or executive dysfunction.[75–79] These might initially go unrecognised, because demands on the mental capacity of inpatients are low. Early cognitive testing, however, identifies impairment in most patients who survive cardiac arrest.[77] Most cognitive recovery occurs during the first 3 months,[80,81] with minor improvements in individual patients up to 12 months after cardiac arrest.[81] The reported prevalence of cognitive impairment in the chronic stage varies between studies (30–50%).[76,79] Part of the cognitive dysfunction observed might be unrelated to cardiac arrest, because similar problems were identified in an age-matched control group with myocardial infarction.[76] Potential alternative reasons include vascular cognitive impairment, age, sleep disturbances, chronic pain, or emotional problems.[76,82] Although cognitive complaints because of emotional problems should be separated from brain injury, emotional problems such as apathy might also be a symptom of cognitive impairment.[78] Emotional problems are common and often long-lasting in patients who survive cardiac arrest;[80] in a large US inpatient sample (n=184 567), emotional issues justifying a psychiatric diagnosis were detected in a quarter of patients who survived, depression being the most common and more frequent in women and younger patients (18–64 years).[83]

	Good prognosis	Poor prognosis
Neurological examination	Motor response localising[13]	Absent pupillary and corneal reflexes bilaterally ≥72 h. Status myoclonus <48 h with associated highly malignant EEG pattern
EEG	Early return of a continuous, reactive, normal voltage background[15,30]	Highly malignant EEG pattern[28] (suppressed or burst-suppressed, with or without epileptiform discharges)
Somatosensory-evoked potentials	Amplitude >2·5 μV[26]	Bilaterally absent N20 responses 48 h or later
Neuron-specific enolase	Serum neuron-specific enolase ≤17 μg/L[63]	High concentrations at 48 h or later; increasing serial concentrations
CT brain	..	Diffuse anoxic injury (reduced grey-white matter differentiation and sulcal effacement)
MRI brain	..	Diffuse and extensive anoxic injury

Good prognosis means a predicted outcome of a cerebral performance category of 1–2, and a poor prognosis means a predicted outcome of a cerebral performance category of 3–5. EEG=electroencephalogram.

Table 2: **Indicators of good and poor prognosis**

Anxiety is also commonly reported;[82,84] in addition to having general anxiety, patients who survive cardiac arrest also have cardiac-related anxiety, including the need to seek medical attention regularly and the avoidance of activities increasing heart rate.[85] Additionally, post-traumatic stress disorder can also occur.[80,86]

Focusing on the perspective of the patient, the most prevalent symptom at 6 months is fatigue (69–71%),[75,87] which can be associated with emotional problems, sleep disturbances, stress, physical exhaustion, or cognitive impairment.[88] The cause of fatigue after cardiac arrest is unknown, but among patients with brain injuries, it might arise from increased efforts to compensate for cognitive impairment.[88] Supporting this theory is the common occurrence of decreased mental processing after cardiac arrest[75,76] and cognitive fatigue.[89] Fatigue is also reported in other patients after a long-term stay in the intensive care unit.[90]

After discharge, most patients who survive can return home and live independently; only 1–10% need long-term institutionalised care.[80,91] Health-related quality of life after cardiac arrest is generally good, with overall scores approaching that of the healthy population.[91–93] Risk factors for a lower quality of life are female sex,[92,93] unmarried status,[94] emotional problems,[81,94] and cognitive impairment.[81] Physical and emotional problems might restrict daily activities and participation in society.[87,92] An important measure is the ability to return to work, which, reassuringly, occurs in 70–85% of patients who survive and were working before cardiac arrest,[80,91] although sometimes on reduced schedules.[80,87] Factors reported to decrease the chances to return to work include cognitive impairment and fatigue.[87,95]

Practical management of recovery from brain injury

Inpatient brain injury rehabilitation

Early rehabilitation could start when the patient is still in the intensive care unit and include mobilisation and

