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European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care☆

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Abstract

The European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) have collaborated to produce these post-resuscitation care guidelines for adults, which are based on the 2020 International Consensus on Cardiopulmonary Resuscitation Science with Treatment Recommendations. The topics covered include the post-cardiac arrest syndrome, diagnosis of cause of cardiac arrest, control of oxygenation and ventilation, coronary reperfusion, haemodynamic monitoring and management, control of seizures, temperature control, general intensive care management, prognostication, long-term outcome, rehabilitation, and organ donation.

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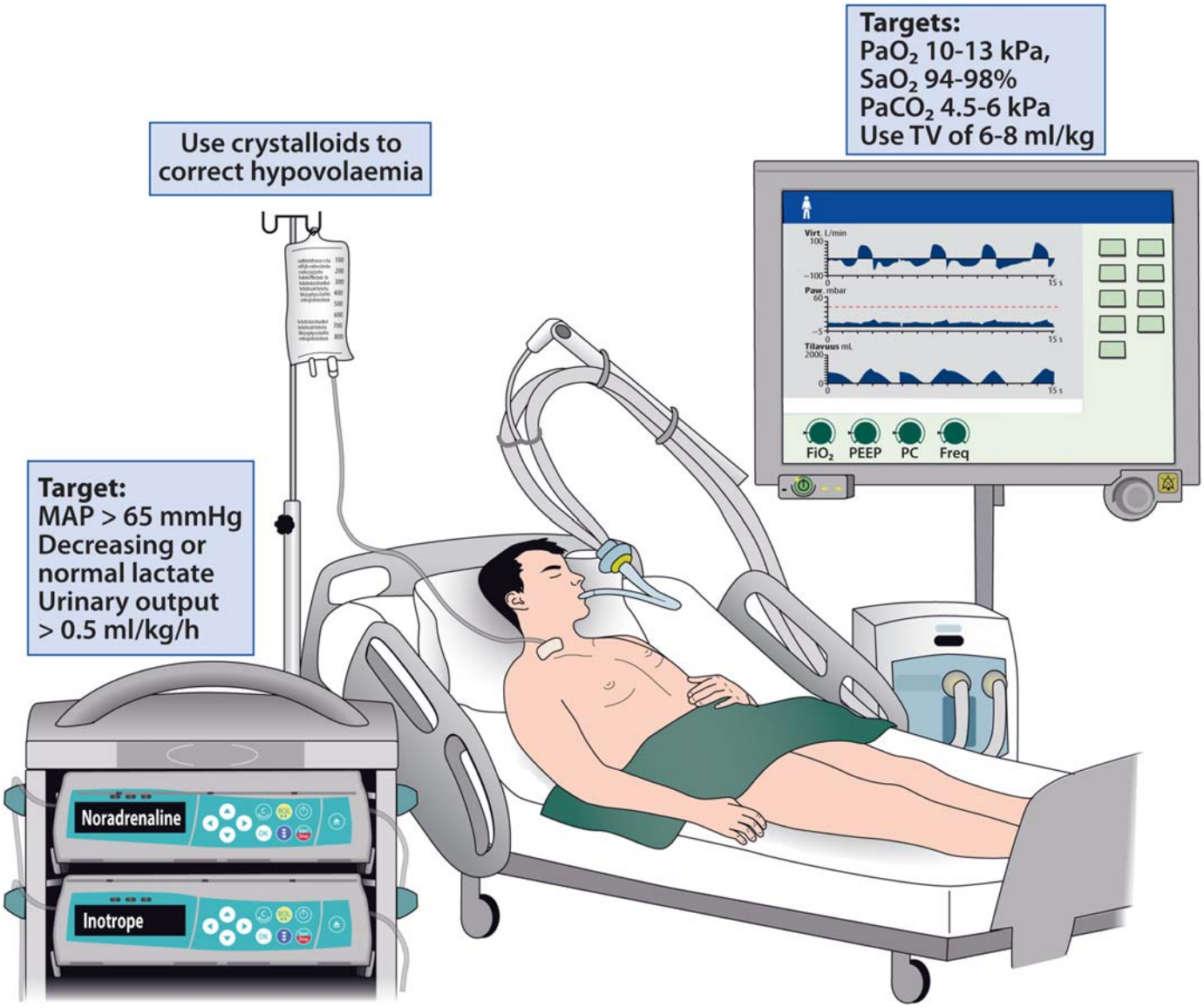


Fig. 3 – Haemodynamic, oxygenation and ventilation targets.

treatments based on the patient's chances of achieving a neurologically meaningful recovery (Fig. 4).

- No single predictor is 100% accurate. Therefore, a multimodal neuroprognostication strategy is recommended.
- When predicting poor neurological outcome, a high specificity and precision are desirable, to avoid falsely pessimistic predictions.
- The clinical neurological examination is central to prognostication. To avoid falsely pessimistic predictions, clinicians should avoid potential confounding from sedatives and other drugs that may confound the results of the tests.
- When patients are treated with TTM, daily clinical examination is advocated but final prognostic assessment should be undertaken only after rewarming.
- Clinicians must be aware of the risk of a self-fulfilling prophecy bias, occurring when the results of an index test predicting poor outcome is used for treatment decisions, especially regarding life-sustaining therapies.
- Index tests for neurological prognostication are aimed at assessing the severity of hypoxic-ischaemic brain injury. The neurological prognosis is one of several aspects to consider in discussions around an individual's potential for recovery.

Multimodal prognostication

- Start the prognostication assessment with an accurate clinical examination, to be performed only after major confounders (e.g. residual sedation, hypothermia) have been excluded (Fig. 5).
- In a comatose patient with M $\leq$ 3 at $\geq$72 h from ROSC, in the absence of confounders, poor outcome is likely when two or more of the following predictors are present: no pupillary and corneal reflexes at $\geq$72 h, bilaterally absent N20 SSEP wave at $\geq$24 h, highly malignant EEG at >24 h, neuron specific enolase (NSE) >60 $\mu g\,L^{-1}$ at 48 h and/or 72 h, status myoclonus $\leq$72 h, or a diffuse and extensive anoxic injury on brain CT/MRI. Most of these signs can be recorded before 72 h from ROSC, however their

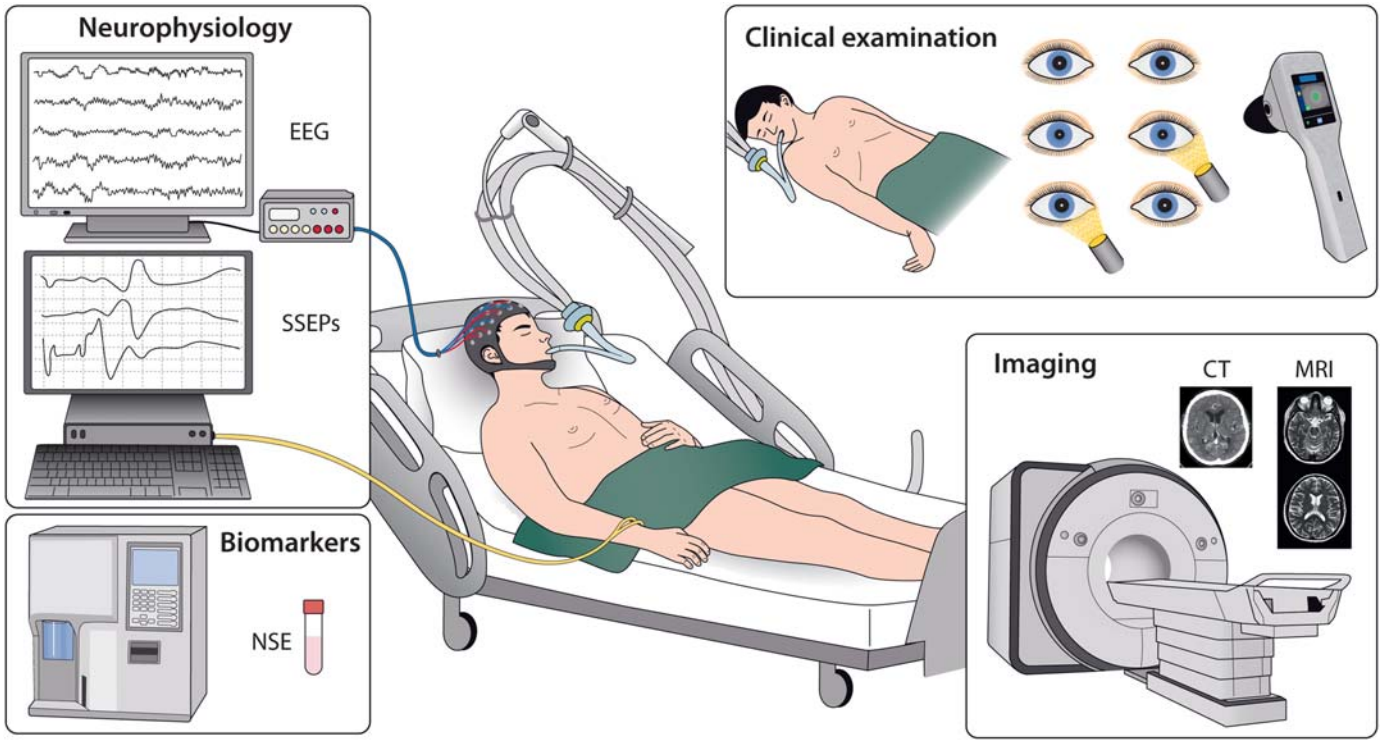


Fig. 4 – Prognostication modes. EEG electroencephalography; NSE neuron specific enolase; SSEP somatosensory evoked potential.

results will be evaluated only at the time of clinical prognostic assessment.

