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Society Position Statement

Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology Position Statement on the Optimal Care of the Postarrest Patient

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ABSTRACT

Out of hospital cardiac arrest (OHCA) is associated with a low rate of survival to hospital discharge and high rates of neurological morbidity among survivors. Programmatic efforts to institute and integrate OHCA best care practices from the bystander response through to the in-hospital phase have been associated with improved patient outcomes. This Canadian Cardiovascular Society position statement was developed to provide comprehensive yet practical recommendations to guide the in-hospital care of OHCA patients. Using the Grading of

RÉSUMÉ

**L'arrêt cardiaque extrahospitalier (ACEH) est à l'origine d'une importante mortalité et morbidité, en particulier neurologique. La mise en place de programmes spécifiques pour améliorer les pratiques actuelles, à la fois au niveau de la réponse immédiate du public mais également de la phase intra-hospitalière ont été associés à une réduction de la morbidité et mortalité des patients. Cet énoncé de position de la Société canadienne de cardiologie a été développé afin de guider les soins hospitaliers de patients post ACEH. En utilisant le système GRADE (*Grading of*

Out of hospital cardiac arrest (OHCA) is a leading cause of morbidity and mortality, with an estimated 55 cases per 100,000 people annually.[1] Clinical outcomes after OHCA are poor, with survival to hospital discharge between 3.9% and 7.1%.[2-5] Recent reports have noted improved survival to discharge with rates > 10%,[6] and OHCA patients who survive to hospital discharge often have good long-term outcomes.[7,8] Therefore, efforts aimed at improving initial survival rates are warranted.[7] Development of regional- and national-level programs for improving prehospital responses,

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*For a full listing of the CCS Post Cardiac Arrest Guidelines Committee primary and secondary panel members, see Supplemental Appendix S1.

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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Recommendations Assessment, Development, and Evaluation (GRADE) system recommendations have been generated. Recommendations on initial care delivery on the basis of presenting rhythm, appropriate use of targeted temperature management, postarrest angiography, and revascularization in the initial phase of care of the OHCA patient are detailed within this statement. In addition, further description of best practices on sedation, use of neuromuscular blockade, oxygenation targets, hemodynamic monitoring, and blood product transfusion triggers in the critical care environment are contained in this document. Last, discussion of optimal care systems for the OHCA patient is provided. These guidelines aim to serve as a practical guide to optimize the in-hospital care of survivors of cardiac arrest and encourage the adoption of "best practice" protocols and treatment pathways. Emphasis is placed on integrating these aspects of in-hospital care as part of a postarrest "care bundle." It is hoped that this position statement can assist all medical professionals who treat survivors of cardiac arrest.

***Recommendations Assessment, Development and Evaluation*), des recommandations détaillées ont été développées sur les soins à apporter selon le rythme initial, l'utilisation appropriée d'hypothermie thérapeutique, la coronarographie et les indications de revascularisation post-arrêt cardiaque. De plus, on retrouve des recommandations sur la sédation, l'utilisation de curares, les cibles d'oxygénation, la surveillance hémodynamique et les cibles de transfusions sanguines aux soins intensifs. Finalement, une discussion sur les systèmes de soins optimaux pour le patient pris en charge pour l'ACEH est inclus. Ces recommandations sont un guide pratique pour optimiser les soins intra-hospitaliers des survivants d'un ACEH et encouragent l'adoption de protocoles de meilleure pratique et un cheminement thérapeutique optimal, en insistant sur l'intégration de tous ces aspects dans la mise en place d'un ensemble de stratégies permettant l'optimisation de la prise en charge. Il est souhaité que cet énoncé de position puisse constituer un outil efficace pour assister les professionnels de la santé qui soignent les survivants d'un arrêt cardiaque.**

implementation of hospital-level best practices, and integration of the chain of survival for postarrest patients have all resulted in improved survival for OHCA patients.[2-4,9]

There exists a need for a comprehensive yet practical guideline that emphasizes an integrated management approach for the postarrest patient. Our objective in writing this document was to provide practical recommendations for the in-hospital care of these patients. We focus on 4 key aspects of care as part of a postarrest "care bundle"[10]: (1) practical use of targeted temperature management (TTM); (2) angiography and revascularization; (3) critical care management (Fig. 1); and (4) regionalization of postarrest care.

Methods

This document was developed in accordance with the Framework for Application of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) in CCS Guideline and Position Statement Development.[11] The Primary Writing Panel was composed of cardiologists and critical care specialists from the Canadian CCU Director's Working Group, Canadian Association of Interventional Cardiology (CAIC), and the **Can**adian **Car**diovascular Critical Car**e** (CANCARE) Society. The methods are provided in Supplemental Appendix S2.

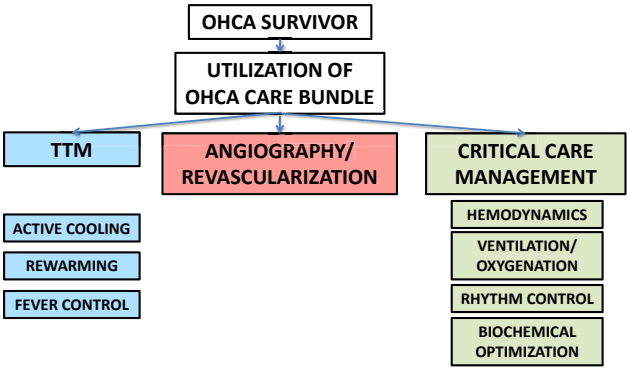

Figure 1. Proposed components of an OHCA care bundle. OHCA, out of hospital cardiac arrest; TTM, targeted temperature management.