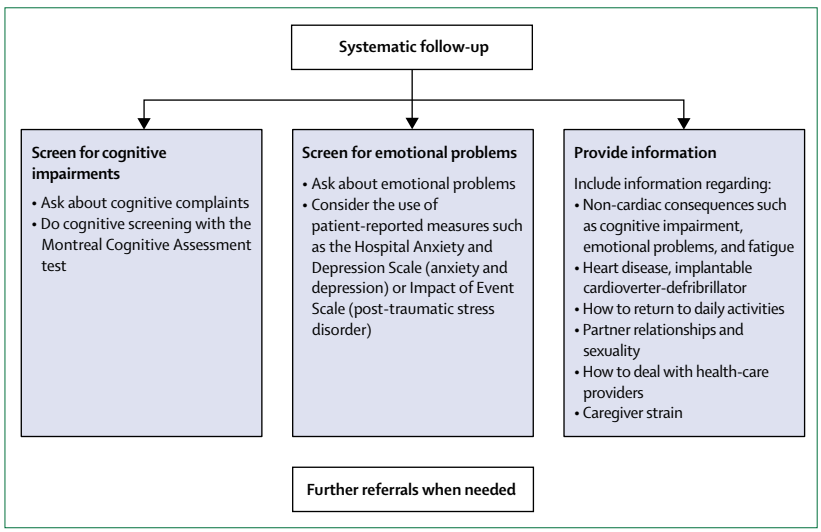


Figure 3: **Systematic follow-up according to the 2015 European Resuscitation Council and European Society for Intensive Care Medicine guidelines for post-resuscitation care**

For **examples of this peer support group** see http://www.SuddenCardiacArrestUK.org

the prevention of delirium;[96] however, studies targeting patients with cardiac arrest are warranted. For the small number of patients who survive cardiac arrest with severe hypoxic-ischaemic brain injury, discharge home is often not possible and inpatient rehabilitation should be considered. The effects appear similar to patients with traumatic brain injuries.[97,98] Rehabilitation might improve everyday functioning[97,98] and lessen caregiver burden.[99] However, recovery can take a long time, and reaching full independence is unlikely in severe cases.[74,99]

Early follow-up and screening

For patients who survived and are discharged home, it is important that surveillance is organised, preferably within 3 months: this is the key to identify remaining consequences and to provide referrals for further interventions when needed.[100] There is a wide variation in follow-up care, but according to current guidelines[1] this care should be organised systematically and always include: screening for cognitive impairments, screening for emotional problems, and provision of information (figure 3).[1] Information should preferably be provided both in oral and written forms, not only covering topics concerning medical care, but also explaining potential cognitive and emotional problems and how to deal with them.[1] Evidence for a structured follow-up was found in a randomised controlled trial, in which the effects of an early intervention service provided by trained specialised nurses were evaluated (n=185). The intervention included screening for cognitive and emotional problems. Up to six 1-h consultations could be provided, tailored to the needs of patients, and referral to further specialised care was arranged when needed. At 1 year, patients who received the intervention showed significantly improved emotional wellbeing (improvement 40–43%), higher scores on three domains of health-related quality of life (improvements 9–24%), and were more able to return to work (at 3 months: 50% *vs* 21%).[101] Additionally, the intervention was cost effective.[102]

Psychosocial interventions

If emotional problems are identified, referral to a psychologist or psychiatrist should be considered, because these problems can persist and are, at least to some extent, treatable. This referral is especially important since emotional problems (depression, anxiety, post-traumatic stress disorder) might predispose a patient to future cardiovascular events.[103,104] Two interventions were specifically designed for patients with cardiac arrest, with positive effects substantiated by findings from a randomised controlled trial. Interventions addressed physiological relaxation, self-management, coping strategies, and information including issues related to living with an implantable cardioverter-defibrillator and health education.[105,106] Additionally, emotional problems in caregivers need to be taken into consideration, since they are common and the burden can be high, especially in those who have witnessed the resuscitation.[107] In the UK, a peer support group for patients who have survived cardiac arrest and their families is well established.

Cognitive rehabilitation

Cognitive rehabilitation is mainly provided by an occupational therapist or neuropsychologist, or both, within a programme for brain injury rehabilitation. The goal is to reduce the everyday consequences of impaired cognitive functioning. There are no specific guidelines for patients who survive cardiac arrest, but recommendations for patients with other types of acquired brain injury, such as stroke or traumatic brain injury, might be helpful.[108] The most recent evidence-based recommendations for cognitive rehabilitation from 2019 state that strategies to improve or compensate for common cognitive deficits involving, for example, attention, memory, and executive functioning, should be provided.[108]

Fatigue management

Fatigue management can be included in cognitive rehabilitation programmes or provided alone. There is currently no evidence-based treatment for fatigue after brain injury, but encouraging results have been reported for some commonly used interventions.[88] Management often starts with the identification and treatment of modifiable risk factors, such as sleep and mood disturbances, pain, and medication side-effects. Other interventions include education or symptom management strategies, or both; cognitive-behavioural interventions, mindfulness-based stress reduction, working memory training, physical exercise, and medications.[88] For patients who have survived cardiac arrest with moderate-to-severe fatigue, a telephone intervention was developed based on Energy Conservation and Problem Solving Therapy.[109] This intervention showed positive results in a small

single-centre study (n=18), substantially reducing physical and cognitive fatigue (with a moderate effect size).[110]

