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## **Brain injury after cardiac arrest**

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1 **Post cardiac arrest brain injury**

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50 <h1> Summary

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

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67 Word count: 150

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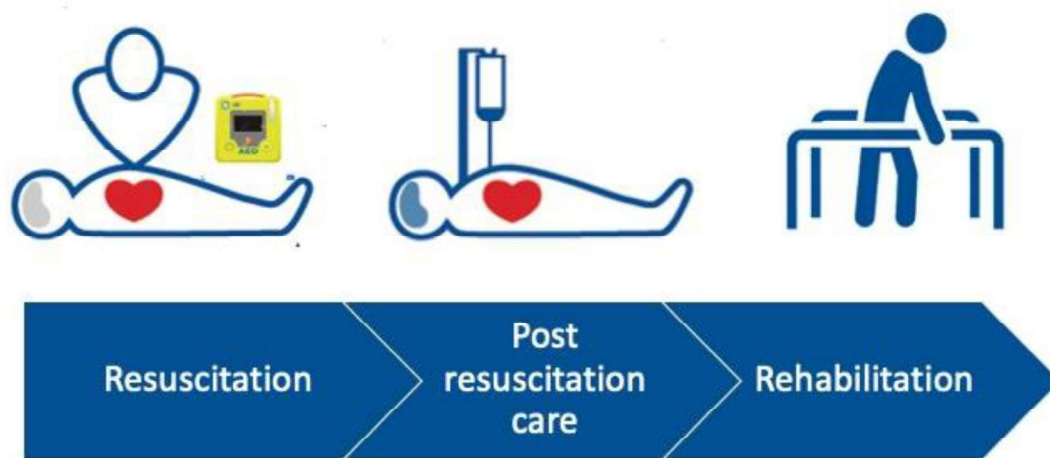
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## 70 <h1> Introduction

71

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

87



88

89

90 **Figure 1: Strategy for optimising outcomes from post cardiac arrest brain injury. The**  
91 **resuscitation phase comprises rapid recognition of cardiac arrest, early CPR and**  
92 **defibrillation to achieve rapid return of spontaneous circulation, minimising primary**  
93 **brain injury. The post resuscitation care phase, focuses on targeted temperature**  
94 **management and normalising physiology to reduce secondary brain injury. The third**  
95 **phase requires interdisciplinary assessment of rehabilitation needs and development**  
96 **of an individual treatment plan to promote restoration of a normal quality of life.**

97

98

#### 99 **Box 1 Search strategy and article selection**

100 We searched Medline (from 2000 to September 2020) using the terms “post cardiac arrest  
101 brain injury”; “post cardiac arrest syndrome”, “cardiac arrest” and “brain injury” and relevant  
102 section headings (epidemiology, pathophysiology, treatment, rehabilitation). The International  
103 Liaison Committee on Resuscitation Consensus on Science and Treatment  
104 Recommendations database (costr.ilcor.org) was also searched for relevant systematic

105 reviews. No language restrictions were applied. We prioritised articles published in the last  
106 five years but also included key references published outside this period.

107

108

## 109 <h1> Epidemiology

110

111 A review of global cardiac arrest registries identified that over 500,000 people receive  
112 treatment for out of hospital cardiac arrests (OHCA) each year with an annual incidence  
113 between 30 to 97 per 100,000 people<sup>6</sup> (equivalent to 1/10<sup>th</sup> the number of myocardial  
114 infarctions). Return of spontaneous circulation (ROSC) is achieved by the time of hospital  
115 handover in approximately one third of patients.<sup>7</sup> Higher rates of ROSC are seen in North  
116 America, Australasia and Europe than in Asia.<sup>7</sup> The majority of cardiac arrests have a cardiac  
117 cause.<sup>7</sup> Those who present with an initially shockable rhythm (ventricular fibrillation or  
118 ventricular tachycardia) have much better outcomes than those who present with pulseless  
119 electrical activity or asystole.<sup>6</sup> The best outcomes from resuscitation occur in those who regain  
120 consciousness rapidly after return of ROSC. In a study from Denmark involving 13,953  
121 patients with OHCA, on hospital arrival 776 (5.6%) had ROSC and were conscious, 5205  
122 (37.3%) had ROSC, but were comatose, and 7972 (57.1%) had ongoing CPR at hospital  
123 arrival.<sup>8</sup> Most patients who were conscious on arrival were alive 30 days later (89.0% (95%  
124 confidence interval [CI] 86.8%–91.2%)) and few developed anoxic brain injury or required  
125 nursing home admission (2.4% (95% CI 1.2%–3.6%)).<sup>8</sup> The majority of patients who are  
126 comatose on arrival at hospital are admitted to an intensive care unit (ICU) where they spend  
127 on average 3-5 days and represent up to 10% of ICU admissions.<sup>9,10</sup> Here, attention is focused  
128 on identifying and treating the underlying cause of the cardiac arrest and optimising  
129 neurological recovery. Deaths within the first few days of intensive care are usually due to  
130 refractory shock, respiratory failure or withdrawal of treatment because of the presence of  
131 severe co-morbidities.<sup>11</sup> Patients who wake up in in the first 4 days of ICU care have the best  
132 outcomes.<sup>12</sup> In patients who do not wake up quickly, guidelines recommend prognostic