Clinical examination

- Clinical examination is prone to interference from sedatives, opioids or muscle relaxants. A potential confounding from residual sedation should always be considered and excluded.
- A Glasgow Motor Score of $\leq$3 (abnormal flexion or worse in response to pain) at 72 h or later after ROSC may identify patients in whom neurological prognostication may be needed.
- In patients who remain comatose at 72 h or later after ROSC the following tests may predict a poor neurological outcome:
  - The bilateral absence of the standard pupillary light reflex.
  - Quantitative pupillometry
  - The bilateral absence of corneal reflex
  - The presence of myoclonus within 96 h and, in particular, status myoclonus within 72 h
- We also suggest recording the EEG in the presence of myoclonic jerks to enable detection of any associated epileptiform activity or EEG signs, such as background reactivity or continuity, suggesting a potential for neurological recovery.

Neurophysiology

- Perform an EEG in patients who are unconscious after the arrest.
- Highly malignant EEG-patterns include suppressed background with or without periodic discharges and burst-suppression. We suggest using these EEG-patterns after the end of TTM and after sedation has been cleared as indicators of a poor prognosis.
- The presence of unequivocal seizures on EEG during the first 72 h after ROSC is an indicator of a poor prognosis.
- Absence of background reactivity on EEG is an indicator of poor prognosis after cardiac arrest.
- Bilateral absence of somatosensory evoked cortical N20-potentials is an indicator of poor prognosis after cardiac arrest.
- Always consider the results of EEG and somatosensory evoked potentials (SSEP) in the context of clinical examination findings and other tests. Always consider using a neuromuscular blocking drug when performing SSEP.

Biomarkers

- Use serial measurements of NSE in combination with other methods to predict outcome after cardiac arrest. Increasing values between 24 and 48 h or 72 h in combination with high values at 48 and 72 h indicate a poor prognosis.

Imaging

- Use brain imaging studies for predicting poor neurological outcome after cardiac arrest in combination with other predictors, in centres where specific experience in these studies is available.
- Use presence of generalised brain oedema, manifested by a marked reduction of the grey matter/white matter ratio on brain CT, or extensive diffusion restriction on brain MRI to predict poor neurological outcome after cardiac arrest.
- Always consider findings from imaging in combination with other methods for neurological prognostication.

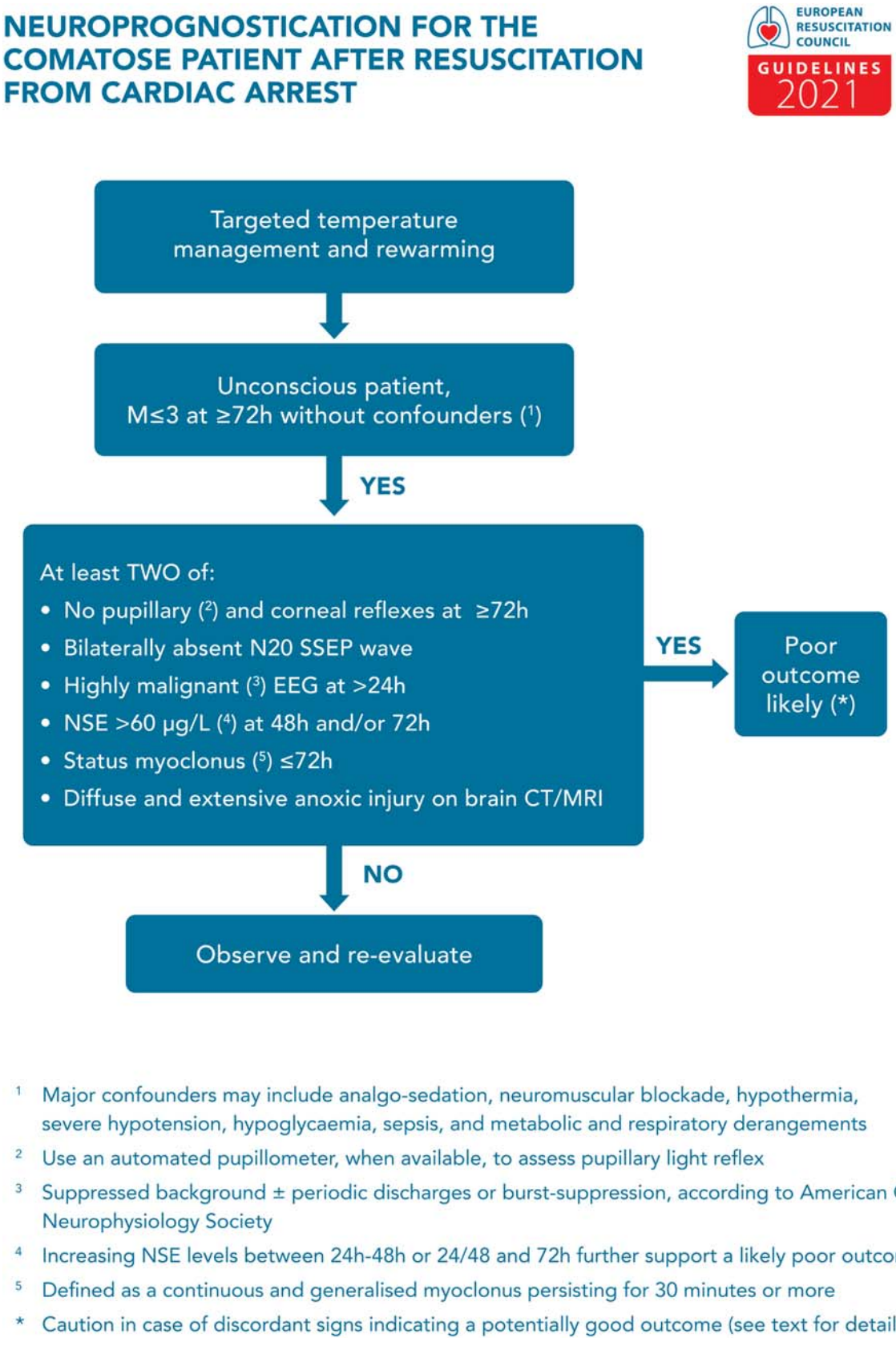


Fig. 5 – Prognostication strategy algorithm.

EEG electroencephalography; NSE neuron specific enolase; SSEP somatosensory evoked potential; ROSC return of spontaneous circulation.

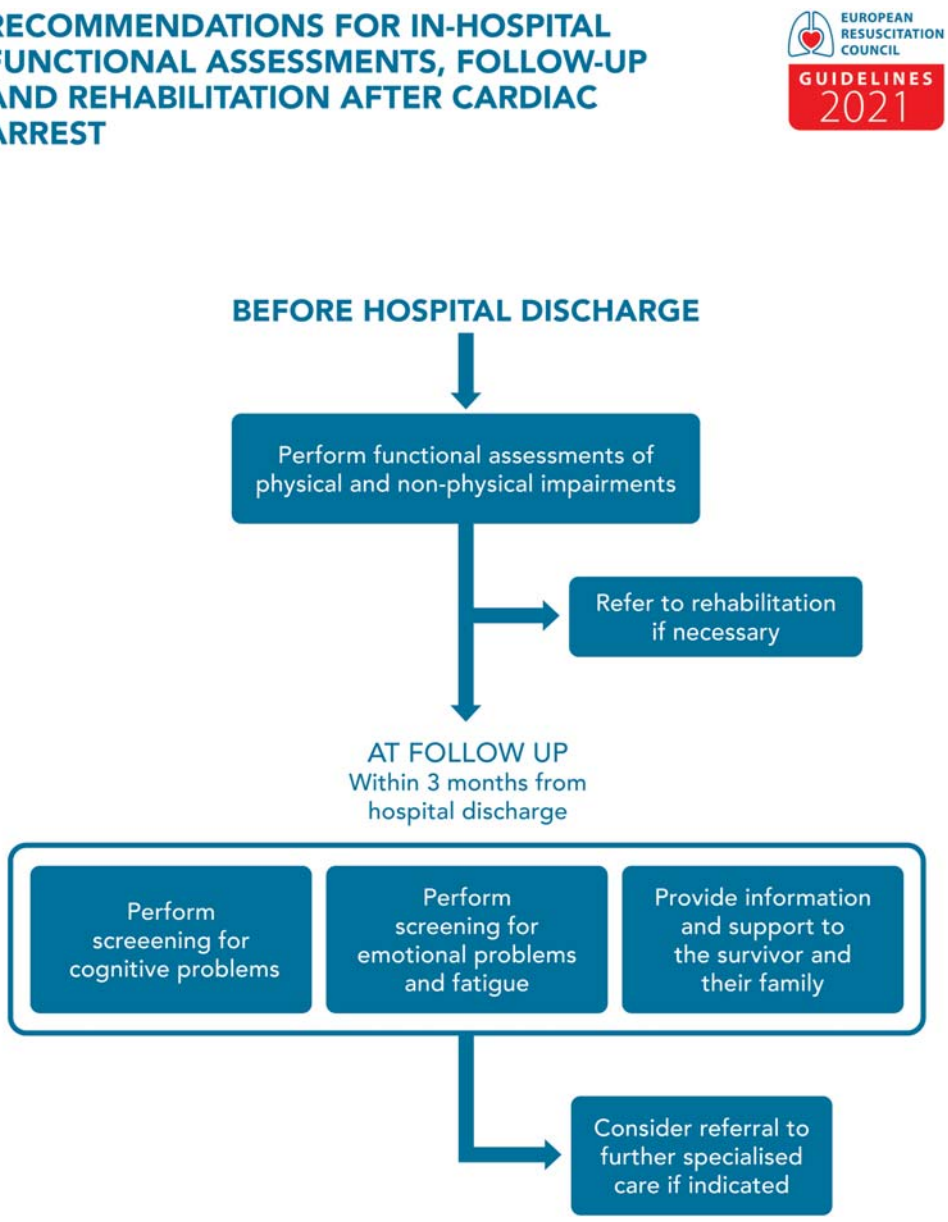


Fig. 6 – Recommendations for in-hospital functional assessments, follow-up and rehabilitation after cardiac arrest.