Integrated rehabilitation

Most survivors have a cardiac cause of arrest and are eligible for a cardiac rehabilitation programme involving exercise training, risk factor management, lifestyle advice, education, and psychological support.[111] There is evidence that this programme is cost effective, decreases cardiovascular mortality, reduces hospital admissions, and improves quality of life.[112] However, within cardiac rehabilitation there is generally little attention paid to cognitive issues. This problem is an area for improvement.

There are examples of integrated care paths, combining cognitive rehabilitation, psychosocial care, and cardiac rehabilitation.[113,114] In the Netherlands, an integrated approach was developed, in which patients were screened for cognitive and emotional problems before rehabilitation.[113] For those with cognitive impairments, the training was adjusted, and neuropsychological examination and cognitive rehabilitation were offered. More research on the effectiveness of this integrated approach is still needed, and importantly, not all patients who survive cardiac arrest are eligible for cardiac rehabilitation in this integrated pathway because of other causes of their arrest.

Conclusions and future directions

Brain injury after cardiac arrest constitutes a rapidly developing research field. It is most likely that ongoing advances in neurophysiology, neuroimaging, and serum biomarkers will enable the more accurate and earlier estimation of prognosis for most patients, even within 24–72 h after cardiac arrest. However, important concerns regarding standardisation and the implementation of methods outside large academic centres still exist. Therefore, there is currently insufficient evidence to support crucial prognostic decisions before 72 h after cardiac arrest. When assessing a patient who is comatose after cardiac arrest, use of international guidelines and local protocols is strongly encouraged to reduce the risk of bias. Because guidelines were constructed prioritising safety, many patients will remain with an unclear prognosis after the first assessment and need a longer observation period free from confounding from sedation. Neurologists, neurointensivists, and clinical neurophysiologists with a sound knowledge of the strengths and limitations of the available methods to diagnose a brain injury have a central role in these assessments and should encourage the treatment of the large proportion of these patients with seizures along with a potentially favourable prognosis in multimodal assessments. Indicators of a poor prognosis should be balanced against indicators of a more favourable outcome, as shown in table 2. Although the extent of brain injury is usually most important, other patient-related factors should be considered for the ethically challenging decision to discontinue or extend intensive care.

Search strategy and selection criteria

We did two searches, one covering prognosis-related terms, the other covering patient-related and long-term outcome terms. An information specialist was consulted to co-develop and run the search strategies. We searched PubMed, Embase (Elsevier), CINAHL (EBSCO), and PsycInfo (EBSCO) using building blocks strategy with free-text terms. Key concept terms were: "cardiac arrest", "prognosis methods", "patient perspective", and "long-term follow-up". The search strategies covered possible synonyms and terms related to key concepts. We restricted the searches to Title/Abstract fields for PubMed and Embase, and publication dates were limited to "Last 5 years" for the searches covering prognosis-related terms. We excluded studies in PubMed and Embase containing the terms (pediatr* OR child* OR neonat* OR animal OR experimental). In Embase, unique records from Embase were retrieved by the Source-function, excluding MEDLINE records. Conference abstracts and case reports were excluded in Embase. A combined search in CINAHL and PsycInfo focused on key concepts, patient perspectives, and long-term follow-up, with synonyms and related terms included in the free text search strategy. No language restriction or publication type or study type filter was used in any of the databases. References were included on the basis of their relevance to the aims of our Review.

The widespread practice of WLST has made patients who have survived cardiac arrest long-term with severe brain injuries uncommon in many countries. However, mild-to-moderate cognitive impairments are common and might complicate the lives of these patients in many ways, as the perspective in the panel illustrates. Although the need for the follow-up of a cognitive disability after cardiac arrest is apparent, there is still insufficient evidence to support any specific strategy for follow-up or rehabilitation. Consequently, randomised controlled trials are urgently needed.

Contributors

TC outlined and coordinated the review. All authors drafted separate parts of the text and edited all parts. GL, VM, DG, and AOR provided the figures.