133 assessment no earlier than 72 hours after admission to intensive care. The practice of  
134 withdrawal of life sustaining treatment based on prognostication of a poor neurological  
135 outcome varies around the world.<sup>13</sup> In centres that withdraw treatment because of a predicted  
136 poor outcome, this accounts for approximately 60% of deaths in ICU.<sup>2</sup> In the most severe  
137 cases, post-cardiac arrest brain injury progresses to brain death in around 1 in 10 of patients  
138 admitted to an ICU.<sup>14</sup> (Figure 2). Depending on national laws, non-heart beating organ  
139 donation and donation after brain stem death may occur in up to 5-10% of non-survivors  
140 following cardiac arrest.<sup>10,14</sup> Box 2 highlights a family's story about the devastating  
141 consequences of post resuscitation brain injury.

142

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

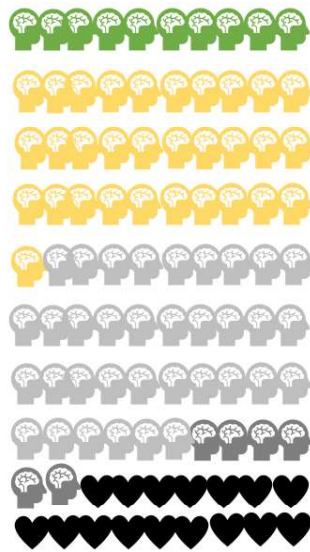
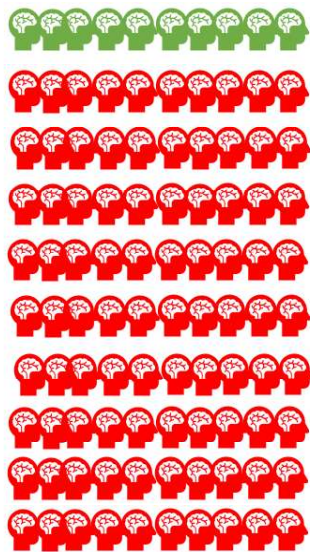
156

157

Hospital admission

Hospital stay

Discharge



158

159 **Figure 2: Diagrammatic representation of outcomes following return of spontaneous**  
160 **circulation after out of hospital cardiac arrest. Key: Hospital admission / hospital stay:**

161 – conscious; - comatose; – neurological improvement; - death following  
162 **withdraw of life sustaining treatments due to predicted adverse neurological outcome;**

163 – brain death, death due to refractory shock / multi-organ failure, Hospital

164 **discharge: - favourable neurological outcome - no symptoms to moderate**

165 **disability (requiring some help; but able to walk without assistance); - poor**

166 **neurological outcome – (unable to walk and / or attend to bodily needs without**  
167 **assistance or bedridden, incontinent, requiring constant nursing care and attention);**

168 – dead.