Withdrawal of life-sustaining therapy

- Separate discussions around withdrawal of life-sustaining therapy (WLST) and the assessment of prognosis for neurological recovery; WLST decisions should consider aspects other than brain injury such as age, co-morbidity, general organ function and the patients' preferences.
- Allocate sufficient time for communication around the level-of-treatment decision within the team and with the relatives.

Long-term outcome after cardiac arrest

- Perform functional assessments of physical and non-physical impairments before discharge from the hospital to identify early rehabilitation needs and refer to rehabilitation if necessary (Fig. 6).
- Organise follow-up for all cardiac arrest survivors within 3 months after hospital discharge, including:
  1. Screening for cognitive problems.
  2. Screening for emotional problems and fatigue.
  3. Providing information and support for survivors and family members.

Organ donation

- All decisions concerning organ donation must follow local legal and ethical requirements.
- Organ donation should be considered in those who have achieved ROSC and who fulfil neurological criteria for death (Fig. 7).
- In comatose ventilated patients who do not fulfil neurological criteria for death, if a decision to start end-of-life care and withdrawal of life support is made, organ donation should be considered for when circulatory arrest occurs.

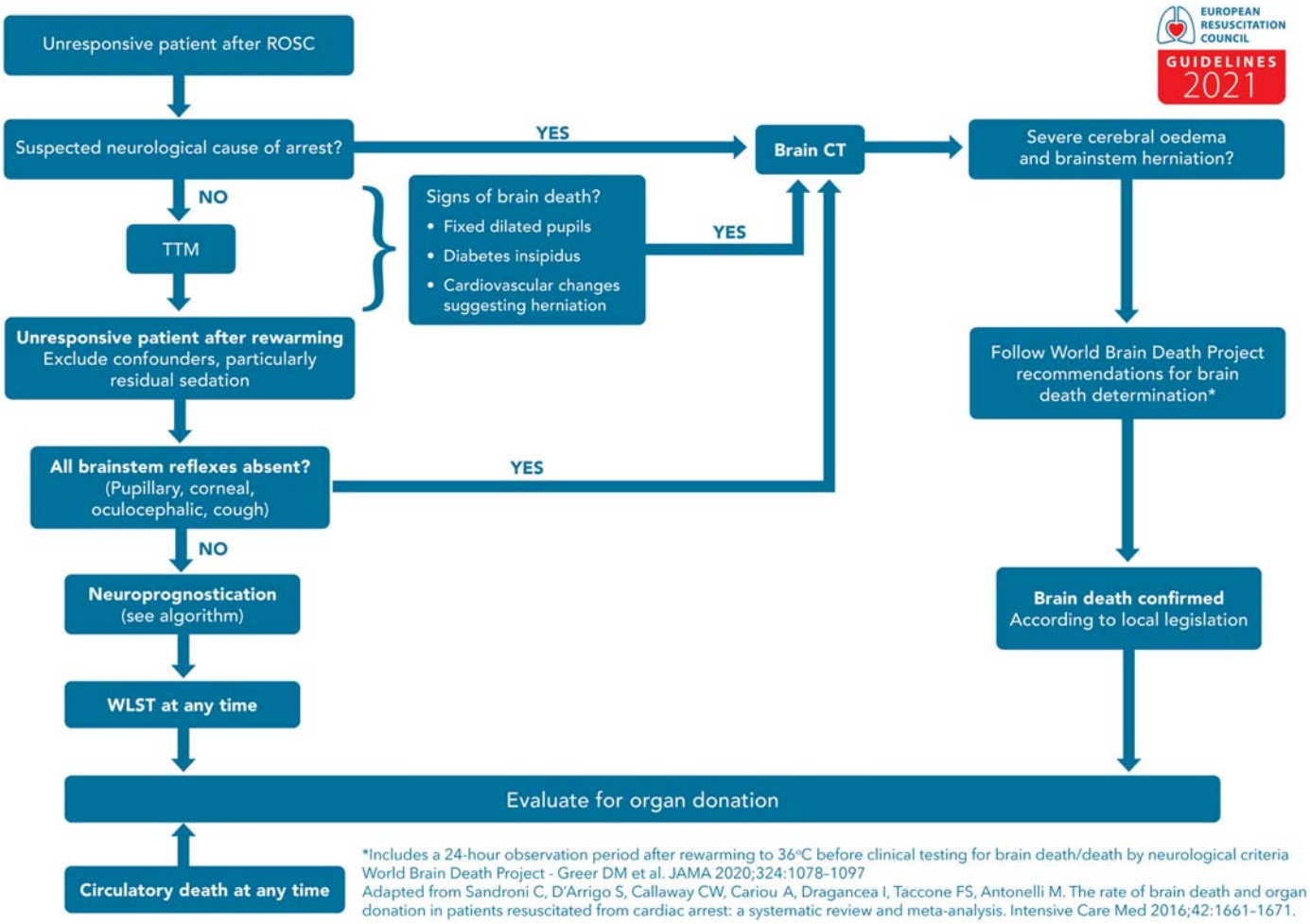


Fig. 7 – Organ donation after cardiac arrest algorithm.

Cardiac arrest centres

- Adult patients with non-traumatic OHCA should be considered for transport to a cardiac arrest centre according to local protocol.

Evidence informing the guidelines

Post-cardiac arrest syndrome

The post-cardiac arrest syndrome comprises post-cardiac arrest hypoxic-ischaemic brain injury, post-cardiac arrest myocardial dysfunction, the systemic ischaemia/reperfusion response, and the persistent precipitating pathology.[18–21] The severity of this syndrome will vary with the duration and cause of cardiac arrest. It may not occur at all if the cardiac arrest is brief. Among patients surviving to intensive care unit (ICU) admission but subsequently dying in-hospital, withdrawal of treatment following prognostication of poor neurological outcome is the cause of death in approximately two-thirds after OHCA and approximately 25% after in-hospital cardiac arrest.[22–26] Cardiovascular failure accounts for most deaths in the first three days, while, in many countries, WLST based on a prognostication of severe hypoxic-ischaemic brain injury accounts for most of the later deaths.[23,26,27] Post-cardiac arrest hypoxic-ischaemic brain injury is associated with hypotension, hypoxaemia, hyperoxaemia, pyrexia, hypoglycaemia, hyperglycaemia and seizures. Significant myocardial dysfunction is common after cardiac arrest but typically starts to recover by 2–3 days, although full recovery may take significantly longer.[28–33] The whole-body ischaemia/reperfusion of cardiac arrest, CPR and ROSC activates immune and coagulation pathways contributing to multiple organ failure and increasing the risk of infection.[34–43] Thus, the post-cardiac arrest syndrome has many features in common with sepsis, including intravascular volume depletion, vasodilation, endothelial injury and abnormalities of the microcirculation.[44–53]

Diagnosis of cause of cardiac arrest

These guidelines are informed by expert consensus.

Cardiac causes of OHCA have been studied extensively in the last few decades; conversely, little is known about non-cardiac causes. Early identification of a respiratory or neurological cause would enable transfer of the patient to a specialised ICU for optimal care. Improved knowledge of prognosis also enables discussion about the appropriateness of specific therapies, including TTM. Several case series showed that this strategy enables diagnosis of non-cardiac causes of

In prognostic accuracy studies, a predictor (index test) is assessed for its ability to predict an outcome. This design is like that of diagnostic accuracy studies. However, while in diagnostic accuracy studies the index test is evaluated against another test which represents the reference standard, or gold standard, prognostic accuracy studies evaluate the index test against the occurrence of the predicted event (target condition) after test recording.[295] When test results are expressed in binary format (i.e., positive vs. negative) the accuracy is expressed using sensitivity and specificity, which measure the ability of the test to identify those who will develop or not develop the target condition, respectively. Since most neuroprognostic tests predict poor neurological outcome, having a high specificity (i.e., a very low rate of falsely pessimistic predictions potentially leading to an inappropriate WLST) is desirable. Ideally, an index test should be 100% specific, i.e., its false positive rate (FPR) should be zero, but this is difficult to achieve in practice. There is no universal consensus on how specific an index test should be for neuroprognostication after cardiac arrest. In a recent survey of 640 healthcare providers, the majority (56%) felt an acceptable FPR for WLST from patients who might otherwise have recovered was $\leq$0.1%.[296] Along with the absolute value of specificity, precision of its estimate is important. A very specific test predicting poor outcome is of little clinical use when its precision is low, (i.e., when the confidence intervals [CIs] around the point estimate of its specificity are wide), because this indicates a high degree of uncertainty around the estimated specificity. In the 2014 ERC-ESICM Advisory Statement on neuroprognostication after cardiac arrest,[297] the most robust predictors were identified as those in which the upper boundary of the 95% CI of the FPR was below 5%.