Declaration of interests

TC and VM participated in the 2015 European Resuscitation Council and European Society for Intensive Care Medicine guidelines for post-resuscitation care. DG receives research support from the National Institute of Health as the principal investigator of clinical trial R01NS102574-01A1, and from Becton Dickenson as the principal investigator of the INTREPID study (NCT02996266). He also receives compensation as the Editor-in-Chief for *Seminars in Neurology*. All other authors declare no competing interests.

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References

1 Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med* 2015; **41:** 2039–56.

2 Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA* 2019; **321:** 1200–10.

3 Dyson K, Brown SP, May S, et al. International variation in survival after out-of-hospital cardiac arrest: a validation study of the Utstein template. *Resuscitation* 2019; **138:** 168–81.

4 Kim YJ, Ahn S, Sohn CH, et al. Long-term neurological outcomes in patients after out-of-hospital cardiac arrest. *Resuscitation* 2016; **101:** 1–5.

5 Scarpino M, Lolli F, Lanzo G, et al. Neurophysiology and neuroimaging accurately predict poor neurological outcome within 24 hours after cardiac arrest: the ProNeCA prospective multicentre prognostication study. *Resuscitation* 2019; **143:** 115–23.

6 Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol* 2016; **15:** 597–609.

7 Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. *Ann Neurol* 2005; **58:** 585–93.

8 Almojuela A, Hasen M, Zeiler FA. The Full Outline of UnResponsiveness (FOUR) Score and its use in outcome prediction: a scoping systematic review of the adult literature. *Neurocrit Care* 2019; **31:** 162–75.

9 Maciel CB, Youn TS, Barden MM, et al. Corneal reflex testing in the evaluation of a comatose patient: an ode to precise semiology and examination skills. *Neurocrit Care* 2020; published online Jan 9. https://doi.org/10.1007/s12028-019-00896-0.

10 Javaudin F, Leclere B, Segard J, et al. Prognostic performance of early absence of pupillary light reaction after recovery of out of hospital cardiac arrest. *Resuscitation* 2018; **127:** 8–13.

11 Schefold JC, Storm C, Krüger A, Ploner CJ, Hasper D. The Glasgow Coma Score is a predictor of good outcome in cardiac arrest patients treated with therapeutic hypothermia. *Resuscitation* 2009; **80:** 658–61.

12 Lybeck A, Friberg H, Aneman A, et al. Prognostic significance of clinical seizures after cardiac arrest and target temperature management. *Resuscitation* 2017; **114:** 146–51.

13 Seder DB, Sunde K, Rubertsson S, et al. Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. *Crit Care Med* 2015; **43:** 965–72.

14 Dhakar MB, Sivaraju A, Maciel CB, et al. Electro-clinical characteristics and prognostic significance of post anoxic myoclonus. *Resuscitation* 2018; **131:** 114–20.

15 Rossetti AO, Tovar Quiroga DF, Juan E, et al. Electroencephalography predicts poor and good outcomes after cardiac arrest: a two-center study. *Crit Care Med* 2017; **45:** e674–82.

16 van Zijl JC, Beudel M, de Jong BM, et al. The interrelation between clinical presentation and neurophysiology of posthypoxic myoclonus. *Ann Clin Transl Neurol* 2018; **5:** 386–96.

17 van Zijl JC, Beudel M, Elting JJ, et al. The inter-rater variability of clinical assessment in post-anoxic myoclonus. *Tremor Other Hyperkinet Mov (NY)* 2017; **7:** 470.

18 Elmer J, Rittenberger JC, Faro J, et al. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. *Ann Neurol* 2016; **80:** 175–84.

19 Aicua Rapun I, Novy J, Solari D, Oddo M, Rossetti AO. Early Lance-Adams syndrome after cardiac arrest: prevalence, time to return to awareness, and outcome in a large cohort. *Resuscitation* 2017; **115:** 169–72.

20 Solari D, Rossetti AO, Carteron L, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. *Ann Neurol* 2017; **81:** 804–10.

21 Oddo M, Sandroni C, Citerio G, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. *Intensive Care Med* 2018; **44:** 2102–11.

22 Amorim E, Ghassemi MM, Lee JW, et al. Estimating the false positive rate of absent somatosensory evoked potentials in cardiac arrest prognostication. *Crit Care Med* 2018; **46:** e1213–21.

23 Rothstein TL. SSEP retains its value as predictor of poor outcome following cardiac arrest in the era of therapeutic hypothermia. *Crit Care* 2019; **23:** 327.

24 Fredland A, Backman S, Westhall E. Stratifying comatose postanoxic patients for somatosensory evoked potentials using routine EEG. *Resuscitation* 2019; **143:** 17–21.