169

170

171

172

173

174 **Box 2 : Post cardiac arrest brain injury – a family’s perspective.**

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

178

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

184

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

189

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

193

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

198

199

200

201 <h1> Pathophysiology

202

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

208

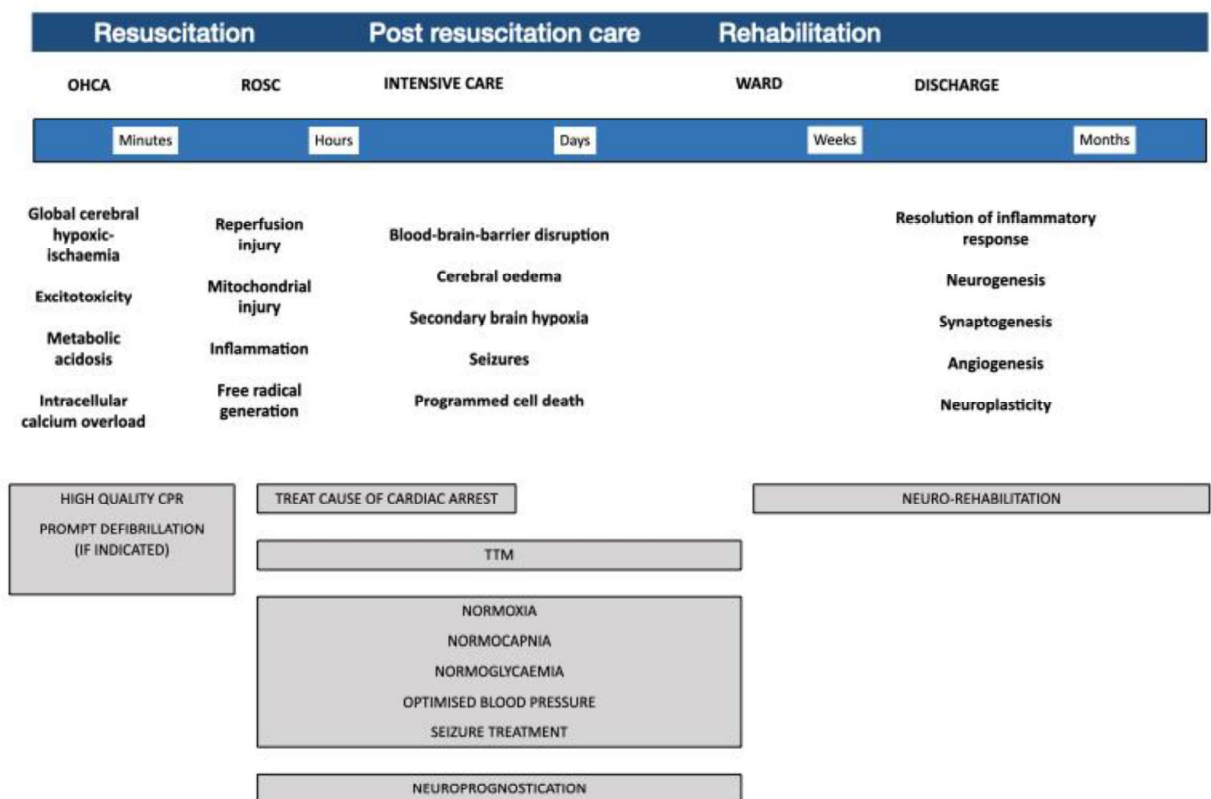
209 **Table 1: Mechanisms associated with post cardiac arrest brain injury.**

Primary Injury Mechanisms	Secondary Injury Mechanisms
<ul style="list-style-type: none"><li>• Impaired oxygen/substrate delivery</li><li>• Excitotoxicity</li><li>• Disrupted calcium homeostasis</li><li>• Oxidative stress</li><li>• Mitochondrial damage and dysfunction</li><li>• Pathologic protease activation</li><li>• Inflammation</li></ul>	<ul style="list-style-type: none"><li>• Hypotension</li><li>• Hypoxaemia</li><li>• Elevated intracranial pressure (ICP)</li><li>• Seizures</li><li>• Dysglycaemia</li><li>• Hyperthermia</li></ul>

210

211

212



213

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

216

217 **<h2>** Primary injury (minutes–hours)

218

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

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

235

## 236 <h2> Secondary injury (hours-days)

237

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

253

254

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

262

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

264

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

269

### 270 <h2> Primary injury

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

277

### 278 <h2> Secondary injury

279

#### 280 <h3> Pre-hospital interventions

281 Immediately following ROSC, guidelines recommend avoidance of hypoxaemia and  
282 hypotension, based on their association with poor outcomes.<sup>23</sup> Despite experimental data