For some neuroprognostic tests used after cardiac arrest, such as the blood values of biomarkers of neurological injury or the grey matter to white matter density ratio on brain CT, the results are expressed as a continuous variable. In this case, sensitivity and specificity will depend on the value of the variable that is chosen as a threshold to separate positive from negative test results, and the values of sensitivity and specificity that are obtained by varying the positivity threshold across all its possible values are expressed by a receiver operating characteristic (ROC) curve. The problem with dichotomising continuous predictive variables to obtain a binary test result is that finding a consistent threshold for 100% specificity is difficult. Very high values of test results can be caused by outliers, which cause distortion and reduce test sensitivity.

Main sources of bias in neuroprognostication

One of the major biases in neuroprognostication after cardiac arrest is self-fulfilling prophecy. This occurs when the treating team is aware of the result of the prognostic test and uses it for decisions that affect patient's outcome, e.g., WLST. This leads to an overestimation of the test performance, and - potentially - to an inappropriate WLST. In a systematic review on neuroprognostication after cardiac arrest published in 2013,[298,299] 64/73 (88%) studies were at risk of self-fulfilling prophecy bias.

Ideally, to avoid self-fulfilling prophecy bias, the index tests should be investigated blindly. However, this is difficult to achieve in practice. Concealing results of clinical examination from the treating team is almost impossible, while concealing results of EEG or brain imaging would be unethical, since they may reveal the presence of potentially treatable complications (e.g., seizures or intracranial hypertension, respectively). Nevertheless, some predictors such as biomarkers have been evaluated blindly.[230] A special condition limiting the risk of self-fulfilling prophecy bias is the absence of an active WLST policy. This has been described in some studies conducted in countries or communities where treatment limitations are not accepted due to cultural, legal or religious reasons.[300,301]

Other strategies to reduce the risk of falsely pessimistic predictions include avoiding confounding from treatments (e.g., sedatives or other drugs) affecting the results of some predictors, such as clinical examination or EEG; avoiding basing decisions on life-sustaining treatments on the results of a single index test, but rather using a multimodal approach (Fig. 5); and always interpreting the results of the index tests within the clinical context.

A specific source of bias in neuroprognostic studies after cardiac arrest is the presence of a time lag between the recording of the index test, which is usually done very early after the arrest, and the assessment of the target condition, i.e., neurological outcome. Since recovery from hypoxic-ischaemic brain injury following cardiac arrest requires time, the minimum recommended timing for its assessment is 30 days or later from the event or neurological discharge.[290] However, further neurological recovery can occur later. Consequently, an early prediction of outcome which is confirmed by CPC or mRS measured at hospital discharge may occasionally prove false when the outcome is reassessed later.[302] For that reason, guidelines suggest reassessing neurological outcome at three or six months after the event.[295] The majority of studies included in the systematic review informing the present guidelines reports neurological outcome at least six months after cardiac arrest.[15]

Another bias which is partly related to the time delay between index test assessment and outcome is the interference from extracerebral causes of death after cardiac arrest. These include cardiovascular instability, which is the second most common cause of in-hospital death after cardiac arrest,[23] and multiple organ failure due to global ischaemia-reperfusion injury.[303,304] Although the incidence of these complications is maximal early after arrest, death from extracerebral organ failure may occur after neurological recovery.[305] The prevalence of death after awakening was 16% in ICU in a single-centre study,[306] and 4.2% during hospital stay in a recent multicentre European study including 4646 patients.[307] In that study, death occurred at a median time of 9 (3−18) days after awakening, and it was more common after IHCA than after OHCA.

Clinical examination

These guidelines are supported by evidence derived from a systematic review on prognostication and 2020 ILCOR CoSTRs.[9,15] The relevant treatment recommendations in the 2020 ILCOR CoSTR are:

- We suggest using pupillary light reflex at 72 h or later after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).
- We suggest using quantitative pupillometry at 72 h or later after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).
- We suggest using bilateral absence of corneal reflex at 72 h or later after ROSC for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
- We suggest using presence of myoclonus or status myoclonus within 96 h after ROSC, in combination with other tests, for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty

evidence). We also suggest recording EEG in presence of myoclonic jerks in order to characterise the phenotype of the myoclonus.

Ocular reflexes. Ocular reflexes currently used for neurological prognostication after cardiac arrest include pupillary reflex and corneal reflex. The pupillary light reflex (PLR) comprises a temporary reduction of pupil size induced by a light stimulus. Standard PLR (s-PLR) is evaluated visually and elicited generally using a penlight. In recent years, a quantitative evaluation of PLR using portable pupillometers has become available in the ICU. A bilaterally absent s-PLR has low specificity for predicting poor outcome in the first hours after ROSC, but its accuracy progressively increases, and it achieves 100% specificity after 96 h from ROSC with 20−25% sensitivity.[15] This is presumably due to the process of brain recovery after anoxic-ischaemic injury, but it may be due partly to interference from sedatives used in the early post-resuscitation phase to maintain TTM. Standard PLR is inexpensive and easy to use, but it is subjective and prone to interrater variability.[308]

Quantitative evaluation of PLR (automated pupillometry) provides an objective and quantifiable measurement of the pupillary response. The most common pupillometry measures are the percentage reduction of pupillary size, generally indicated as qPLR[309] and the neurological pupil index (NPi).[310] NPi is calculated from several dynamic parameters of the pupillary response (including constriction and dilation velocity, size, and percentage size reduction after stimulation) using a proprietary algorithm. A NPi value $\geq$3 is considered normal. Limited evidence showed that, unlike s-PLR, NPi can predict unfavourable outcome with no false positive results from 24 h or less to 72 h from ROSC.[15] In one study this was because of the ability of pupillometer to detect a response even when the pupil size was very small, presumably from sedation.[310] Results of pupillometry are expressed as a continuous measure, and threshold for 100% specificity varied among studies. In three studies included in a recent review this threshold for NPi was <2.4 before 24 h and 2.0 at 24−72 h.[15] Another limitation of automated pupillometry is its additional cost.

The corneal reflex (CR) is elicited by touching the outer margin (limbus) of the cornea with a cotton wisp. Alternatively, in order to minimise the risk of corneal abrasion, an air or water squirt can be used.[311] The corresponding response is represented by an eye blink. In patients who are comatose after cardiac arrest, an absent CR predicts poor neurological outcome after 72 h from ROSC with 100% specificity and 25-−40% sensitivity.[15] Like PLR, CR is prone to interference from sedation. In addition, it may be affected by muscle relaxants. A recent survey showed that the modalities with which CR is assessed in comatose patients are inconsistent.[312]

Motor response

An absent or extensor motor response to pain (motor component [M] 1 or 2 of the Glasgow Coma Score) is associated with poor neurological outcome after cardiac arrest.[15] However, its specificity is low, almost never achieving 100%, even when it is assessed after 96 h from ROSC. Like CR, motor response is based on striate muscle contraction and, as such, it can be affected by muscle relaxants. Because of its high sensitivity (>60% at 72 h or later from ROSC) a M = 1−2 can be used as a criterion for identifying patients needing prognostication after cardiac arrest. However, recent evidence showed that using M $\leq$ 3 as an entry point increases the sensitivity for prediction of poor outcome without reducing specificity.[313]

Myoclonus and status myoclonus

Myoclonus consists of sudden, brief, involuntary jerks caused by muscular contractions or inhibitions. Their distribution can be focal, multifocal, or generalised.[314] Presence of myoclonus within 96 h from ROSC in patients who are comatose after cardiac arrest is associated with poor neurological outcome in most cases.[15] However, a false positive rate of up to 22% has been described.[315] Most prognostication studies did not provide a definition or description of myoclonus. In some patients with favourable outcome, myoclonus may persist after recovery of consciousness in a chronic form of action myoclonus (i.e., triggered by spontaneous movements) known as Lance-Adams syndrome.[182,316]

Clinical myoclonus can inconsistently be associated with electrical seizures, therefore recording an EEG can be useful. Some studies have identified specific EEG features associated with benign myoclonus, such as a reactive[179,184] and/or continuous EEG background.[179,181] The presence of diffuse and continuous myoclonic jerks is usually described as status myoclonus. However, a consensus definition of status myoclonus is lacking. The 2014 ERC-ESICM Advisory Statement on neurologic prognostication after cardiac arrest suggested that in comatose survivors of cardiac arrest status myoclonus should be defined as a continuous and generalised myoclonus persisting for 30 min or more.[297] Evidence from two studies that did not distinguish electrographic features of status myoclonus[15] showed that status myoclonus within 24 h[317] or within seven days from ROSC[178,317] is almost invariably associated with poor neurological outcome (specificity 99−100%).