25 Carrai R, Scarpino M, Lolli F, et al. Early-SEPs' amplitude reduction is reliable for poor-outcome prediction after cardiac arrest? *Acta Neurol Scand* 2019; **139:** 158–65.

26 Endisch C, Storm C, Ploner CJ, Leithner C. Amplitudes of SSEP and outcome in cardiac arrest survivors: a prospective cohort study. *Neurology* 2015; **85:** 1752–60.

27 Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. *J Clin Neurophysiol* 2013; **30:** 1–27.

28 Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology* 2016; **86:** 1482–90.

29 Beuchat I, Solari D, Novy J, Oddo M, Rossetti AO. Standardized EEG interpretation in patients after cardiac arrest: correlation with other prognostic predictors. *Resuscitation* 2018; **126:** 143–46.

30 Ruijter BJ, Tjepkema-Cloostermans MC, Tromp SC, et al. Early electroencephalography for outcome prediction of postanoxic coma: a prospective cohort study. *Ann Neurol* 2019; **86:** 203–14.

31 Ruijter BJ, van Putten MJAM, van den Bergh WM, Tromp SC, Hofmeijer J. Propofol does not affect the reliability of early EEG for outcome prediction of comatose patients after cardiac arrest. *Clin Neurophysiol* 2019; **130:** 1263–70.

32 Admiraal MM, van Rootselaar AF, Hofmeijer J, et al. Electroencephalographic reactivity as predictor of neurological outcome in postanoxic coma: a multicenter prospective cohort study. *Ann Neurol* 2019; **86:** 17–27.

33 Duez CHV, Ebbesen MQ, Benedek K, et al. Large inter-rater variability on EEG-reactivity is improved by a novel quantitative method. *Clin Neurophysiol* 2018; **129:** 724–30.

34 Lee JW. EEG reactivity in coma after cardiac arrest: is it enough to wake up the dead? *Epilepsy Curr* 2019; **19:** 369–71.

35 Ruijter BJ, van Putten MJ, Horn J, et al. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. *Trials* 2014; **15:** 433.

36 Backman S, Westhall E, Dragancea I, et al. Electroencephalographic characteristics of status epilepticus after cardiac arrest. *Clin Neurophysiol* 2017; **128:** 681–88.

37 Beretta S, Coppo A, Bianchi E, et al. Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. *Neurology* 2018; **91:** e2153–62.

38 Westhall E, Rosén I, Rundgren M, et al. Time to epileptiform activity and EEG background recovery are independent predictors after cardiac arrest. *Clin Neurophysiol* 2018; **129:** 1660–68.

39 Solanki P, Coppler PJ, Kvaløy JT, Baldwin MA, Callaway CW, Elmer J. Association of antiepileptic drugs with resolution of epileptiform activity after cardiac arrest. *Resuscitation* 2019; **142:** 82–90.

40 Forgacs PB, Devinsky O, Schiff ND. Independent functional outcomes after prolonged coma following cardiac arrest: a mechanistic hypothesis. *Ann Neurol* 2020; **87:** 618–32.

41 Fatuzzo D, Beuchat I, Alvarez V, Novy J, Oddo M, Rossetti AO. Does continuous EEG influence prognosis in patients after cardiac arrest? *Resuscitation* 2018; **132:** 29–32.

42 Tjepkema-Cloostermans MC, Hofmeijer J, Hom HW, Bosch FH, van Putten M. Predicting outcome in postanoxic coma: are ten EEG electrodes enough? *J Clin Neurophysiol* 2017; **34:** 207–12.

43 Amorim E, van der Stoel M, Nagaraj SB, et al. Quantitative EEG reactivity and machine learning for prognostication in hypoxic-ischemic brain injury. *Clin Neurophysiol* 2019; **130:** 1908–16.

44 Jonas S, Rossetti AO, Oddo M, Jenni S, Favaro P, Zubler F. EEG-based outcome prediction after cardiac arrest with convolutional neural networks: performance and visualization of discriminative features. *Hum Brain Mapp* 2019; **40:** 4606–17.

45 Noirhomme Q, Lehembre R, Lugo ZR, et al. Automated analysis of background EEG and reactivity during therapeutic hypothermia in comatose patients after cardiac arrest. *Clin EEG Neurosci* 2014; **45:** 6–13.

46 Velly L, Perlbarg V, Boulier T, et al. Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. *Lancet Neurol* 2018; **17:** 317–26.

