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# Recent developments in the management of patients resuscitated from cardiac arrest☆,☆☆

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ABSTRACT

Cardiac arrest is the leading cause of death in Europe and the United States. Many patients who are initially resuscitated die in the hospital, and hospital survivors often have substantial neurologic dysfunction. Most cardiac arrests are caused by coronary artery disease; patients with coronary artery disease likely benefit from early coronary angiography and intervention. After resuscitation, cardiac arrest patients remain critically ill and frequently suffer cardiogenic shock and multiorgan failure. Early cardiopulmonary stabilization is important to prevent worsening organ injury. To achieve best patient outcomes, comprehensive critical care management is needed, with primary goals of stabilizing hemodynamics and preventing progressive brain injury. Targeted temperature management is frequently recommended for comatose survivors of cardiac arrest to mitigate the neurologic injury that drives outcomes. Accurate neurologic assessment is central to managing care of cardiac arrest survivors and should combine physical examination with objective neurologic testing, with the caveat that delaying neurologic prognosis is essential to avoid premature withdrawal of supportive care. A combination of clinical findings and diagnostic results should be used to estimate the likelihood of functional recovery. This review focuses on recent advances in care and specific cardiac intensive care strategies that may improve morbidity and mortality for patients after cardiac arrest.



**Contents**



## 1. Introduction

Cardiac arrest is a leading public health problem, claiming the lives of more than 400 000 adult Americans each year and representing a major mode of cardiovascular death [1,2]. Cardiac arrest is the first manifestation of cardiac disease in many of its victims [1,2], encompassing both out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) [2,3]. Survival after OHCA remains poor: only 1 in 4 patients achieves a return of spontaneous circulation (ROSC), and only 1 in 10 patients survives to hospital discharge [1,4]. The survival rate after IHCA is approximately twice that of OHCA, likely because of earlier and more effective resuscitation that achieves ROSC in about half of patients [3,5]. Studies based on national claims data have shown a gradual improvement in cardiac arrest survival in recent years, coincident with an increased focus on postresuscitation critical care [6,7].

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Recently updated consensus guidelines from the American Heart Association and International Consensus of Cardiopulmonary Resuscitation provide algorithms for managing care of patients resuscitated from cardiac arrest [8-10]. In this review, we will highlight several areas of new scientific knowledge and discuss newly published consensus guidelines. These topics include the role of coronary angiography, targeted temperature management, comprehensive critical care, and delayed neurologic prognostication.

### 1.1. Coronary artery disease and coronary angiography after OHCA

Studies of coronary angiography in OHCA patients have found obstructive CAD in at least two thirds of patients without an obvious noncardiac cause of cardiac arrest [11-13]. Approximately 20% to 30% of OHCA patients have ST-segment elevation (STE) on electrocardiography (ECG), and nearly all of these patients have an acute coronary occlusion (ACO) or an identifiable culprit artery [11,13,14]. Up to two thirds of the remaining cardiac arrest survivors without STE also have obstructive CAD, including an identifiable culprit artery lesion warranting percutaneous coronary intervention (PCI) in 25% to 30% [11,13,14]. Coronary angiography is performed less frequently in OHCA patients without STE, which may lead to a delay in both diagnosis and intervention for patients with unstable CAD [7].

Detecting CAD in survivors of OHCA is challenging because clinical histories are frequently unavailable and post-ROSC ECGs and cardiac biomarkers are not as accurate as those for patients presenting with an acute coronary syndrome not associated with cardiac arrest. Short of coronary angiography, there is no highly reliable method of diagnosing obstructive coronary disease in patients after cardiac arrest. Clinical predictors of ACO include a brief, shockable-rhythm cardiac arrest requiring few doses of epinephrine, evidence of heart failure, and predictors of underlying CAD, such as older age, male sex, preexisting CAD, smoking, diabetes, or chest pain [15-18]. Despite its high specificity, STE on ECG is only 50% to 60% sensitive for ACO after OHCA and has poor negative predictive value because of the high pretest probability of CAD in this population [11,14,15,19]. Severe coronary stenosis, ACO, or impaired culprit vessel flow may be found in nearly 20% of survivors of OHCA without any ischemic ECG abnormalities and in more than one third of patients with ischemic ECG changes other than STE [20]. An ECG algorithm combining STE with ST-segment depression increased sensitivity for ACO, especially when abnormal QRS prolongation was included [19]. A risk score incorporating presence of preceding angina, evidence of heart failure, shockable-arrest rhythm, and presence of STE was predictive of ACO in OHCA patients undergoing coronary angiography [18]. Cardiac biomarkers are frequently elevated after cardiac arrest even in the absence of myocardial infarction (MI), with normal troponin values found in as few as 8% of survivors of OHCA [15,21]. Higher troponin levels are associated with ACO, but the optimal troponin cutoff values for predicting ACO remain uncertain [15,21].

Observational studies show a favorable prognosis for OHCA patients who undergo coronary angiography, with overall survival on the order of 50% to 60% and good neurologic outcomes in more than 85% of patients who received concurrent targeted temperature management (TTM) [7,13,14,22,23]. A 2014 meta-analysis of 50 observational studies, including more than 3800 patients, showed a short-term survival rate of 58.8% for patients who underwent early coronary angiography compared with a rate of 30.5% for patients who did not undergo coronary angiography (odds ratio 2.77 for survival with early coronary angiography) [22]. The apparent benefit of coronary angiography may be exaggerated by selection bias favoring coronary angiography in patients with lower-risk cardiac arrest characteristics and likely better neurological function. Geri et al [24] showed better long-term survival rates for patients who underwent early PCI within 6 hours after OHCA compared with patients who underwent early coronary angiography alone, who in turn had better long-term survival rates than patients who did not undergo coronary angiography. The survival benefit of early coronary angiography without PCI was no longer significant after multivariate adjustment, consistent with other studies showing that the benefit of coronary angiography is limited to patients who receive revascularization [24,25]. Not all studies have shown benefits of coronary angiography after OHCA: a post hoc analysis of patients without STE in the TTM trial did not show any benefit of early coronary angiography after OHCA after adjusting for severity of illness [26]. Despite these uncertainties, rates of coronary angiography in OHCA survivors have increased over recent years [7].