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

287

288 <h3> Interventions after arrival in hospital

289

290 <h4> Targeted temperature management

291 A large randomised controlled trial demonstrated that targeted temperature management  
292 (TTM) at 32-34°C versus no TTM increased the proportion of good neurological outcomes by  
293 16% in comatose patients presenting in cardiac arrest with ventricular fibrillation.<sup>32</sup> A more  
294 recent trial reported that TTM at 33°C versus TTM at 37°C increased the proportion of good  
295 neurological outcomes from 4.5% to 10% in patients presenting with non-shockable rhythms.  
296 Interpretation is however limited by a fragility index of 1 which is lower than the number of  
297 patients who withdrew or were lost to follow-up.<sup>33</sup> The optimal depth of hypothermia for TTM  
298 is less certain, because the largest multicentre trial to date detected no difference in outcomes  
299 of comatose post-cardiac arrest survivors between TTM at 33°C versus TTM at 36°C  
300 treatment.<sup>9</sup> The duration of TTM in practice is typically 24 hours as in the original trials, though  
301 a smaller multi-centre trial observed a non-significant 4.9% increase in the proportion of good  
302 neurological outcomes with TTM for 48 hours versus TTM for 24 hours.<sup>34</sup> Current consensus  
303 is that care for post-cardiac arrest patients with coma should include TTM. A large 1900 patient  
304 trial comparing 33° versus active fever prevention has finished randomization and follow-up  
305 and will be published in spring 2021. Guidelines, based on low certainty evidence, suggest  
306 following the completion of TTM, fever should be actively treated.<sup>23</sup>

307

308 <h4> Oxygenation and ventilation

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

311 ROSC.<sup>23,35</sup> However, unintentional hyperoxia occurs following inadvertent and prolonged use  
312 of 100% oxygen.<sup>36</sup> Sub-group analyses from the ICU-ROX trial suggested improved  
313 outcomes with tightly controlled compared with more liberal oxygen use in patients at risk of  
314 brain injury after OHCA,<sup>37</sup> however this was not significantly different when corrected for  
315 baseline differences between groups.<sup>38</sup> On the other hand a sub-group analysis of 332  
316 patients at risk of cardiac arrest related brain injury included in the multi-centre HOT-ICU trial,  
317 did not show any difference in outcome with an oxygen target of 60 mmHg (8 kPa) compared  
318 to 90 mmHg (12 kPa).<sup>39</sup> Given the absence of conclusive evidence, it is prudent to target  
319 normoxia (PaO<sub>2</sub> 10-12 kPa) but to carefully avoid hypoxia (PaO<sub>2</sub> < 8 kPa), as multiple studies  
320 have shown association between hypoxia and poor functional outcome.<sup>40</sup> A slightly elevated  
321 carbon dioxide may act as a vasodilator and has been shown to increase cerebral oxygenation  
322 when measured with near infrared spectroscopy.<sup>41</sup> However, the potential vasodilatory  
323 benefits of hypercarbia cannot be realised if cerebral perfusion pressure is inadequate. Some  
324 experimental studies have shown anti-convulsive and anti-inflammatory effects with mild  
325 hypercapnia.<sup>42</sup> Whether this results in better outcome is unclear and a large multicentre trial  
326 is underway (NCT03114033). Until then normocapnia should be targeted, taking care to avoid  
327 hypocapnia which causes vasoconstriction leading to cerebral ischaemia.<sup>23</sup>

328

#### 329 <h4> Blood pressure

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

339 65 mmHg and target a MAP that is sufficient to achieve adequate urine output ( $>0.5 \text{ mL kg}^{-1}$   
340  $\text{hr}^{-1}$ ) and normal or decreasing lactate.<sup>23</sup>

341

342 <h4> Other interventions

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

349

350

351

352 <h2> Ongoing trials

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

359

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

361

<b>Timing</b>	<b>Intervention</b>	<b>Primary Outcome</b>	<b>Planned Enrollment</b>
Intra-arrest	Ketamine / Morphine	Pre-hospital, blinded, randomized, placebo-controlled trial to determine in adults if intra-arrest ketamine or morphine improves survival and neurological outcome following out of hospital cardiac arrest. (NCT04009759)	2100
Immediately post ROSC	Optimised PaO <sub>2</sub>	Multi-centre, randomised, controlled trial (RCT) to determine whether reducing oxygen administration to target an oxygen saturation of 90-94%, compared to 98-100%, as soon as possible following successful resuscitation from OHCA improves outcome at hospital discharge. (NCT03138005).	
Post ROSC ICU	Optimising TTM	Targeted Hypothermia Versus Targeted Normothermia After Out-of-hospital Cardiac Arrest (TTM2). Multi-centre randomised controlled trial	1900