47 Cristia C, Ho ML, Levy S, et al. The association between a quantitative computed tomography (CT) measurement of cerebral edema and outcomes in post-cardiac arrest-a validation study. *Resuscitation* 2014; **85:** 1348–53.

48 Wijman CA, Mlynash M, Caulfield AF, et al. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. *Ann Neurol* 2009; **65:** 394–402.

49 Wu O, Sorensen AG, Benner T, Singhal AB, Furie KL, Greer DM. Comatose patients with cardiac arrest: predicting clinical outcome with diffusion-weighted MR imaging. *Radiology* 2009; **252:** 173–81.

50 Lopez Soto C, Dragoi L, Heyn CC, et al. Imaging for neuroprognostication after cardiac arrest: systematic review and meta-analysis. *Neurocrit Care* 2020; **32:** 206–16.

51 Zhou SE, Maciel CB, Ormseth CH, Beekman R, Gilmore EJ, Greer DM. Distinct predictive values of current neuroprognostic guidelines in post-cardiac arrest patients. *Resuscitation* 2019; **139:** 343–50.

52 Hong JY, Lee DH, Oh JH, et al. Grey-white matter ratio measured using early unenhanced brain computed tomography shows no correlation with neurological outcomes in patients undergoing targeted temperature management after cardiac arrest. *Resuscitation* 2019; **140:** 161–69.

53 Oh JH, Choi SP, Wee JH, Park JH. Inter-scanner variability in Hounsfield unit measured by CT of the brain and effect on gray-to-white matter ratio. *Am J Emerg Med* 2019; **37:** 680–84.

54 Hahn DK, Geocadin RG, Greer DM. Quality of evidence in studies evaluating neuroimaging for neurologic prognostication in adult patients resuscitated from cardiac arrest. *Resuscitation* 2014; **85:** 165–72.

55 Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; **132** (suppl 2): S465–82.

56 Stammet P, Dankiewicz J, Nielsen N, et al. Protein S100 as outcome predictor after out-of-hospital cardiac arrest and targeted temperature management at 33 °C and 36 °C. *Crit Care* 2017; **21:** 153.

57 Stammet P, Collignon O, Hassager C, et al. Neuron-specific enolase as a predictor of death or poor neurological outcome after out-of-hospital cardiac arrest and targeted temperature management at 33°C and 36°C. *J Am Coll Cardiol* 2015; **65:** 2104–14.

58 Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation* 2016; **104:** 83–90.

59 Jakkula P, Reinikainen M, Hästbacka J, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med* 2018; **44:** 2112–21.

60 Rundgren M, Cronberg T, Friberg H, Isaksson A. Serum neuron specific enolase - impact of storage and measuring method. *BMC Res Notes* 2014; **7:** 726.

61 Stammet P. Blood biomarkers of hypoxic-ischemic brain injury after cardiac arrest. *Semin Neurol* 2017; **37:** 75–80.

62 Stern P, Bartos V, Uhrova J, et al. Performance characteristics of seven neuron-specific enolase assays. *Tumour Biol* 2007; **28:** 84–92.

63 Streitberger KJ, Leithner C, Wattenberg M, et al. Neuron-specific enolase predicts poor outcome after cardiac arrest and targeted temperature management: a multicenter study on 1,053 patients. *Crit Care Med* 2017; **45:** 1145–51.

64 Moseby-Knappe M, Mattsson N, Nielsen N, et al. Serum neurofilament light chain for prognosis of outcome after cardiac arrest. *JAMA Neurol* 2019; **76:** 64–71.

65 Dragancea I, Wise MP, Al-Subaie N, et al. Protocol-driven neurological prognostication and withdrawal of life-sustaining therapy after cardiac arrest and targeted temperature management. *Resuscitation* 2017; **117:** 50–57.

66 Paul M, Bougouin W, Dumas F, et al. Comparison of two sedation regimens during targeted temperature management after cardiac arrest. *Resuscitation* 2018; **128:** 204–10.

67 Rey A, Rossetti AO, Miroz JP, Eckert P, Oddo M. Late awakening in survivors of postanoxic coma: early neurophysiologic predictors and association with ICU and long-term neurologic recovery. *Crit Care Med* 2019; **47:** 85–92.

68 Cronberg T, Kuiper M. Withdrawal of life-sustaining therapy after cardiac arrest. *Semin Neurol* 2017; **37:** 81–87.

69 Greer DM, Rosenthal ES, Wu O. Neuroprognostication of hypoxic-ischaemic coma in the therapeutic hypothermia era. *Nat Rev Neurol* 2014; **10:** 190–203.