The advantages of predictors based on clinical examination include minimal equipment and costs (except pupillometry) and availability at the bedside. Their major limitations include interference from sedatives, opioids, and − except for the PLR − from muscle relaxants. In addition, their assessment is prone to subjectivity. Use of automated assessment, like pupillometry for PLR, may at least address these limitations. Finally, results of clinical examination cannot be concealed from the treating team, potentially causing a self-fulfilling prophecy bias.

Neurophysiology

These guidelines are supported by evidence derived from a systematic review on prognostication and 2020 ILCOR CoSTRs.[9,15] The relevant treatment recommendations in the 2020 ILCOR CoSTR are:

- We recommend that neuroprognostication always be undertaken using a multi-modal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very-low-certainty evidence).
- We suggest using a bilaterally absent N20 wave of somatosensory evoked potential (SSEP) at $\geq$24 h from ROSC in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
- We suggest against using the absence of EEG background reactivity alone to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
- We suggest using the presence of seizure activity on EEG in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
- We suggest using burst-suppression on EEG at $\geq$24 h from ROSC in combination with other indices to predict poor outcome in adult

patients who are comatose and who are off sedation after cardiac arrest (weak recommendation, very low-certainty evidence).

Electroencephalography (EEG)

Electroencephalography (EEG) is one of the most widely used and studied methods to assess brain function and prognosis after cardiac arrest.[318] EEG is also important for diagnosing and treating seizures.

The main aspects when assessing EEG are the background activity, superimposed discharges and reactivity. The EEG background continuity is most important for the prognosis and is commonly categorised as continuous, discontinuous, burst suppression (50 −99% suppression periods) or suppression (>99% activity <10 μV amplitude).[319] A standardised terminology for critical care EEG has been proposed by the ACNS.[187]

Immediately after a cardiac arrest, the EEG is suppressed in many patients, but it returns to a continuous normal voltage EEG within the first 24 h in most patients who ultimately achieve a good outcome.[320,321] The time for this restitution is correlated with outcome.[319,322] The EEG-background is often discontinuous and of low frequency on its first appearance.[320,323] Sedative drugs affect background continuity and have the potential to induce discontinuous or burst-suppression background in a dose-dependent manner.[324,325]

Background patterns

Suppression

A suppressed (<10 μV) or low-voltage (<20 μV) background is relatively common during the first day after a cardiac arrest in patients who later recover.[300,320,321] However, 24 h after ROSC, a suppressed EEG-background <10 μV is a reliable sign of a poor prognosis,[326−331] although two false positive predictions by this pattern 48−72 h after cardiac arrest were reported in one study.[328] There was moderate interrater agreement for suppressed background among senior neurophysiologists.[328,332]

Burst suppression

According to the ACNS-terminology, burst suppression (BS) is defined as 50−99% of the recording consisting of suppression alternating with bursts. The terminology does not have any amplitude criteria for the bursts but these may be defined further as 'highly epileptiform bursts', based on appearance [187] 'Presence of 'identical bursts' (either the first 0.5 s of each burst or each stereotyped cluster of ≥2 bursts appears visually similar in >90% of bursts in each channel) portend a poor prognosis in post-anoxic coma.[333] One research group also proposed a separation of BS-patterns into 'synchronous' (with highly epileptiform or identical bursts) and 'heterogenous' (not 'synchronous').[331] The criteria used for burst amplitude and appearance varies considerably between studies. A substantial portion of patients with BS during the first 24 h and occasional patients with BS-pattern after 24 h still have a good outcome, which is possibly related to sedation use.[302,320,326−328,334−336] There was substantial interrater agreement among experienced neurophysiologists for BS.[328]

Discontinuous

A discontinuous background with suppression periods >10% of the recording has low prognostic performance during the first 24 h after cardiac arrest[337,338] and an inconsistent performance after 24 h.[326−328,338]

Reactivity

EEG-reactivity is a measurable change in amplitude or frequency upon external stimulation (auditory and pain). There is no generally acknowledged standard for reactivity testing and the prognostic performance of this feature varied substantially between studies.[15,339] Absence of EEG-reactivity during the first 24 h after cardiac arrest is an indicator of a poor outcome with high sensitivity but low specificity (41.7−87.5%).[336,340−342] After 24 h, the sensitivity of absent reactivity remains high but the specificity varied from 50 to 100%.[326,328,334,336,341−345] Interrater agreement for the assessment of EEG-reactivity varied from slight-almost perfect.[328,346] Stimulus-evoked rhythmic, periodic or ictal discharges (SIRPIDS) are not a manifestation of normal background reactivity−their prognostic significance is still undefined.[203,347]

Superimposed patterns

Periodic discharges

A 'periodic' pattern is a waveform that occurs repeatedly, with a quantifiable interval between discharges. If no such interval exists, the pattern is termed 'rhythmic'.[187] Periodic discharges (PDs) may be superimposed on various backgrounds and are related to a worse prognosis. Generalised periodic discharges (GPDs) are a sign of a poor prognosis with limited specificity.[326,327,330,334] In general, the background on which PDs appear is more related to the neurological outcome.[319] PDs on a continuous and reactive EEG-background should not be considered as an indicator of a poor outcome.[181]

Sporadic epileptiform discharges

'Sporadic epileptiform discharges' describes sharp waves or spikes resembling those seen in patients with epilepsy, but without the regularity of a periodic pattern. The frequency by which they appear may vary extensively from 'rare' (<1 h^{-1}) to 'abundant' (≥1/10 s), bordering on periodic discharges. While their appearance is related to a worse outcome, their specificity to predict poor outcome ranges from 66.7 to 100%[15] and reports on the potentially important frequency or number of discharges was lacking in studies.[300,328,330,331] Presence of sporadic epileptiform discharges is NOT a reliable indicator of a poor neurological prognosis.

Electrographic seizures and electrographic status epilepticus

The ACNS defines 'unequivocal seizures' as generalised rhythmic spike-and-wave discharges with a frequency ≥3 Hz or clearly evolving discharges of any type >4 Hz.[187] This definition was inconsistently used in studies. Seizures had a low sensitivity but high specificity for a poor outcome regardless of timing.[326,328,330,334,348]

The term 'electrographic status epilepticus' (ESE) is defined as an electrographic seizure for ≥10 continuous minutes or for a total duration of ≥20% of any 60-min period of recording. This definition has been included for the first time in the 2021 update of the ACNS terminology and none of the currently available prognostic studies has incorporated it yet. Some studies based their definition of ESE on the ACNS classification of unequivocal seizures extending ≥30 min but also included epileptiform discharges ≥1 Hz,[197,322] and in one study ≥0.5 Hz as ESE.[349] Other studies had an unclear definition of ESE.[302,334,335,341] The proportion of patients classified with ESE varied considerably between studies, possibly reflecting differences in definitions. One study showed that ESE evolves from high frequency discharges early after onset to progressively slower frequencies

during the following days and weeks.[186] Regardless of the classification used, ESE is associated with a worse prognosis after cardiac arrest, but some patients have a good outcome.[196,197,199] As with periodic discharges, it is important to consider if the EEG-background is continuous and reactivity is present, which are both favourable features.[197,199] Because of the lack of a standardised classification, we recommend avoiding the term 'status epilepticus' for assessments of prognosis but instead to classify the EEG-background and superimposed discharges and unequivocal seizures according to the standardised ACNS terminology.[187]

Categories of patterns

In several studies, the most unfavourable patterns were grouped as 'malignant' or 'highly malignant'. The most common grouping included suppressed background with or without periodic discharges and burst-suppression as 'highly malignant patterns'.[326] There was substantial interrater agreement for these 'highly malignant patterns',[346] and the specificity for poor outcome was 90.6−100%.[326,327,329,336,338,340,350] An alternative categorisation of 'unfavourable patterns' using a stricter definition of burst-suppression has been suggested.[331]

Quantitative EEG-indices

Automated assessment of quantitative EEG-features such as the burst-suppression amplitude ratio and reactivity has been tested in individual studies.[351,352] Combinations of quantitative EEG-features include the Bi-spectral index (BIS) and the Cerebral Recovery Index.[353] The threshold value and specificity for BIS to predict poor outcome varied widely between studies.[354−356] Automated assessments may decrease subjectivity in EEG assessments. Prospective multi-centre studies are needed to assess the prognostic performance after cardiac arrest.

Evoked potentials

Somatosensory evoked potentials (SSEPs)

When performing SSEPs the median nerve is electrically stimulated and the ascending signals are recorded from the peripheral plexus brachialis, cervical level, subcortical level and the sensory cortex (N20-potential). SSEPs may be depressed by barbiturate coma but are preserved with other sedative drugs such as propofol and midazolam.[357] A bilateral absence of the short-latency N20-potentials over the sensory cortex is a reliable sign of a poor prognosis after cardiac arrest with high specificity and limited sensitivity both early and late after cardiac arrest.[201,202,302,310,331,335,337,338,340,342,343,350,352,358−366] Occasional false positive predictions were reported.[367] The interrater reliability for interpretation of SSEPs was moderate to good.[368,369] The quality of the recording is very important and noise from muscle activity is an important limiting factor which may be eliminated by neuromuscular blocking drugs.[357,368]

Visual evoked potentials (VEP) and auditory evoked potentials (AEP)

There are few data supporting the use of visual evoked potentials (VEPs)[358] and auditory evoked potentials (AEPs)[361,364] to prognosticate outcome after cardiac arrest. These results need validation before VEPs or AEPs can be recommended in this context.