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

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

362

363 **<h1> Prognostication**

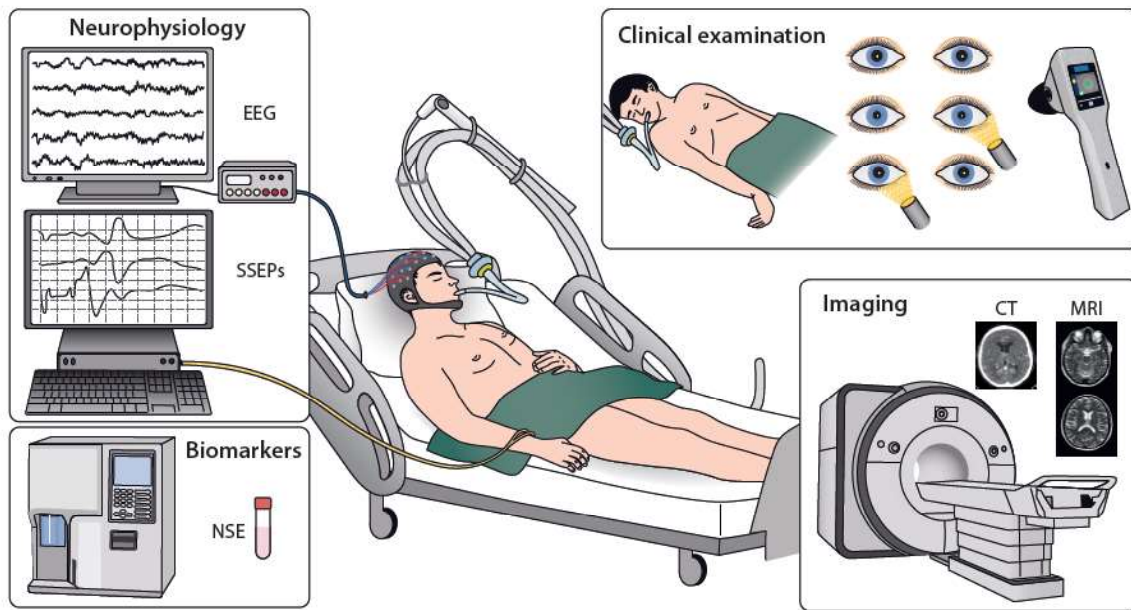
364

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

374

375 To date, most prognostication studies have focused on tests aimed at predicting a poor  
376 outcome. The challenge is to identify tests that have both high sensitivity (the ability to detect  
377 most of those destined to have a poor outcome) and high specificity (very low false positive  
378 rate). Of these, the very low false positive rate is particularly important because the risk of self-  
379 fulfilling prophecy is very high in this patient population (withdrawal of life sustaining treatment  
380 is likely to result in death even if a patient might have had delayed awakening). Self-fulfilling  
381 prophecy can create a false sense of accuracy among clinicians, because the true outcomes  
382 of patients are never observed.<sup>47</sup> Current evidence emphasises the importance of multimodal  
383 prognostication.<sup>48</sup> The main prognostic test modalities are summarised in Figure 4 and Table  
384 3.

385



386

387 **Figure 4: Key tests used to assess prognosis after cardiac arrest. Guidelines**  
 388 **recommend that recommend that neuro-prognostication always be undertaken using a**  
 389 **multi-modal approach to reduce the risk of false positive results leading to premature**  
 390 **withdrawal of life sustaining treatments. Figure reproduced with permission from the**  
 391 **European Resuscitation Council.**