70 Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. *Resuscitation* 2016; **102:** 127–35.

71 Sandroni C, D'Arrigo S, Callaway CW, et al. The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis. *Intensive Care Med* 2016; **42:** 1661–71.

72 Russell JA, Epstein LG, Greer DM, et al. Brain death, the determination of brain death, and member guidance for brain death accommodation requests: AAN position statement. *Neurology* 2019; published online Jan 2. DOI:10.1212/WNL.0000000000006750.

73 Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the international liaison committee on resuscitation. *Circulation* 2018; **137:** e783–801.

74 Estraneo A, Moretta P, Loreto V, et al. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. *Neurology* 2013; **80:** 464–70.

75 Juan E, De Lucia M, Beaud V, et al. How do you feel? Subjective perception of recovery as a reliable surrogate of cognitive and functional outcome in cardiac arrest survivors. *Crit Care Med* 2018; **46:** e286–93.

76 Lilja G, Nielsen N, Friberg H, et al. Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C. *Circulation* 2015; **131:** 1340–49.

77 Sabedra AR, Kristan J, Raina K, et al. Neurocognitive outcomes following successful resuscitation from cardiac arrest. *Resuscitation* 2015; **90:** 67–72.

78 Frisch S, Thiel F, Schroeter ML, Jentzsch RT. Apathy and cognitive deficits in patients with transient global ischemia after cardiac arrest. *Cogn Behav Neurol* 2017; **30:** 172–75.

79 Tiainen M, Poutiainen E, Oksanen T, et al. Functional outcome, cognition and quality of life after out-of-hospital cardiac arrest and therapeutic hypothermia: data from a randomized controlled trial. *Scand J Trauma Resusc Emerg Med* 2015; **23:** 12.

80 Moulaert VRM, van Heugten CM, Gorgels TPM, Wade DT, Verbunt JA. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. *Neurorehabil Neural Repair* 2017; **31:** 530–39.

81 Ørbo M, Aslaksen PM, Larsby K, Schäfer C, Tande PM, Anke A. Alterations in cognitive outcome between 3 and 12 months in survivors of out-of-hospital cardiac arrest. *Resuscitation* 2016; **105:** 92–99.

82 Lilja G, Nilsson G, Nielsen N, et al. Anxiety and depression among out-of-hospital cardiac arrest survivors. *Resuscitation* 2015; **97:** 68–75.

83 Desai R, Singh S, Patel K, Fong HK, Kumar G, Sachdeva R. The prevalence of psychiatric disorders in sudden cardiac arrest survivors: a 5-year nationwide inpatient analysis. *Resuscitation* 2019; **136:** 131–35.

84 Wachelder EM, Moulaert VR, van Heugten C, Gorgels T, Wade DT, Verbunt JA. Dealing with a life changing event: the influence of spirituality and coping style on quality of life after survival of a cardiac arrest or myocardial infarction. *Resuscitation* 2016; **109:** 81–86.

85 Rosman L, Whited A, Lampert R, Mosesso VN, Lawless C, Sears SF. Cardiac anxiety after sudden cardiac arrest: severity, predictors and clinical implications. *Int J Cardiol* 2015; **181:** 73–76.

86 Agarwal S, Presciutti A, Cornelius T, et al. Cardiac arrest and subsequent hospitalization-induced posttraumatic stress is associated with 1-year risk of major adverse cardiovascular events and all-cause mortality. *Crit Care Med* 2019; **47:** e502–05.

87 Lilja G, Nielsen N, Bro-Jeppesen J, et al. Return to work and participation in society after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes* 2018; **11:** e003566.

88 Wylie GR, Flashman LA. Understanding the interplay between mild traumatic brain injury and cognitive fatigue: models and treatments. *Concussion* 2017; **2:** CNC50.

89 Sulzgruber P, Kliegel A, Wandaller C, et al. Survivors of cardiac arrest with good neurological outcome show considerable impairments of memory functioning. *Resuscitation* 2015; **88:** 120–25.

90 Steenbergen S, Rijkenberg S, Adonis T, Kroeze G, van Stijn I, Endeman H. Long-term treated intensive care patients outcomes: the one-year mortality rate, quality of life, health care use and long-term complications as reported by general practitioners. *BMC Anesthesiol* 2015; **15:** 142.