### 1.2. Timing of coronary angiography after arrest

Noninvasive testing has inadequate sensitivity for predicting obstructive CAD after OHCA, and we advocate coronary angiography for all eligible OHCA patients without an obvious noncardiac primary cause of their cardiac arrest (Table 1) [13]. Consensus guidelines give a strong (class I) recommendation to emergent coronary angiography for all OHCA patients with STE on ECG, in the absence of contraindications; early coma should not influence the decision to perform coronary angiography [8,27-29]. A moderate (class IIa) recommendation is given to perform emergent coronary angiography for OHCA patients without STE on ECG when acute MI is suspected or when hemodynamic or electrical instability exists [8,30]. A weaker (class IIb) recommendation is to consider angiography for all eligible OHCA patients without contraindications in the absence of an obvious noncardiac cause of cardiac arrest [29]. OHCA patients who have ventricular fibrillation (VF) should undergo coronary angiography to exclude ACO before an implantable cardioverter/defibrillator is placed [15-18,24,31,32]. As in patients with acute coronary syndromes, the benefit of coronary angiography after OHCA parallels the clinical stability of the patient and likelihood of ACO. In the absence of contraindications, we suggest coronary angiography in eligible OHCA patients with shockable arrest rhythm, left ventricular systolic dysfunction or regional wall motion abnormalities on echocardiography, markedly elevated troponin levels, or ischemic ECG changes (Table 1) [11,15-21,24,31].

A recent position statement discussing patient selection for coronary angiography after OHCA recommended excluding patients who were too ill to benefit [13]. The authors of this statement proposed that predictors of adverse neurologic outcome after OHCA be used to identify patients in whom a benefit of coronary angiography is less likely (Box); the authors suggest that all OHCA patients without any of these relative contraindications should be considered for coronary angiography in the absence of an obvious noncardiac cause unless they show definite evidence of severe neurologic injury [13]. Patients with more than 1 of these criteria have a poor neurologic prognosis, and coronary angiography is unlikely to reduce mortality. Patients with only 1 of these exclusion criteria are still at high risk of adverse neurologic outcomes, and we advise offering coronary angiography to those patients with STE or suspected acute MI who would be most likely to benefit from PCI [11,15,24,25]. Patients with severe neurologic injury who are unresponsive to pain and missing multiple brainstem reflexes on early neurologic examination do not appear to benefit from coronary angiography after OHCA [23].

The decision for a patient to undergo coronary angiography must therefore balance markers of neurologic injury and degree of cardiovascular dysfunction (Table 1 and Box). Our suggested approach to selecting survivors of OHCA for coronary angiography integrates assessment of neurologic injury before coronary angiography in patients without STE (Fig. 1). Rather than universally recommending coronary angiography for all patients

**Table 1**
suggested indications for coronary angiography after OHCA

| Guideline-recommended indications for emergent coronary angiography after OHCA | Additional suggested indications for coronary angiography after OHCA |
|---|---|
| STE on ECG (class I) | Shockable arrest rhythm (ie, VF) |
| Hemodynamic instability or shock (class IIa) | Markedly elevated cardiac troponin levels |
| Recurrent VF (class IIa) | Ischemic ECG changes (other than STE) |
| Suspected acute MI (class IIa) | Left ventricular systolic dysfunction |
| | High pretest probability of CAD |

Data from Callaway et al [8,9], Steg et al [27], O'Gara et al [28], Noc et al [29], and Windecker et al [30].

Box
Early clinical predictors of adverse neurologic outcome.[a]

| |
|---|
| Unwitnessed cardiac arrest |
| Nonshockable arrest rhythm |
| Lack of bystander CPR |
| >30 min to ROSC or ongoing CPR |
| Severe acidosis (pH <7.2) |
| Serum lactate >7 mEq/L |
| Age >85 y |
| Chronic organ failure, eg, dialysis |
| Multiple missing brainstem reflexes with lack of motor response to pain |
| Myoclonic status epilepticus |
| Brain edema on head CT scan |

Data from Rab et al [13] and Reynolds et al [23]. CT indicates computed tomographic.
[a]Predictors may serve as relative contraindications for coronary angiography after OHCA.

after OHCA without an apparent noncardiac cause, it may be reasonable to selectively offer coronary angiography for patients without severe brain injury who have clinical findings suggesting underlying CAD and ACO (Fig. 1). It remains uncertain whether hemodynamically stable patients with a normal ECG, low troponin level, and normal left ventricular systolic function after OHCA due to a nonshockable rhythm will benefit from systematic coronary angiography. Performing delayed coronary angiography in these patients after neurologic recovery appears to be associated with favorable outcomes [14,33].

For patients without STE on ECG, the optimal timing of coronary angiography remains unclear. Patients who are hemodynamically unstable or who have a high probability of ACO are more likely to benefit from emergent angiography and revascularization, whereas stable patients may safely undergo delayed coronary angiography. Recent observational studies suggest improved outcomes for patients who had early coronary angiography and reperfusion when they were compared with patients without reperfusion or with delayed reperfusion, but the definition of *early* differed in these studies by up to 1 day [23,24,31]. Geri et al [24] showed that a longer time from cardiac arrest to PCI predicted higher short-term mortality, supporting the importance of early coronary angiography for these patients. Current guidelines recommend emergent coronary angiography within 2 hours for eligible patients with STE on ECG, suspected acute MI, hemodynamic instability, or electrical instability [8,9,27-30]. We suggest early coronary angiography for eligible patients who do not meet these criteria but who have other indications (Table 1). Our institutional practice is to perform urgent coronary angiography within 2 hours whenever ACO is suspected to be the trigger for OHCA. Multiple randomized clinical trials are ongoing to further define the urgency of coronary angiography in otherwise stable OHCA patients without STE on ECG.

The mortality rate for OHCA patients is far higher than that of other populations undergoing PCI; therefore, patients and surrogate decision makers need to be counseled regarding the risks [34,35]. Patients with cardiogenic shock after OHCA have a very high mortality rate, even with PCI; early revascularization is recommended, particularly in the presence of STE on ECG or suspected acute MI [28-30,34,35]. Interventional cardiologists may be hesitant to perform coronary angiography on OHCA patients given their high risk of death driven by brain injury, and concern has been raised that mandatory reporting of PCI outcomes may provide a harmful disincentive for aggressive use of coronary angiography in these patients [12]. Cardiogenic shock has a stronger association with mortality than OHCA among patients with acute MI undergoing PCI, emphasizing that OHCA alone should not exclude patients from coronary angiography [34].