392

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

Test modality	Explanatory notes
<p>Clinical examination</p> <ul style="list-style-type: none"> <li>• Pupillary light reflex (standard or automated pupillometry)</li> <li>• Corneal reflex</li> <li>• Glasgow motor score</li> <li>• Myoclonus</li> </ul>	<ul style="list-style-type: none"> <li>• Pupillary light reflex and corneal reflex are often absent in the hours shortly after arrest, but these reflexes recover in survivors. Persistent absence of brainstem reflexes for days after removal of sedatives is associated with unfavourable outcome. Quantitative pupillometry appears more reliable than visual inspection.<sup>49</sup></li> <li>• Improving Glasgow motor score represents clinical signs of recovering cortical function. However, motor exam alone is not reliable for predicting poor outcome.<sup>50</sup></li> <li>• Myoclonus occurring in the early days after cardiac arrest may be malignant myoclonus which is associated with poor outcome or Lance-Adams syndrome which may have a favourable outcome.<sup>51,52</sup> Electrophysiological investigations are required to distinguish these syndromes.<sup>51</sup></li> </ul>
<p>Blood markers of brain injury</p> <ul style="list-style-type: none"> <li>• Neuron specific enolase (NSE)</li> <li>• S-100B protein</li> <li>• Glial fibrillary acidic protein (GFAP)</li> <li>• Serum neurofilament light chain (NFL)</li> </ul>	<ul style="list-style-type: none"> <li>• NSE is released from neurons and rises over at least 72 hours after severe brain injury. Higher peak values are associated with unfavourable outcome. NSE may not be specific for brain injury, because it is also released from extracerebral sites.<sup>53</sup></li> <li>• S-100B and GFAP are released from glia and peak shortly after cardiac arrest. Prognostic significance of specific values is less clear.<sup>53</sup></li> <li>• NFL is released from axons. Higher NFL values correlate with unfavourable outcome more accurately than NSE in some cohorts, but experience with NFL is more limited.<sup>53</sup></li> </ul>
<p>Electrophysiology</p> <ul style="list-style-type: none"> <li>• Bilaterally absent N20 somatosensory evoked potential (SSEP) wave</li> <li>• Electroencephalogram (EEG)</li> </ul>	<ul style="list-style-type: none"> <li>• SSEP measures the presence or absence of cortical response to electrical stimulation of the median nerve. The test can be performed at the bedside. Absent cortical response from a technically adequate study in the absence of sedative or other confounders is very specific for unfavourable outcome.<sup>35,48</sup></li> <li>• EEG can demonstrate highly malignant patterns at various times after cardiac arrest that are associated with unfavourable outcome.<sup>54</sup> Unequivocal seizures on the EEG increases the likelihood of unfavourable outcome. Return of reactive, continuous EEG is associated with awakening. Reliable interpretation of EEG requires special expertise.<sup>35,48</sup></li> </ul>
<p>Imaging</p> <ul style="list-style-type: none"> <li>• Brain computed tomography (CT) grey matter/white matter ratio (GWR)</li> <li>• Brain magnetic resonance imaging (MRI) diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC)</li> </ul>	<ul style="list-style-type: none"> <li>• CT can demonstrate early, severe cerebral oedema (low GWR at &lt; 24 hours after arrest) that is associated with unfavourable outcome, including risk of progressive oedema leading to brain death.<sup>1,35,48</sup></li> <li>• After 72 hours, areas of brain injury are visible as areas of restricted diffusion on MRI. Widespread cortical damage is associated with unfavourable outcome, but the significance of focal lesions and subcortical lesions is less clear.<sup>35,55</sup></li> </ul>

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

405

406 Ultimately, the only way to reliably determine the performance of prognostic tests is to remove  
407 any element of self-fulfilling prophecy by continuing to support patients for a prolonged period  
408 regardless of the test results. The ability of a 30-minute EEG, SSEPs and brain CT within 24  
409 h of the event to predict poor neurological outcome at 6 months (defined as dead or  
410 unresponsive wakefulness syndrome) was evaluated in 346 comatose cardiac arrest survivors  
411 who had no withdrawal of life sustaining treatment unless brain death was diagnosed.<sup>57</sup>  
412 Bilaterally absent or abnormal SSEPs, a gray matter:white matter ratio  $< 1.21$  on brain CT and  
413 isoelectric/burst suppression EEG patterns predicted poor outcome with 0% false positive rate  
414 (95% CI 0–3%). Another study examined the prognostic performance of SSEPs for 262  
415 patients in a health care setting where withdrawal of life sustaining treatment is not practiced.<sup>58</sup>  
416 Bilaterally absent cortical responses predicted poor outcome with 0% false positive rate (95%  
417 CI 0.0–4.3%). Despite the need for more data such as these, the many patients surviving with  
418 unresponsive wakefulness syndrome in these studies presents an ethical challenge to  
419 conducting similar cohort studies in many systems.