91 Tiainen M, Vaahersalo J, Skrifvars MB, Hästbacka J, Grönlund J, Pettilä V. Surviving out-of-hospital cardiac arrest: the neurological and functional outcome and health-related quality of life one year later. *Resuscitation* 2018; **129:** 19–23.

92 Bohm M, Lilja G, Finnbogadóttir H, et al. Detailed analysis of health-related quality of life after out-of-hospital cardiac arrest. *Resuscitation* 2019; **135:** 197–204.

93 Smith K, Andrew E, Lijovic M, Nehme Z, Bernard S. Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. *Circulation* 2015; **131:** 174–81.

94 Verberne D, Moulaert V, Verbunt J, van Heugten C. Factors predicting quality of life and societal participation after survival of a cardiac arrest: A prognostic longitudinal cohort study. *Resuscitation* 2018; **123:** 51–57.

95 Kearney J, Dyson K, Andrew E, Bernard S, Smith K. Factors associated with return to work among survivors of out-of-hospital cardiac arrest. *Resuscitation* 2020; **146:** 203–12.

96 Sawyer KN, Camp-Rogers TR, Kotini-Shah P, et al. Sudden cardiac arrest survivorship: a scientific statement from the American Heart Association. *Circulation* 2020; **141**: e654–85.

97 Adigüzel E, Yaşar E, Kesikburun S, et al. Are rehabilitation outcomes after severe anoxic brain injury different from severe traumatic brain injury? A matched case-control study. *Int J Rehabil Res* 2018; **41:** 47–51.

98 Tazopoulou E, Miljkovitch R, Truelle JL, et al. Rehabilitation following cerebral anoxia: an assessment of 27 patients. *Brain Inj* 2016; **30:** 95–103.

99 Heinz UE, Rollnik JD. Outcome and prognosis of hypoxic brain damage patients undergoing neurological early rehabilitation. *BMC Res Notes* 2015; **8:** 243.

100 Boyce LW, Goossens PH, Moulaert VR, Pound G, van Heugten CM. Out-of-hospital cardiac arrest survivors need both cardiological and neurological rehabilitation! *Curr Opin Crit Care* 2019; **25:** 240–43.

101 Moulaert VR, van Heugten CM, Winkens B, et al. Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: a randomised controlled trial. *Int J Cardiol* 2015; **193:** 8–16.

102 Moulaert VR, Goossens M, Heijnders IL, Verbunt JA, Heugten CM. Early neurologically focused follow-up after cardiac arrest is cost-effective: a trial-based economic evaluation. *Resuscitation* 2016; **106:** 30–36.

103 Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. *Psychosom Med* 2010; **72:** 563–69.

104 van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004; **66:** 814–22.

105 Cowan MJ, Pike KC, Budzynski HK. Psychosocial nursing therapy following sudden cardiac arrest: impact on two-year survival. *Nurs Res* 2001; **50:** 68–76.

106 Dougherty CM, Thompson EA, Lewis FM. Long-term outcomes of a telephone intervention after an ICD. *Pacing Clin Electrophysiol* 2005; **28:** 1157–67.

107 Van't Wout Hofland J, Moulaert V, van Heugten C, Verbunt J. Long-term quality of life of caregivers of cardiac arrest survivors and the impact of witnessing a cardiac event of a close relative. *Resuscitation* 2018; **128:** 198–203.

108 Cicerone KD, Goldin Y, Ganci K, et al. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. *Arch Phys Med Rehabil* 2019; **100:** 1515–33.

109 Kim YJ, Rogers JC, Raina KD, et al. An intervention for cardiac arrest survivors with chronic fatigue: a feasibility study with preliminary outcomes. *Resuscitation* 2016; **105:** 109–15.

110 Kim YJ, Rogers JC, Raina KD, et al. Solving fatigue-related problems with cardiac arrest survivors living in the community. *Resuscitation* 2017; **118:** 70–74.

111 Piepoli MF, Corrà U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. *Eur J Prev Cardiol* 2014; **21:** 664–81.

112 Anderson L, Thompson DR, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016; **1:** CD001800.

113 Boyce LW, Goossens PH. Rehabilitation after cardiac arrest: integration of neurologic and cardiac rehabilitation. *Semin Neurol* 2017; **37:** 94–102.

114 Mion M, Al-Janabi F, Islam S, et al. Care After REsuscitation: implementation of the United Kingdom's first dedicated multidisciplinary follow-up program for survivors of out-of-hospital cardiac arrest. *Ther Hypothermia Temp Manag* 2020; **10:** 53–59.