### *1.3. Hypothermia or TTM: elevated body temperature is harmful after cardiac arrest*

Widespread cellular ischemia-reperfusion injury may occur when cardiac arrest is followed by ROSC. The mechanism is likely reactive oxygen species that trigger a number of potentially harmful cellular and metabolic effects that most severely affect organs with high oxygen demands, such as the brain and heart [36]. Immune activation and cytokine release in response to ischemia-reperfusion injury produce a systemic inflammatory response syndrome, which may itself harm tissues beyond the effects of ischemia-reperfusion injury [37-39]. A characteristic post–cardiac arrest

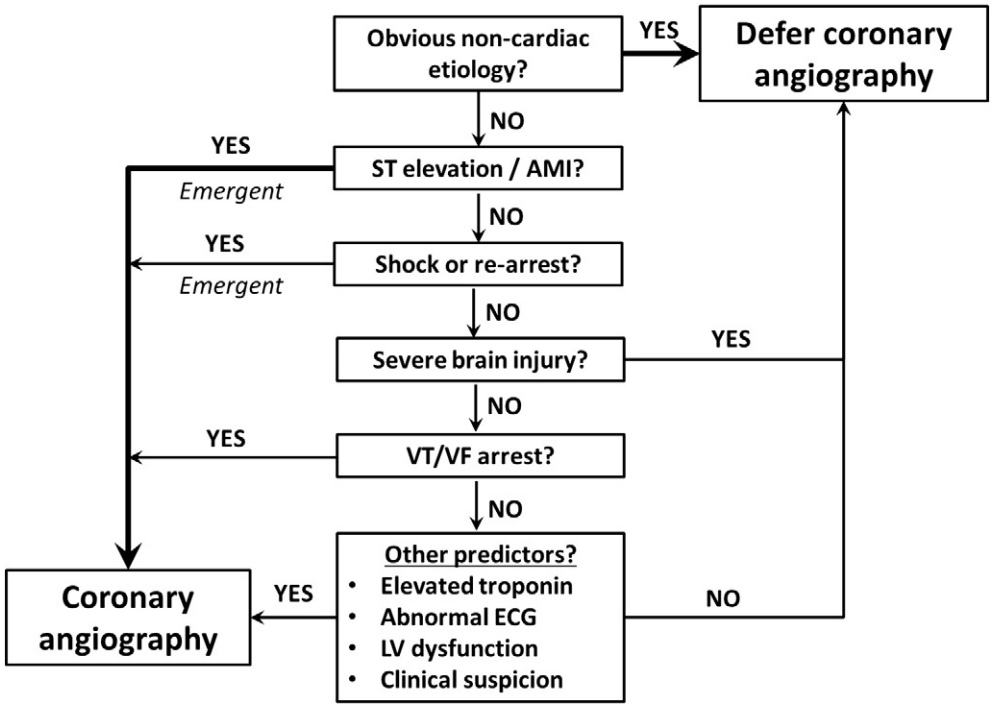


**Fig. 1.** Patient selection for coronary angiography after OHCA. *Emergent coronary angiography* is defined as within 2 hours, and *routine coronary angiography* is defined as within 24 hours. AMI indicates acute myocardial infarction; LV, left ventricular; VT, ventricular tachycardia.

syndrome after ROSC has been described, consisting of anoxic brain injury, systemic inflammatory response syndrome, postarrest myocardial dysfunction, and persistent precipitating pathology [36].

Neurologic injury is the major driver of poor outcomes after cardiac arrest, being the main cause of death after OHCA and a major cause of death after IHCA [40-42], as well as contributing to a substantial morbidity and functional incapacity for surviving patients. The no-blood-flow state of cardiac arrest produces primary anoxic brain injury, which is followed by a more severe secondary wave of neuronal injury and apoptosis after reperfusion, which progresses after ROSC [36]. Injured neurons are highly susceptible to further injury with body temperature elevation, yet neurologic injuries often trigger central fevers because of disordered thermoregulatory mechanisms [43,44]. Fever is associated with adverse neurologic outcomes after cardiac arrest, similar to fever following other forms of neurologic injury [43,45]. Cytokine release and systemic inflammatory response syndrome can produce fevers after ROSC in the absence of infection [37], and elevated cytokine levels such as interleukin-6 predict poor neurologic outcomes after OHCA [38,39]. Infectious complications are common after OHCA and can trigger or aggravate fever and systemic inflammation [46].

*TTM* is defined as precise control of body temperature to prevent complications. *Therapeutic hypothermia* refers to TTM at a low body temperature, typically 32°C to 34°C, but is no longer the preferred terminology [47,48]. The goal of cooling is neuroprotection and prevention of the harmful effects of elevated body temperature after cardiac arrest. Potential harms from aggressive cooling are listed in Table 2 [49].

Two landmark 2002 studies showed marked improvement in neurologic recovery and survival rates without an increase in major complication rates when TTM of 32°C to 34°C was used for up to 24 hours after ROSC in comatose survivors of OHCA due to witnessed VF [48,50,51]. Patients not receiving TTM often had prolonged fevers, making it unclear whether cooling the patient was beneficial per se or whether aggressive fever suppression alone (controlled normothermia) is adequate for preventing secondary brain injury after cardiac arrest [47]. The subsequent, larger TTM trial randomized comatose OHCA patients to a temperature goal of either 33°C or 36°C for 24 hours after ROSC, followed by active fever suppression [52]. This study included patients with both shockable and nonshockable arrest rhythms, although most enrolled patients had shockable rhythms, and patients with unwitnessed asystole were excluded. Patients in the TTM trial had a 6-month survival rate of 47%, which was much higher than survival rates of other contemporary observational studies of OHCA, likely because of the high rates of witnessed, shockable arrests and bystander cardiopulmonary resuscitation (CPR) [1,4,52]. In addition, neurologic assessment was delayed and standardized to minimize premature withdrawal of care. Most subset analyses from the TTM study did not show any significant difference between the 33°C and 36°C groups for major clinical outcomes [52]. A number of study limitations may have potentially favored the 36°C group and could have masked a benefit of 33°C [47]. Patients with favorable arrest characteristics and milder neurologic injury clearly may have good outcomes with TTM at 36°C. It has been speculated that cardiac arrest patients with more severe degrees of neurologic injury or patient subgroups who were underrepresented in the TTM trial might benefit from either a lower goal temperature or a longer duration of TTM [47]. However, there was no difference between patients in the 33°C and 36°C groups in the TTM trial with longer times to ROSC despite more severe markers of postcardiac arrest syndrome and worse outcomes [53].

Interventions that attempt to hasten the induction of TTM or facilitate maintenance of TTM have not improved neurologic outcomes despite earlier reports of better outcomes in patients who reached target temperatures sooner [44]. Prehospital cooling using boluses of cold saline after ROSC is not recommended, as this strategy failed to improve neurologic outcomes and increased rates of pulmonary edema [8,54]. Prehospital cooling using rapid, cold saline boluses may reduce the likelihood of ROSC and increase the risk of recurrent arrest, and should be distinguished from use of cooled crystalloid as a resuscitation fluid when indicated for hemodynamic support [54,55]. Initial studies of TTM used simple and inexpensive surface-cooling methods, but computer-controlled surface and intravascular cooling systems can provide more stable body temperature [44]. These devices have not clearly translated into outcomes benefits, and any effective method of cooling and maintaining a stable temperature goal (with avoidance of fever) appears adequate [56]. Computer-controlled temperature management devices may be advantageous when using a goal temperature of 36°C to ensure that temperature does not rise above this level because failure to maintain target temperature during TTM may be associated with adverse outcomes.