Biomarkers

These guidelines are supported by evidence derived from a systematic review on prognostication and 2020 ILCOR CoSTRs.[9,15] The relevant treatment recommendations in the 2020 ILCOR CoSTR are:

- We recommend that neuroprognostication always be undertaken using a multi-modal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very-low-certainty evidence).
- We suggest using neuron specific enolase (NSE) within 72 h after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence). There is no consensus on a threshold value.
- We suggest against using S-100B protein for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).
- We suggest against using serum levels of glial fibrillary acidic protein (GFAP), serum tau protein, or neurofilament light chain (Nfl) for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Protein biomarkers that are released following injury to neurons and glial cells may be measured in blood and are likely to correlate with the extent of brain injury and with neurological outcome. Neuron-specific biomarkers include NSE, Nfl and tau protein, while S100B and GFAP originate from astrocytes. Neuron specific enolase has been recommended for assessment of brain injury and to help prognosticate outcome after cardiac arrest since the last revision in 2015.[2] Their actual use in clinical practice, however, is not known. Several reports on novel biomarker candidates have been published since 2015.[231,370−372]

Importantly, a multimodal approach should be used for assessment of comatose survivors after cardiac arrest. Advantages of biomarkers include quantitative results, the relative ease of sampling and interpretation and their independence from the effects of sedatives. Limitations include availability, lack of robust laboratory references, insufficiently large study populations, and lack of external validation for some. Most of the available evidence is limited to a time span of up to 72 h after cardiac arrest which is relevant for most patients. However, it necessitates a strategy for prospective sampling before the assessment of prognosis >72 h post-arrest. Very limited evidence supports the use of biomarkers after 72 h in patients who fail to awaken. Large studies investigating and validating promising novel biomarkers are needed to confirm their predictive value, to assess their reproducibility, and to identify consistent thresholds for a specificity that should be close to 100%. The rationale for accepting a specificity of less than 100% would be that using blood biomarkers, there will always be outliers that must be taken into consideration, e.g. due to poor calibration or issues with laboratory standards, haemolysis or due to poor technique in handling of samples. Demanding 100% specificity from a blood biomarker will lower the sensitivity to levels where their clinical use can be questioned, while allowing an FPR of 1% or 2% will increase their clinical relevance. With a multimodal approach, every prognostic method used for assessment of an individual patient must point in the same direction in order to be trusted. This may be particularly true for biomarkers because of their continuous nature; normal or mildly elevated levels (at correct sampling time) should always alert the clinician of potential error in other methods indicating poor prognosis.

Neuron-specific enolase (NSE)

Neuron specific enolase has been studied extensively; since the last systematic reviews,[298,299] at least 13 observational studies have been published with threshold values ranging from 33−120 $\mu g\,L^{-1}$ within 72 h

predicting poor neurological outcome from hospital discharge to 6 months with specificity ranging from 75−100% and sensitivity ranging from 7.8% to 83.6%. In the largest study to date, outliers were described.[373] Patients with high NSE (>90 μg L^{-1}) and good outcome had confounders for NSE elevation and most patients with low NSE (<17 μg L^{-1}) who died had a cause of death other than hypoxic/ischaemic encephalopathy. The study was excluded from the recent systematic review because the primary outcome was CPC at ICU discharge.[15] A large substudy of the TTM-trial identified a threshold of 48 μg L^{-1} at 48 h and a threshold of 38 μg L^{-1} at 72 h with a specificity of 98% (FPR 2%) for poor neurological outcome at 6 months.[230] In another study, NSE with a threshold of 50.2 μg L^{-1} at day 4 predicted poor neurological outcome at one month with 100% specificity and 42.1% sensitivity.[374]

NSE decreases after 24 h in patients with good outcome and typically increases in patients with a poor outcome to peak at 48−96 h. NSE performs poorly at 24 h and best at 48 or 72 h. High NSE at 48 or 72 h after cardiac arrest is a robust predictor of a poor outcome.[230,365,373–378] Increasing NSE from 24−48 or 48−72 h is a reliable indicator of a poor prognosis with similar performance as the absolute value.[379] One small study found that a 48:24 h NSE ratio ≥1.7 had a 100% specificity for poor outcome.[375] In a recent study, the prognostic performance of NSE was clearly dependent on age and severity of the insult (time to ROSC).[380] It performed best in the youngest quartile and in patients with longer time to ROSC. Several different analytical assays were used in the included studies but the methodology for routine clinical use provided by Roche and Brahms were most frequent. NSE has been used as a surrogate marker for brain injury in two recent trials.[75,96]

Thresholds for high NSE values must be established in collaboration with the local laboratory considering the analytical method. Red blood cells contain NSE so haemolysis (free haemoglobin) must be measured and samples discarded if the haemolysis index threshold is exceeded because this may generate a falsely high NSE value.[381] The half-life of free haemoglobin is approximately 2 −4 h compared with the 30-h half-life of NSE. Thus, the NSE value may be inappropriately increased (by NSE from red blood cells) at a time when free haemoglobin is no longer detectable, which is a concern when using NSE for prognostication after cardiac arrest.[381]

S100B

Three observational studies have been published since 2013,[376,377,382] two of them investigated S100B immediately after ROSC and identified threshold values ranging from 3.56 to 16.6 with 100% specificity of poor outcome but with low sensitivities of 2.8% to 26.9%. In the largest study, S100B discriminated best at 24 h with a threshold value of 2.59 μg L^{-1} for 100% specificity but with a low sensitivity of 10%, the corresponding sensitivity for 98% specificity (2% FPR) was 32% (threshold value 0.36 μg L^{-1}).[382] The authors concluded that S100B did not add any real value to present prognostication models with or without NSE. S100B is also very rarely used in clinical practice and for these reasons is not included in our recommendations.

Glial fibrillary acidic protein (GFAP)

In one observational study with 100 patients, GFAP with a threshold value of 0.08 μg L^{-1} at 48 h ± 12 h predicted poor neurological outcome at one month with 100% specificity and 21.3% sensitivity.[370]

Serum Tau

In one study, serum tau protein with a threshold value ranging from 72.7 to 875.6 ng L^{-1} predicted poor neurological outcome at 6 months with 100% specificity and a sensitivity of 4% to 42% (very low certainty of evidence).[371] An ultra-sensitive single molecule assay (SIMoA) was used, with a detection limit at the single molecular level.[383]

Serum neurofilament light chain (Nfl)

In one large study, serum Nfl with a threshold value ranging from 1539 to 12,317 pg mL^{-1} at 24−72 h predicted poor neurological outcome (CPC 3−5) at 6 months with 100% specificity and sensitivity ranging from 53.1% to 65% (moderate certainty of evidence).[231] The same ultra-sensitive SIMoA technique was used for detection of Nfl as was used for tau protein (see above). In a post hoc analysis of the COMACARE trial, which used the same SIMoA technique for analysis, thresholds for serum Nfl that achieved 99% specificity for a poor outcome were 127, 262, and 344 pg mL^{-1} at 24 h, 48 h and 72 h respectively; sensitivities ranged from 78% to 85%.[384] In another study that did not use the SIMoA technique, serum Nfl with a threshold value ranging from 252 to 405 pg mL^{-1} from day 1 to day 7 predicted poor neurological outcome (CPC 4−5) at 6 months with 100% specificity and sensitivity ranging from 55.6% to 94.4%.[372]

Imaging

These guidelines are supported by evidence derived from a systematic review on prognostication and 2020 ILCOR CoSTRs.[9,15] The relevant treatment recommendations in the 2020 ILCOR CoSTR are:

- We suggest using brain imaging studies for prognostication only in centres where specific experience is available (weak recommendation, very-low-quality evidence).
- We suggest using the presence of a marked reduction of the grey matter/white matter (GM/WM) ratio on brain CT within 72 h after ROSC or the presence of extensive diffusion restriction on brain MRI at 2 to 7 days after ROSC in combination with other predictors for prognosticating a poor neurologic outcome in patients who are comatose after cardiac arrest and who are treated with TTM (weak recommendation, very-low-quality evidence).

Computed tomography (CT) of the brain

Following cardiac arrest, hypoxic-ischaemic brain injury causes cytotoxic oedema, which appears as an attenuation of the GM/WM interface, and vasogenic oedema leading to brain swelling, visible as an effacement of cortical sulci.[385] Measurement of the ratio between the GM and the WM densities (GWR), expressed in Hounsfield units is a method to quantify the degree of oedema. The density of the GM is higher than that of the WM, so that GWR is normally higher than 1. The lower the GWR, the greater the severity of brain oedema.