420

## 421 <h1> Clinical and patient focused outcomes

422 Patients and the public involved in developing a Core Outcome Set for Cardiac Arrest  
423 highlighted the importance of outcomes beyond survival and gross assessments of  
424 neurological function.<sup>59</sup> Common sequelae of post cardiac arrest brain injury include  
425 impairments in cognition, emotional wellbeing, physical function, pain and fatigue, participation  
426 and return to work, which reduce health related quality of life.<sup>59</sup>

427

428

### 429 <h2> Cognition

430

431 Mild to severe cognitive impairment occurs in 25-55% of survivors.<sup>60-63</sup> Even mild cognitive  
432 impairment may be associated with reduced emotional status, exercise tolerance, quality of  
433 life, and social autonomy.<sup>61,62,64</sup> Most cognitive recovery occurs within the first three to six-  
434 months.<sup>60,61,63,65</sup> Further changes up to 12-months post-arrest are reported.<sup>60,61</sup> Some  
435 however report increased problems over time, potentially due to increased awareness of  
436 cognitive limitations as survivors return to activities with higher demands on their mental  
437 capacity.<sup>64,65</sup> Routine screening for impairments that are amenable to post-hospital  
438 rehabilitative interventions is recommended before hospital discharge, with re-assessment at  
439 1-3-months, and up to a year.<sup>60,61</sup> The association between objective cognitive assessments  
440 and survivor-reported complaints is weak, and screening should measure both patient  
441 performance and patient-reported symptoms. The Montreal Cognitive Assessment is one  
442 potential screening assessment before more intense objective assessment.<sup>64</sup> The IQ-CODE-  
443 CA is an observer-reported questionnaire which explores the caregiver's perspective of  
444 deficits.<sup>66</sup>

445

### 446 <h2> Emotional wellbeing

447

448 Up to one third of survivors report symptoms of anxiety at 3-6-months (15-36%), with similar  
449 levels reported at 12-months (15-34%).<sup>60,65</sup> High levels of depression are similarly reported at  
450 3-6-months (13-32%), with some reduction by 12-months (7-15%).<sup>60,65</sup> Post-traumatic stress  
451 is reported in approximately 25% of survivors at 6-12 months.<sup>65</sup> Up to one third of caregivers  
452 report high levels of post-traumatic stress at 1-2-years post-event, especially those who  
453 witnessed resuscitation.<sup>67</sup> Symptoms of anxiety and depression are more common in female  
454 and younger survivors and are strongly associated with health-related quality of life (health  
455 related quality of life) and cognition.<sup>60</sup>

456

## 457 <h2> Physical function and activities of daily life

458

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

464

465

## 466 <h2> Fatigue

467

468 Reports of physical and cognitive fatigue remain high throughout the first year of survival (25-  
469 71% at 6-months; 50% at 12-months)<sup>61,62,65,68</sup> and may be associated with emotional problems,  
470 sleep, stress, physical and cognitive impairment.<sup>60</sup>

471

## 472 <h2> Pain

473

474 Problems with pain are reported in 61% of survivors at 3-6 months,<sup>70</sup> 21% at 6-months,<sup>68</sup> and  
475 23%-39% at 12-months.<sup>63,65,69</sup> Pain may be the result of CPR, in-hospital procedures, or other  
476 factors but so far such evaluations are limited.

477

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

479

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

489

490

491 <h1> Rehabilitation

492

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

498

499 <h2> Early rehabilitation

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

502 delirium management<sup>73</sup> and ICU diaries. Although there have been positive results in  
503 individual trials, there is only limited evidence for such interventions for long-term outcomes.  
504 ICU diaries are effective in decreasing emotional problems.<sup>74</sup>

505

## 506 <h2> In-hospital brain-injury rehabilitation

507

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

519

## 520 <h2> At hospital discharge

521

522 Systematic discharge planning is not routinely provided routinely for cardiac arrest survivors,  
523 which may lead to decreased access to, or priority for, patient-centered care and  
524 rehabilitation.<sup>60,61</sup> A standard multidisciplinary discharge checklist may be useful.<sup>61</sup>

525

## 526 <h2> Follow-up programs/services

527

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

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

537

538 <h2> Further referral/support

539

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

549

550

551

552 <h1> Conclusion

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

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

565

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574 authors contributed to article revision and approved the final version.

575

## 576 <h1> Conflicts of interest

577 Callaway (National Institute for Health; American Heart Association); Neumar (National  
578 Institute for Health; American Heart Association); Nolan ((National Institute for Health  
579 Research), Perkins (National Institute for Health Research, British Heart Foundation,  
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584 (ERC), ERC Research net and national resuscitation councils.

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