**Table 2**
Potential complications of TTM and therapeutic hypothermia

| Organ system | Common complications |
|---|---|
| Neurologic | Shivering |
| | Decreased sedative clearance |
| Cardiovascular | Bradycardia |
| | Decreased cardiac output |
| | Vasoconstriction |
| | Need for vasopressors and inotropes |
| | Endothelial dysfunction |
| Pulmonary | Pneumonia |
| | Decreased $CO_2$ production |
| Renal | Autodiuresis with hypovolemia |
| | Loss of potassium, magnesium, phosphorous |
| Gastrointestinal | Impaired gut motility |
| | Gastrointestinal bleeding |
| | Decreased hepatic metabolism with slowed lactate and drug clearance |
| Hematologic | Impaired platelet and clotting factor function; hypocoagulable state |
| Immune | Impaired immune function with immunosuppression |
| Endocrine | Insulin resistance and hyperglycemia |
| | Adrenal insufficiency |

Data from Polderman [49].

Patient selection for TTM after cardiac arrest remains controversial, and predictors of benefit from TTM after cardiac arrest remain uncertain. Current guidelines recommend TTM for all cardiac arrest patients with ROSC who are unable to follow commands. The best-established indication for TTM is the original one: comatose patients with witnessed OHCA who have a shockable cardiac arrest rhythm. These patients, who accounted for most of those enrolled in studies of TTM [48,50-52], have the best outcomes after cardiac arrest, and neurologically intact survival rates exceed 55% to 60% after TTM. The few, high-quality studies exploring TTM in patients with nonshockable rhythms have produced mixed results that generally support a benefit of TTM, although only limited randomized trial data exist that compare TTM to no temperature control [57-60]. Outcomes in patients with nonshockable rhythms are markedly worse than in patients with shockable rhythm, and there is a higher frequency of adverse cardiac arrest features and worse neurologic injury [57,59]. For patients in the TTM trial with nonshockable rhythms (approximately 20% of enrolled survivors of OHCA), there was no significant difference in survival, neurologic outcomes, or severity of organ failure between the 33°C and 36°C arms [59]. Randomized studies have not examined TTM in comatose survivors of IHCA, and observational studies show mixed results regarding benefits from TTM in this population [8,47,61-63]. IHCA patients typically have more comorbidities and are relatively less likely to die of neurologic injury after IHCA, which might limit the relative benefit of TTM.

The most recent American Heart Association guidelines give a class I recommendation for TTM for essentially all comatose survivors of cardiac arrest, either OHCA or IHCA (Fig. 2) [8]. These guidelines recommend that TTM be rapidly initiated to maintain a constant, target core temperature between 32°C and 36°C for all comatose patients after ROSC who are eligible for aggressive care because of the relatively low risk of complications and the potential benefit [8]. The major contraindications to TTM are severe, uncontrolled bleeding or refractory shock [8]. A higher target temperature is advantageous in patients at risk of bleeding, whereas a lower target temperature may be preferred for patients with neurologic

complications [8]. The optimal duration of TTM remains uncertain, but at least 24 hours is recommended followed by 48 to 72 hours of active fever suppression to keep temperature at less than 38°C [8]. A preferred goal temperature of 36°C is reasonable because of the lack of demonstrated benefit of a temperature goal of 33°C for clinical or physiological end points in the TTM trial coupled with more frequent hypokalemia and the need for increased vasopressor doses at lower goal temperatures [52,64]. *Controlled normothermia,* denoting active fever suppression to maintain body temperature at less than 38°C without lowering the body temperature to less than normal, has been proposed as a less labor-intensive alternative to TTM. In our clinical experience, active fever suppression often requires a similar degree of effort and equipment as standard TTM, and simply administering antipyretics is typically inadequate. Care must be taken to ensure tight temperature control when using a higher goal temperature (such as 36°C or controlled normothermia) because brain temperature frequently exceeds measured core temperature and may be above goal [65]. Although TTM at 36°C may be associated with fewer adverse physiologic effects than TTM at 33°C, shivering is typically more severe and difficult to suppress at 36°C; various institutional shivering protocols have been published, which serve as useful clinical guidance [47,66].

### *1.4. Management of postarrest shock*

After ROSC, cardiac arrest patients require intensive care management to prevent complications. Up to two thirds of patients initially resuscitated from either OHCA or IHCA die in the hospital, underscoring the importance of high-quality critical care to ensure optimal patient outcomes [3-5]. Studies have suggested better outcomes when patients are cared for in high-volume, cardiac arrest centers, implying that high-quality critical care at cardiac arrest referral centers is one of the keys to improving outcomes of patients after ROSC [67-69]. Formal guideline recommendations have recently been developed for intensive care unit management of patients resuscitated from cardiac arrest [10].

Cardiovascular dysfunction, secondary infection, and multiorgan failure are major nonneurologic causes of death after cardiac arrest [40-42]. Early deaths after ROSC occur because of hemodynamic instability, recurrent cardiac arrest, and multiorgan failure. Deaths due to multiorgan failure may outnumber deaths due to neurologic injury after IHCA [40-42]. The systemic inflammatory response syndrome that occurs after ROSC can closely mimic sepsis, with resultant cardiovascular dysfunction and multiorgan failure driven in part by elevated inflammatory mediators [37,39,70]. Elevated levels of cytokines (eg, interleukin-6) and endotoxin in the blood predict increased vasopressor requirements and adverse outcomes after OHCA [38,39,71,72]. Infectious complications, including pneumonia and occult bacteremia, are one of the most common complications after OHCA and may occur in more than half of patients [46,73]. Early antibiotic therapy appears beneficial, and we favor empiric antibiotic therapy in the presence of possible sepsis because differentiation of infectious and noninfectious fevers can be challenging [74].