GWR reduction occurs early in patients with severe hypoxic-ischaemic brain injury. In a recent systematic review most studies on reduced GWR showed that this sign was 100% specific for poor neurological outcome as early as 1 h after ROSC.[15] However, in other studies,[301,386–388] a reduced GWR was 100% specific for poor neurological outcome up to 72 h after ROSC. The methods for GWR measurement varied across studies. In most of them, GWR was calculated between GM and WM areas within the basal ganglia. In others, measurements within the cerebrum (centrum semiovale and high convexity area) were performed.[389–391] In almost all studies, a GWR threshold for 100% specificity was identified. However, its value varied across studies. For instance, the threshold for 100% specificity of the average GWR measured at the basal ganglia and the cerebrum ranged from 1.1 and 1.23 within 2 h from ROSC.[15] GWR sensitivity also varied widely across studies, probably

reflecting differences between scanners and software,[392] in the methods of calculation, or in the aetiology of the arrest.[390,393] In one substudy of the TTM trial, oedema on brain CT was assessed visually without formal GWR measurement.[394] In that study, specificity for poor neurological outcome was 98.4 [94.3–99.6]% with 33.6 [28.1–39.5]% sensitivity. Most studies on brain CT were single centre with retrospective design.

Magnetic resonance imaging (MRI) of the brain

Along with CT, magnetic resonance imaging (MRI) of the brain is the most investigated imaging-based predictive index in patients who are comatose after cardiac arrest.[15] Brain MRI is more challenging to perform in ventilated ICU-patients and MRI was generally performed later than brain CT, usually at 48 h or later from ROSC. On brain MRI, cytotoxic oedema from hypoxic-ischaemic brain injury appears as a hyperintensity on diffusion-weighted imaging (DWI) sequences.[395] In several studies, presence of DWI lesions is associated with poor neurological outcome after cardiac arrest.[389,396–399] However, the assessment was done qualitatively, and specificity was inconsistent (range 55.7–100%). Apparent diffusion coefficient (ADC) enables a semiquantitative assessment of DWI changes, therefore limiting subjectivity. However, the ADC metrics in prognostication studies varied.[15] These include lowest minimum or mean ADC,[400] mean ADC,[401] the proportion of brain volume below a given ADC threshold,[401,402] and the maximum size of the MRI clusters with minimum ADC.[400] Most of these studies assessed global ADC, while one of them assessed regional ADC.[400] In all these studies, an ADC threshold for 100% specificity was identified, often with sensitivities above 50%. All studies on ADC MRI had a small sample size, which limited their precision. In many studies, imaging was performed at the discretion of the treating physician, which may have introduced a selection bias.

Unlike clinical examination and EEG, imaging studies are not prone to interference from sedative drugs. In addition, they can be assessed blindly. Their major limitation is the lack of standardisation of measurement techniques. Despite the available studies showed a high accuracy both for brain CT and MRI, the number of studies was limited with a wide variability in the adopted measurement techniques which greatly limits the reproducibility of their results. For this reason, it is reasonable to reserve the use of imaging studies for prognostication only in centres where specific experience is available. Since there is currently no standard for CT-GWR or MR-ADC measurements these techniques can be recommended to confirm the presence of generalised and extensive ischaemic injury apparent from conventional visual analysis by an experienced neuroradiologist. Finally, imaging studies cannot be performed at the bedside and MRI may not be feasible in the most unstable patients, which limits its applicability especially in the early post-resuscitation period.

Multimodal prognostication

In 2015, the ERC-ESICM Guidelines on Post-Resuscitation Care included an algorithm for the prediction of poor neurological outcome in patients who are comatose after cardiac arrest.[1] This algorithm has been validated in recent retrospective studies. One study in 226 patients showed that the 2015 ERC-ESICM prognostication guidelines had a 0% FPR for predicting poor outcome (CPC from 3 to 5) both at hospital discharge and at six months.[302] Similarly, in a larger single-centre cohort including 485 comatose resuscitated patients the ERC-ESICM algorithm predicted CPC 3–5 with 0% FPR in 155 patients.[403] Among the remaining 330 patients in whom no major predictor or combination of predictors suggesting poor outcome were detected, two thirds had good neurological outcome at three months. Finally, in a retrospective multicentre cohort of 585 patients from the TTM trial, the ERC-ESICM algorithm had 0% (95% CI 0–1.2%) FPR for predicting poor neurological outcome at six months.[313]

The 2015 ERC-ESICM prognostication algorithm was based on a combination of predictors including results of clinical examination (absent or extensor motor response, absent pupillary and corneal reflexes, status myoclonus), biomarkers (high blood values of NSE), electrophysiology (unreactive burst-suppression or status epilepticus on EEG, bilaterally absent N20 SSEP wave) and imaging (signs of diffuse anoxic brain injury on CT or MRI). The evidence supporting these predictors had been assessed in two reviews published in 2013.[298,299] To facilitate an update for the present guidelines, a new review has been conducted and its results are reported in the previous paragraphs of the present guidelines focusing on individual prognostication modalities.[15] The 2020 review largely confirmed the results of the 2013 reviews and the reliability of the predictors suggested in the 2015 algorithm. However, some important differences were noted:

- Absent pupillary and corneal reflexes achieved 0% FPR consistently only after day 4, rather than after day 3 as in the previous review.
- Automated measurement of absent pupillary reflex using pupillometry may enable a more accurate prediction than standard (manual) assessment of pupillary reflex (s-PLR), and it is more reproducible.
- The accuracy of NSE was higher at 48–72 h than at 24 h from ROSC.
- The low FPR of unreactive EEG background documented in a few of the studies on TTM-treated patients in the 2013 review was not confirmed in the 2020 review.
- No consistent definition was found for status epilepticus, a predictor suggested in the 2015 guidelines.
- Presence of a suppressed EEG background or burst-suppression predicted poor outcome with very low FPR, especially when recorded after 24–72 h from ROSC; in the previous reviews, evidence supporting suppression was negligible, and definitions of burst-suppression were heterogeneous.
- Several prognostication studies classified EEG according to the Standardised Critical Care EEG Terminology (2012 version) of the American Clinical Neurophysiology Society (ACNS).[404]

The risk of bias for most of the available studies was high. As in previous reviews, a major limitation in most studies was lack of blinding; furthermore, several predictors of poor neurological outcome were used as criteria for WLST. In both cases, this may have resulted in a self-fulfilling prophecy. However, the 2020 review included studies where no WLST was performed, therefore limiting the risk of self-fulfilling prophecy.[300,358,387,393,398] Predictors assessed in these studies included EEG, SSEPs, and brain CT. Based on results of the 2020 review, most of the recommendations included in the 2015 prognostication algorithm remain valid.

Suggested prognostication strategy

Prognostic assessment should start with an accurate clinical examination.[405] Its main scope is to confirm that the patient is comatose because of hypoxic-ischaemic brain injury. Clinical examination should be performed daily to detect signs of neurological

recovery such as purposeful movements or to identify a clinical picture suggesting impending brain death. The latter may include fixed, dilated pupils, diabetes insipidus, and cardiovascular changes suggesting herniation, such as bradycardia associated with hypertension or an otherwise unexplained haemodynamic instability. Brain death occurs in 5–10% of patients who die after cardiac arrest resuscitated with conventional CPR and in about 25% of patients who die after resuscitation with extracorporeal CPR.[286] In most cases, brain death occurs during the first 3–4 days after ROSC. A suggested algorithm for brain death screening after cardiac arrest is shown in Fig. 7. The World Brain Death Project (WBDP) consensus group has published detailed guidance on the determination of brain death after treatment with targeted temperature management (TTM).[406]

In most patients, awakening from coma following cardiac arrest occurs within 3–4 days from ROSC.[202,305] However, patients who are initially unconscious following cardiac arrest are usually treated with sedatives and neuromuscular blocking drugs to enable targeted temperature management (TTM), and to facilitate mechanical ventilation and other life support measures. Therefore, to enable a reliable clinical examination, these drugs should be stopped for sufficient time to avoid interference from their effects. The WBDP consensus group recommends that clinical examination be delayed until at least 5 elimination half-lives of the drug administered with the longest half-life.[406] Although this recommendation has been made in the context of diagnosing brain death, it is equally relevant to prognostic assessment if this is being used to make a WLST decision. Short-acting drugs are preferred whenever possible but even a short-acting drug such as propofol has a half-life of 2.3–4.7 h, which implies the need to stop sedatives for at least 24 h in most cases. This will be much longer if there is renal and/or hepatic impairment or if longer-acting drugs have been given. When residual sedation or paralysis is suspected, consider using antidotes to reverse the effects of these drugs. Use caution when administering flumazenil to reverse the effect of benzodiazepines because this may precipitate seizures. Apart from sedation and neuromuscular blockade, other major confounders include hypothermia, severe hypotension, sepsis, and metabolic or respiratory derangements.

A poor motor response has a relatively low specificity, but a high sensitivity for prediction of poor neurological outcome after cardiac arrest. Therefore, it can be used to identify patients needing prognostication. An absent or extensor motor response ($M \leq 2$) of the Glasgow Coma Scale was the entry point of the 2015 prognostication algorithm. However, recent evidence showed that using $M \leq 3$ as an entry point increases the sensitivity for prediction of poor outcome without reducing specificity.[313,407] The prognostication strategy described below applies to patients who are comatose with a motor response (M) equal to or below 3 (abnormal flexion, extension, or nil) at ≥72 h after ROSC. Results of earlier prognostic tests are also considered at this time.