Except for neurologic injury, cardiovascular failure is the most prognostically important component of multiorgan failure after cardiac arrest [75,76]. Arterial hypotension and vasopressor-dependent shock occur in up to 70% of patients after ROSC and are important predictors of mortality and poor neurologic outcomes [24,64,75-79]. Postarrest shock is a dynamic, multifactorial disease progressing from low-output cardiogenic shock to vasodilated distributive shock coupled with microvascular dysfunction and tissue injury [70,80]. Postarrest myocardial dysfunction with transient left ventricular systolic dysfunction develops in up to two thirds of patients after ROSC, driven by the interacting effects of ischemia-reperfusion injury and the systemic inflammatory response syndrome superimposed on precipitating cardiac pathology [70,80]. The average left ventricular ejection fraction early after ROSC is approximately 40% but does not appear to predict vasopressor requirements or outcomes [70,81]. Severe or slowly clearing lactic acidosis after cardiac arrest is a major adverse prognostic finding

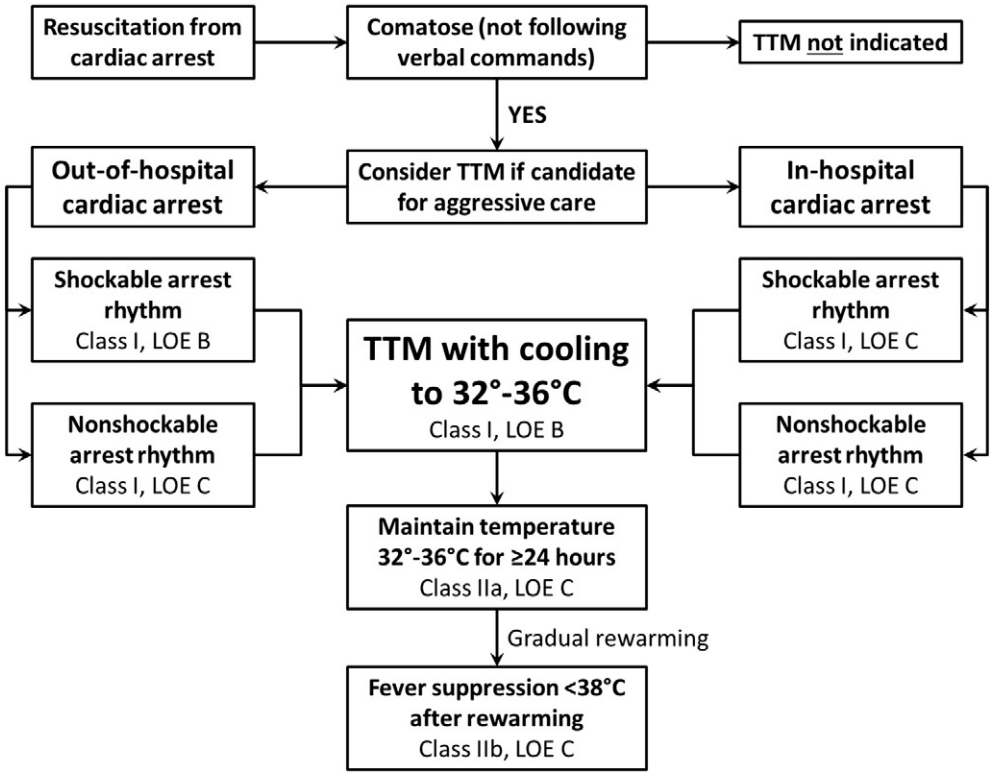


**Fig. 2.** Patient selection for TTM. LOE indicates level of evidence.

that correlates with vasopressor requirements and likely reflects the severity of the ischemic insult [64,82].

Early hemodynamic stabilization may prevent recurrent cardiac arrest, multiorgan failure, and exacerbation of brain injury. Given the similarities between septic shock and the combined cardiogenic and distributive-shock phenotype developing after ROSC, an early quantitative approach to resuscitation after cardiac arrest has been suggested (Fig. 3) [10,36,70,83,84]. Observational studies suggest improved outcomes in survivors of cardiac arrest treated with such early hemodynamic optimization coupled with TTM and coronary angiography as part of a comprehensive care protocol [85-88].

Crystalloid administration is a reasonable, initial empiric therapy for most patients with hypotension or organ hypoperfusion after ROSC [84]. After cardiac arrest, patients typically require at least 1 to 2 L of fluid therapy initially because of relative hypovolemia from vasodilation, venous pooling, and capillary leak despite concerns for cardiac dysfunction and risk of pulmonary edema [80,84]. Some patients will require several liters of fluids during the first 24 hours [80,84]. Additional fluid administration should be guided by measures of fluid responsiveness and intravascular volume status, similar to treatment of sepsis. Appropriate end points for fluid resuscitation remain controversial, but some objective measure of intravascular volume status should be used to avoid excessive fluid administration and the complications associated with volume overload.

Patients who remain hypotensive despite fluid resuscitation warrant vasopressor therapy to augment vascular tone (Fig. 3). Norepinephrine is a reasonable first-line vasopressor based on efficacy in unselected patients with shock and in patients with septic shock [10,84,89,90]. Epinephrine is an effective alternative vasopressor, but its strong $\beta$-adrenergic receptor stimulation may cause adverse effects, including arrhythmias, in these at-risk patients [84]. Dopamine is not recommended because it is inferior to norepinephrine for vasopressor support in critically ill patients (including those with cardiogenic or septic shock) and is associated with significantly higher rates of arrhythmias [89,90]. Despite studies suggesting that relative adrenal insufficiency may contribute to shock and adverse outcomes after ROSC, systemic corticosteroids failed to improve patient outcomes or reverse shock after ROSC in a randomized trial [91,92].

The optimal mean arterial pressure (MAP) goal for post-ROSC patients remains controversial, but failure to maintain adequate MAP of at least 65 mm Hg or systolic blood pressure of at least 90 mm Hg is associated with poor outcomes [64,77,78]. Guidelines recommend maintaining systolic blood pressure at least 90 to 100 mm Hg and MAP at least 65 to 70 mm Hg after ROSC [8,10,36,84]. A higher goal for MAP (>80 mm Hg) may be warranted to maintain cerebral perfusion in the setting of abnormal cerebral blood flow autoregulation in the injured brain, but randomized studies are needed to determine the appropriate MAP goal [85]. When oliguria, lactic acidosis, or low venous oxygen saturation occurs, low-dose dobutamine can help overcome postarrest myocardial dysfunction and improve tissue perfusion if cardiac output remains low despite adequate fluid and vasopressor therapies (Fig. 3) [70,84,93]. Maintenance of adequate urine output indicates satisfactory end-organ perfusion and is a reasonable therapeutic goal, with no other specific hemodynamic targets recommended by guidelines [8,36,84].

TTM produces predictable changes in systemic hemodynamics, including a reduction in heart rate and cardiac output with an increase in systemic vascular resistance, typically with unchanged MAP; these changes are more pronounced at 33°C compared with 36°C [64,93,94]. In the TTM trial, patients randomized to 33°C required administration of more vasopressors despite not having significant differences in myocardial function by echocardiography; patients presenting with moderate degrees of shock had a nonsignificant trend toward worse outcomes at 33°C [64,94,95]. This contrasts with the overall favorable

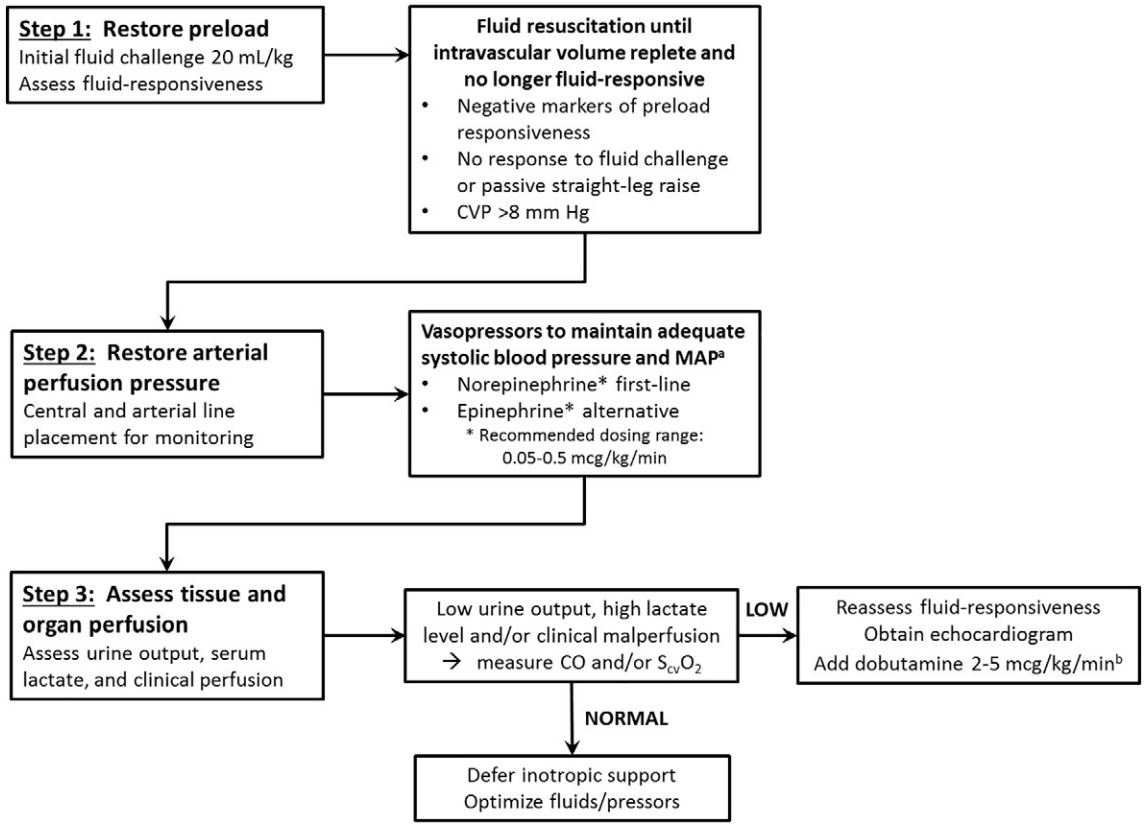


**Fig. 3.** Suggested early hemodynamic optimization strategy for patients with hypotension or hypoperfusion after ROSC after cardiac arrest. CO indicates cardiac output; CVP, central venous pressure; MAP, mean arterial pressure; $Scvo_2$, venous oxygen saturation (normal >70%). [a]We suggest a systolic blood pressure goal of >90-1100 mm Hg and an MAP goal of >65-70 mm Hg. [b]Low-dose epinephrine 0.01-0.05 $\mu$g/(kg min) is an alternative.

hemodynamic effects seen in studies examining TTM to 33°C in patients who had overt cardiogenic shock without cardiac arrest [96,97]. Bradycardia occurring during TTM may be associated with lower mortality and better neurologic outcomes, arguing against treatment of bradycardia in the absence of organ hypoperfusion [98,99]. Regardless of timing, isolated bradycardia after arrest (even with heart rate <40 beats per minute) is not an appropriate target for intervention in post-ROSC patients with adequate markers of systemic perfusion [10].

### 1.5. Respiratory failure and ventilator management after ROSC

Respiratory failure is common in OHCA patients, and the majority of comatose patients are mechanically ventilated [75,76]. Hypoxemic respiratory failure remains independently predictive of poor OHCA outcomes after adjustment for vasopressor requirements and neurologic injury [75,100]. A significant percentage of post-ROSC patients have severe hypoxemic respiratory failure (based on a $Pa_{O_2}$ to fraction of inspired oxygen ratio <100) and may meet criteria for acute respiratory distress syndrome (ARDS) [75]. Common causes of hypoxemic respiratory failure after ROSC include ARDS from aspiration and systemic inflammation, pneumonia, and cardiogenic pulmonary edema. OHCA patients should be considered a population at high risk of both ARDS and pneumonia, and measures should be taken to prevent these complications [74]. As with optimizing hemodynamic parameters after ROSC, the goal of mechanical ventilation after cardiac arrest should be to maintain tissue and organ homeostasis without exacerbating injury to the brain and other organs. Lung-protective ventilation with low tidal volumes (<6 to 8 mL/kg of ideal body weight) and higher levels of positive end-expiratory pressure (≥5 to 8 cm $H_2O$) has become the standard of care for patients with or at risk of ARDS and should be applied to post-ROSC patients as well [10,101]. Higher tidal volume, higher plateau pressure, and lower positive end-expiratory pressure have been associated with increased rates of ARDS and pneumonia after OHCA [102]. Early antibiotic therapy should be considered when pneumonia is suspected because pneumonia is very common in OHCA patients and increases the intensive care unit length of stay and duration of mechanical ventilation [46,74,103].

Metabolic (lactic) acidosis triggers hyperventilation as a physiologic response to reduce $Pa_{CO_2}$ and normalize arterial pH, and brain injury itself can also trigger central hyperventilation. Hyperventilation may be harmful in the setting of anoxic brain injury after cardiac arrest because hypocapnia can trigger cerebral vasoconstriction that can impair brain perfusion [101,104]. Eastwood et al [104] showed that cerebral near-infrared spectroscopy values (a surrogate for cerebral perfusion) increased at a $Pa_{CO_2}$ of 52 mm Hg compared with a $Pa_{CO_2}$ of 37 mm Hg. Multiple studies have associated hypocapnia after ROSC with adverse outcomes after OHCA, with a *U*-shaped relationship between $Pa_{CO_2}$ and neurologic outcomes [105,106]. We suggest allowing permissive hypercapnia for post-ROSC patients up to a $Pa_{CO}$ of 45 to 50 mm Hg (not less than 40 mm Hg). As in patients with ARDS, sodium bicarbonate administration may be considered to maintain an arterial pH greater than 7.25 during permissive hypercapnia, especially for patients in shock. Selective use of sodium bicarbonate to improve vasopressor responsiveness and allow permissive hypercapnia after ROSC must be distinguished from intraarrest use of sodium bicarbonate, which has not shown a clinical benefit [107]. Arterial hyperoxia ($Pa_{O_2}$ >300 mm Hg early after ROSC) has been independently associated with increased in-hospital mortality after OHCA compared with normoxia [105,108]. Excessive free radical generation due to hyperoxia could exacerbate brain injury, and guidelines recommend maintaining $Sp_{O_2}$ in the range of 94% to 96% after ROSC (not 100%) to avoid this effect [10]. A *U*-shaped relationship between $Pa_{O_2}$ and neurological outcomes exists; hypoxemia can impair cerebral oxygen delivery and worsen outcomes and should be avoided [105]. The timing and duration of hyperoxia appear to modify the association with outcomes, and only early and prolonged hyperoxia appears to be harmful.