Signs suggesting the potential for recovery should be actively sought. These are often identified early in the clinical course after resuscitation. In a study on 357 comatose survivors of cardiac arrest, a benign EEG (continuous, reactive, non-suppressed background without epileptiform discharges) recorded within 24 h from ROSC predicted good neurological outcome with 76 [69–82]% sensitivity and 88 [82–92]% specificity.[338] In 250 patients with indeterminate outcome on day 3 according to the 2015 ERC-ESICM prognostication algorithm presence of a benign EEG was associated with good neurological outcome in 184 cases (positive predictive value 74%).[403] Among 14 patients who recovered after their outcome was defined as indeterminate in another validation study, the majority had low and decreasing NSE values and all but one had ventricular fibrillation on the initial ECG.[313] Other potentially useful indices of good neurological outcome include absence of diffusion changes on brain MRI and low blood values of neurofilament light chain within 72 h from ROSC.[231,389,397,398] Recent evidence showed that a benign EEG is not associated with the presence of other predictors of poor neurological outcome, especially a bilaterally absent N20 SSEP wave.[408–410] Therefore, when predictors suggesting a potential for recovery coexist with others suggesting a poor outcome, there is a chance that the latter signal is a false positive. We suggest that in this case the results of predictive indices are reassessed, and index tests be repeated if possible.

In a comatose patient with $M \leq 3$ at ≥72 h from ROSC, in absence of confounders, poor outcome is likely when two or more of the following predictors are present: no pupillary and corneal reflexes at ≥72 h, bilaterally absent N20 SSEP wave at ≥24 h, highly malignant EEG at >24 h, NSE >60 μg/L at 48 h and/or 72 h, status myoclonus ≤72 h, or a diffuse and extensive anoxic injury on brain CT/MRI. Most of these signs can be recorded before 72 h from ROSC, however their results will be evaluated only at the time of clinical prognostic assessment. A recent study has shown that a strategy of using ≥2 predictors had 0 [0–8]% FPR compared with 7 [1–18]% of the 2015 ERC-ESICM stepwise strategy (due to false positives for pupillary light reflexes).[411]

Evidence from both the 2013 and the 2020 reviews showed that a bilaterally absent N20 SSEP wave is the most widely documented predictor of poor outcome and the one most consistently associated with 100% specificity. However, false positive predictions have occasionally been reported. In some of these cases, the cause of a false positive result was an incorrect reading of the SSEP record because of artefacts.[412] Neuromuscular blockade improves readability of SSEPs and it should be considered whenever possible.[413]

Pupillary light reflex and corneal reflex are also very specific for poor outcome when bilaterally absent at 72 h or more after ROSC. Based on expert opinion, we suggest that both reflexes should be absent at the time of prognostic assessment for them to reliably predict poor outcome. Unlike SSEPs, ocular reflexes are prone to interference from sedation. Corneal reflexes may also be affected by neuromuscular blocking drugs. These confounders should be excluded before ocular reflexes are assessed. Visual evaluation of PLR may be hampered when the pupil size is less than 6 mm.[308] Limited evidence shows that in resuscitated comatose patients automated pupillometry is more sensitive than s-PLR in detecting pupil response to light when pupil size is small, which reduces the risk of false positive results.[310] Unlike s-PLR, automated pupillometry delivers a stimulating light source with standard characteristics (intensity, duration, and distance from the eye) and measures pupillary response quantitatively, which ensures reproducibility. For this reason, we suggest detecting the absence of PLR with a pupillometer, if available.

Status myoclonus is a prolonged period of myoclonic jerks. Although there is no universal definition for status myoclonus, based on our previous definition[1] we suggest that, in comatose survivors of cardiac arrest, status myoclonus should be defined as a continuous and generalised myoclonus persisting for 30 min or more. In the 2020 review informing the present guidelines, status myoclonus was documented in two studies, one of which used a definition comparable to that given above. In total, among 113 patients showing this sign, there was only one false positive result. Aside from duration and continuity, other clinical features of myoclonus suggest poor outcome.

donation after circulatory death uDCD (Maastricht category I/II donors) is addressed in the Advanced Life Support section of the guidelines.[523]

A previous 2015 ILCOR CoSTR and an ILCOR Scientific Statement on organ donation following CPR underpin this guideline.[122] Recent CPR should not prevent organ donation. Observational studies show that organs (heart, lung, kidney, liver, pancreas, intestine) from donors who have had CPR have similar graft survival rates compared with donors who have not had CPR.[524,525]

A systematic review identified 26 studies that showed the prevalence of brain death in comatose ventilated patients with hypoxic–ischaemic brain injury who died following CPR was 12.6% (95% CI 10.2–15.2%) with a higher prevalence following eCPR (27.9% [19.7–36.6%] vs. 8.3% [6.5–10.4%]) and that approximately 40% of these proceeded to organ donation.[286] The median time to diagnose brain death was 3.2 days. This systematic review concluded that patients who are unconscious after resuscitation from cardiac arrest, especially when resuscitated using e-CPR, should be assessed for signs of brain death.

Furthermore, in those who do not fulfil criteria for neurological death, WLST because of a poor neurological prognosis is a common cause of death. After OHCA, approximately two thirds of deaths will be following WLST because of a poor neurological prognosis.[22,23] This group of patients provides an increasing source of donors following controlled donation after circulatory death.[526]

There is variation between countries regarding organ donation practices and clinicians must follow local legal and ethical requirements.

Investigating sudden unexplained cardiac arrest

Many sudden cardiac death victims have silent structural heart disease, most often coronary artery disease, but also primary arrhythmia syndromes, cardiomyopathies, familial hypercholesterolaemia and premature ischaemic heart disease. In the course of an autopsy of victims of sudden unexplained death (SUD), blood or tissue samples should be taken and stored for future genetic analysis.[527] Screening for genetic disorders is crucial for primary prevention in relatives as it may enable preventive antiarrhythmic treatment and medical follow-up.[528–530] A multidisciplinary cardiogenetic team should perform the family investigation. Initial evaluation may include clinical examination, electrophysiology and cardiac imaging. A genetic test should be considered according to the combination the results of cardiac family screening and pathology findings. The genetic test should be performed initially on the DNA of the deceased and testing of relatives should then be offered if a pathogenic or likely pathogenic variant is identified.[527,531] Given the implications for relatives, there may be local ethical guidelines for genetic testing.

Cardiac Arrest Centres

There is wide variation among hospitals in the availability and type of post resuscitation care, as well as clinical outcomes.[532–534] Cardiac arrest centres are hospitals providing evidence-based resuscitation treatments including emergency interventional cardiology, and bundled critical care with targeted temperature management, and protocolised cardiorespiratory support and prognostication.[122,207] An expert consensus paper published by the Association of Acute Cardiovascular Care (ACVA), and many other European organisations including the ERC and ESICM, states that the minimum requirements for a cardiac arrest centre are 24/7 availability of an on-site coronary angiography laboratory, an emergency department, an intensive care unit (ICU), imaging facilities, such as echocardiography, computed tomography, and magnetic resonance imaging.[16]

ILCOR suggests that wherever possible, adult patients with non-traumatic OHCA cardiac arrest should be cared for in cardiac arrest centres.[17] This weak recommendation is based on very low certainty evidence from a systematic review that included 21 observational studies.[535–555] and 1 pilot randomised trial.[556] Seventeen of these studies were included in a meta-analysis that found that patients cared for at cardiac arrest centres had improved survival to hospital discharge with favourable neurological outcome, but this was non-significant at 30 days.[535–541,545–552,554,555]

One observational study reported higher adjusted patient survival associated with direct transfer to a cardiac arrest centre compared with secondary interfacility transfer,[552] but two other studies making the same comparisons report no difference in adjusted survival.[536,541] One observational study reported higher adjusted survival in patients who underwent secondary transfer to a cardiac arrest centre compared with remaining at the initial non-cardiac arrest centre.[550]

Conflict of interest statement

Jerry P. Nolan, Editor in Chief *Resuscitation*; Claudio Sandroni, Associate Editor, Intensive Care Medicine; Bernd W. Böttiger, Treasurer of the European Resuscitation Council (ERC); Chairman of the German Resuscitation Council (GRC); Member of the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR); Member of the Executive Committee of the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI), Founder of the Deutsche Stiftung Wiederbelebung; Associate Editor of the European Journal of Anaesthesiology (EJA), Co-Editor of Resuscitation; Editor of Notfall + Rettungsmedizin, Co-Editor of the Brazilian Journal of Anesthesiology. Received fees for lectures from the following companies: Forum für medizinische Fortbildung (FomF), Baxalta Deutschland GmbH, ZOLL Medical Deutschland GmbH, C.R. Bard GmbH, GS Elektromedizinische Geräte G. Stemple GmbH, Novartis Pharma GmbH, Philips GmbH Market DACH, Bioscience Valuation BSV GmbH. Alain Cariou, Speaker's Fee from Bard Medical; Tobias Cronberg; Hans Friberg; Cornelia Genbrugge; Gisela Lilja; Véronique RM Moulaert; Nikolaos Nikolaou; Theresa Mariero Olasveengen – no conflicts of interest. Markus B. Skrifvars, Speaker's Fee from Bard Medical (Ireland); Fabio Silvio Taccone, Speaker's Fees from BD and Zoll; Jasmeet Soar, Editor, Resuscitation.

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