Deep sedation is typically required to allow lung-protective ventilation and to facilitate induction of TTM and suppress shivering; requirements may be higher at 36°C compared with 33°C [47]. Short-acting sedatives, such as propofol and fentanyl, are recommended to allow periodic neurologic examination, although these agents can exacerbate hypotension; continuous benzodiazepine infusions may promote delayed awakening and should be avoided if possible [10,109]. Neuromuscular blockade is often required to completely suppress shivering and allow stable temperature during TTM (especially at 36°C), and may be associated with improved outcomes after OHCA [10,110].

### 1.6. Neurologic prognosis after cardiac arrest

Anoxic brain injury is the key determinant of outcomes after cardiac arrest (especially OHCA), making accurate assessment of neurologic status after ROSC essential. The prognostic value of brain injury outweighs the effects of all other end-organ dysfunctions combined [75]. Patients resuscitated from cardiac arrest may be deeply comatose initially, only to have functional neurologic recovery. Therefore, neurologic prognosis should generally be delayed until TTM is completed, and extreme caution should be used when undertaking early neurologic prognosis. Apart from overt brain death, few isolated clinical findings within the first 24 to 48 hours after ROSC can reliably predict a minimal chance of neurologically intact survival warranting withdrawal of care [111]. The presence of multiple adverse clinical findings (Box) portends very poor outcomes, as demonstrated by a recent study that found no survivors among 772 patients with an unwitnessed OHCA due to a nonshockable rhythm who failed to achieve ROSC after the third dose of epinephrine [112]. Combinations of early clinical examination, neuroimaging, and electroencephalogram (EEG) findings can predict neurologic outcomes more accurately than single markers; careful validation would be useful to further guide their clinical utility [111,113,114]. Unresponsive OHCA patients who are missing multiple brainstem reflexes on their best neurologic examination within the first 6 hours after ROSC appear to have a poor chance of overall survival (approximately 5%) despite TTM [23,100]. These early indicators of poor prognosis may be most useful for guiding the aggressiveness of care and selecting patients for TTM in cases where there is uncertainty.

Objective neurological testing further refines risk stratification in patients with poor neurological function early after ROSC. The majority of tests used for neurologic prognosis after OHCA have limited sensitivity and negative predictive value for poor neurologic outcome, although some tests have high specificity and positive predictive value that can be useful for identifying patients with poor outcomes. Noncontrast computed tomography of the brain showing cerebral edema (a markedly reduced quantitative gray-white ratio) accurately predicted mortality with high specificity, although studies have used variable gray-white ratio cutoffs to define edema [8,111]. An EEG showing myoclonic status epilepticus at 24 hours after ROSC also predicts poor neurologic outcome, but recent data have shown that the specificity is lower than previously believed [8,111]. Combining the presence of myoclonic status epilepticus with missing brainstem reflexes on examination may increase the specificity and overall accuracy for predicting poor outcome [114]. These adverse prognostic findings can be useful to guide surrogate decision making within 24 hours after ROSC but are not reliable enough to declare futility or lack of hope for meaningful neurologic recovery.

Accurate neurologic prognosis in patients who remain comatose after ROSC requires at least 72 hours, including full rewarming after TTM in the absence of sedative medications [8,9]. Withdrawing life-sustaining therapy early because of anticipated neurologic prognosis before 72 hours may be inappropriate. Most patients who have favorable neurologic prognoses will awaken between 72 and 120 hours, so patients undergoing TTM may require up to 5 days before neurologic prognosis is reliable [115]. Age of more than 59 years, renal insufficiency at presentation, and postarrest shock independently predict late

awakening [116]. In patients who survive to discharge, neurologic function rarely improves beyond 1 month and does not significantly improve after 6 months [117].

No findings in isolation have 100% accuracy for predicting lack of awakening in comatose survivors of cardiac arrest, so multiple adverse prognostic findings should be present before determining that a patient will have minimal (<1%) chance of neurologic recovery warranting withdrawal of life-sustaining therapy [8,9,111,118]. Consultation with a neurologist experienced in the care of OHCA patients is often valuable, particularly when objective data and examination findings are inconclusive (Fig. 4). The TTM process affects the accuracy and timing of specific physical examination findings, which were previously validated in patients not receiving TTM [111,118]. The most accurate clinical examination finding for predicting lack of neurologic recovery is the absence of pupillary response to light at least 72 hours after ROSC, especially when the corneal reflex is also absent [8,111,118]. An absent or extensor motor response at 72 hours has limited accuracy for predicting neurologic outcomes and should trigger consideration of confirmatory neurophysiology or neuroimaging studies (Fig. 4) [8,111,114].

Several studies [111,118] have recently highlighted the utility of EEG for neurologic prognosis after cardiac arrest, although the predictive reliability of EEG findings must be considered in the context of the quality of the study and the patient's overall condition. A reactive EEG pattern during or after TTM portends a relatively favorable prognosis and may be one of the few markers with a reasonable positive predictive value for awakening [118]. An unreactive or markedly abnormal EEG pattern, such as burst suppression or (myoclonic) status epilepticus after rewarming, is associated with poor neurologic outcomes; burst suppression on EEG is common with deep sedation during TTM and does not carry the same adverse prognosis as postrewarming burst suppression (unless myoclonic status epilepticus is present) [118].

Somatosensory evoked potential (SSEP) testing is useful for evaluating patients who remain comatose after 72 hours, especially those with a poor motor response and equivocal EEG findings [111,118]. Bilaterally absent N20 responses on upper-extremity SSEP tests are an accurate diagnostic indicator (near 100% accuracy) for predicting lack of neurologic recovery when SSEP testing is performed between 24 and 72 hours after ROSC [8,107]. Recent studies suggest that the accuracy of high-quality EEG and SSEP testing may be similar for neurologic prognosis after cardiac arrest when applying strict criteria for an abnormal test [118]. Diffuse, anoxic brain injury on neuroimaging can predict poor neurologic outcomes but should be combined with other testing to ensure accuracy [8,111,118].

Neuron-specific enolase (NSE) is a neuronal protein that is detected in the bloodstream after brain injury; serum NSE testing is not available at all institutions and can be affected by hemolysis, limiting its clinical utility. Increased serum NSE concentrations are associated with more severe brain injury after cardiac arrest, especially if NSE values show an increasing pattern [118]. Absolute cutoff values for NSE measurement must be interpreted cautiously given the difficulty balancing the sensitivity and specificity of NSE levels at different time points postarrest [111,118]. Markedly elevated NSE values (ie, >60-80 μg/L) at 48 to 72 hours after ROSC predict a very low chance of neurologic recovery, but NSE levels should not be relied on in isolation [8,111,118]. SSEP

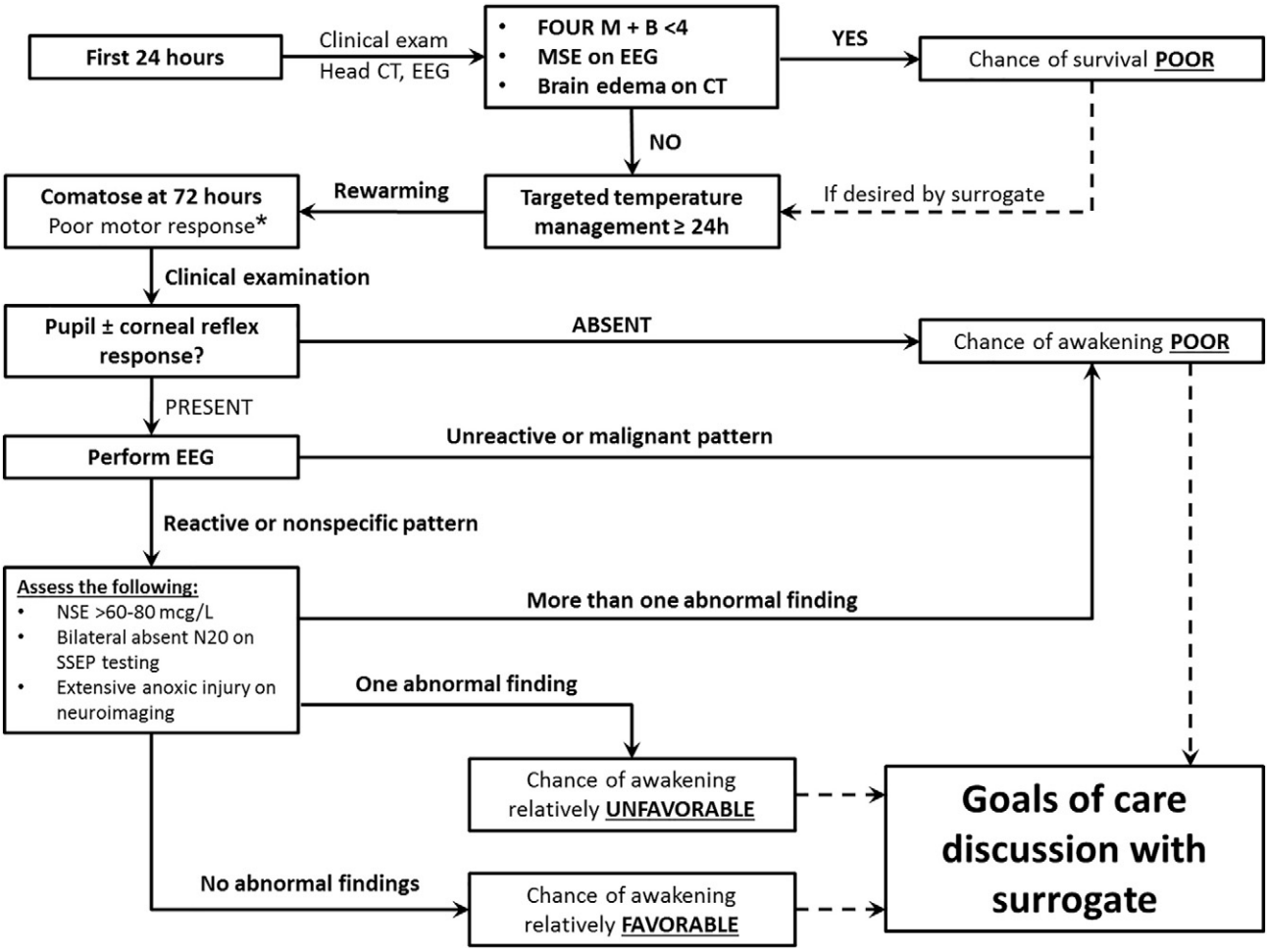


**Fig. 4.** Suggested approach to patients who remain comatose following cardiac arrest. CT indicates computed tomography; FOUR M + B <4, Full Outcome of UnResponsiveness score Motor and Brainstem total subscore less than 4; MSE, myoclonic status epilepticus. *Poor motor response indicates absent or extensor motor response to pain. Patients with a motor response better than this have a relatively favorable chance of awakening.

and NSE tests have been used for neurologic prognosis after only 48 hours, although waiting for 72 hours has been suggested [8,111].

Our suggested algorithm for evaluating neurologic prognosis in comatose survivors of OHCA emphasizes the need for multiple adverse prognostic findings in combination to declare a minimal chance of neurologic recovery warranting discussion of withdrawal of care (Fig. 4) [118]. Comatose patients who lack unequivocal findings suggesting unrecoverable neurologic injury may eventually awaken; more often, a minimally conscious or persistent vegetative state develops, reflecting the poor positive predictive value of the available tests for meaningful recovery. Surrogate decision makers should be informed of the patient's anticipated neurologic prognosis after a full evaluation is performed in conjunction with an experienced neurologist, with subsequent discussions guided by the patient's values regarding quality of life. Studies have reported a high prevalence of neurocognitive impairments in OHCA survivors, even those who were not initially comatose [119,120]. Post–intensive care syndrome is also likely to be prevalent, warranting appropriate rehabilitation and follow-up.

### *1.7. Conclusions*

Patients resuscitated from cardiac arrest remain at high risk of neurologic disability or death. Careful, high-quality, postarrest critical care based on the most recent available evidence improves clinical outcomes. Appropriate use of coronary angiography and PCI, targeted temperature management, and hemodynamic and respiratory stabilization give patients the best chance for recovery. Accurate assessment of neurologic prognosis can be challenging, and patience is required to avoid premature discontinuation of supportive care because of therapeutic nihilism. Processes of care for this challenging group of patients are most important, and synthesizing the interpretation of findings and carefully planning interventions likely have greater impact than each individual component in isolation. In many ways, the individual components of critical care bundles after cardiac arrest may be less important than having a comprehensive approach to care.

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