Practical Use of Targeted Temperature Management

The intentional reduction of core body temperature, or "therapeutic hypothermia," was first described as a potential treatment for comatose survivors of cardiac arrest in 1958.[12] The concept of therapeutic hypothermia evolved into a more comprehensive control of a patient's temperature profile, a strategy now referred to as "targeted temperature management."[13] Modern guidelines have recommended TTM for selected patients after the return of spontaneous circulation (ROSC) who have remained unresponsive after successful resuscitation.[14-16] We define TTM as a strategy of intentional temperature management of a postarrest patient comprising active patient cooling, subsequent rewarming, and extended fever control. There is no consensus regarding what constitutes the magnitude of neurological dysfunction required to define a "comatose" or "unresponsiveness" state. Definitions used in the primary literature have included "unresponsiveness to verbal commands"[17,18] or a score on the Glasgow Coma Scale of < 8.[19] We define "comatose" or "unresponsiveness" in postarrest patients as an absence of purposeful response to verbal commands.

Which Patient Populations Benefit From TTM?

OHCA patients with an initial shockable rhythm

Two landmark randomized controlled trials were published in 2002 that tested TTM for 12-24 hours in comatose survivors of OHCA.[17,20] In the trial by Bernard et al.[20] and in the Hypothermia After Cardiac Arrest trial[17] it was reported that TTM improved survival with good neurological outcomes vs standard therapy, but the trials were limited by methodological issues.[21] In one randomized trial TTM was compared with standard therapy but it was confounded by hemofiltration use for inducing and maintaining hypothermia.[18] Collectively, these studies suggest a substantial benefit for TTM in survivors of OHCA with an initial shockable rhythm with a low number needed to treat. However, the overall small number of patients and methodological issues in these 3 trials resulted in an overall low quality of evidence.

RECOMMENDATION

1. We recommend that TTM be used in unresponsive OHCA survivors with an initial shockable rhythm after ROSC (Strong Recommendation; Low-Quality Evidence).

   Values and preferences. Despite the overall low quality of evidence we considered the low number needed to treat, ease of administration, and low cost of TTM for this strong recommendation.

OHCA patients with an initial nonshockable rhythm

We found 7 observational studies[22-28]; 3 suggested benefit with TTM,[24,26,27] whereas 4 studies suggested no benefit.[22,23,25,28] The 2 highest-quality studies used propensity matching to mitigate potential selection biases.[22,26] However, these studies had conflicting results.

RECOMMENDATION

2. We suggest TTM be used in unresponsive OHCA survivors with an initial nonshockable rhythm after ROSC (Conditional Recommendation; Very Low-Quality Evidence).

   Values and preferences. Although the evidence base is inconclusive, we valued the potential benefit and apparent lack of harm of TTM in this patient group.

Practical tip. Patients with an initial shockable rhythm have improved rates of survival with a good neurological outcome compared with those with an initial nonshockable rhythm. It is important to carefully consider patient age, comorbidities, and the resuscitation history when determining the subset of patients with nonshockable rhythms who are more likely to benefit from TTM. In the highest-quality study, patients who benefited from TTM in this subgroup had age younger than 75 years, a witnessed arrest, or ROSC < 40 minutes.[26]

Patients with in-hospital cardiac arrest with any initial rhythm

Three observational studies, 2 of which contained in-hospital as well as OHCA patients,[24,26] have reported improved outcomes with TTM in patients who survived an in-hospital cardiac arrest with any initial rhythm. Conflicting results were reported, but no evidence of harm.[24,26,29]

RECOMMENDATION

3. We suggest that TTM be considered in unresponsive survivors of in-hospital cardiac arrest with any rhythm after ROSC (Conditional Recommendation; Very Low-Quality Evidence).

   Values and preferences. Because there is no high-quality evidence to support or disprove the use of TTM in this patient population, the potential benefit and lack of harm influenced our recommendation.

Is there a preferred temperature when using TTM?

This question has been addressed by 2 randomized clinical trials. One trial was limited by a small sample size of 36 patients.[30] The larger TTM trial was a multicentre international trial that compared 2 targeted temperature regimens (33°C vs 36°C) in 939 comatose survivors of OHCA with shockable or nonshockable rhythms.[19] The primary end point was all-cause mortality. This superiority trial was powered to find a 20% reduction in the hazard ratio (HR) for mortality in the 33°C group compared with the 36°C group. The trial did not identify a statistical significance between the 2 interventions with an HR slightly favouring the higher temperature (HR, 1.06; 95% confidence interval, 0.89-1.28). Taking the 20% reduction in the HR as the minimal clinically important difference, a clinically important effect was not found. Because of the lack of statistical significance and clinical importance, it can be concluded that there was no clinical difference between the 2 temperature regimens.[31] We believe that the TTM trial remains the most methodologically sound trial to answer this question, and its results are generalizable across a broad population of OHCA survivors.

RECOMMENDATION

4. We recommend that a temperature between 33°C and 36°C, inclusively, be selected and maintained for patients who undergo TTM (Strong Recommendation; Moderate-Quality Evidence).

   Values and preferences. We acknowledge that the evidence does not conclusively favour a temperature of either 33°C or 36°C, so practitioners may use a temperature range. We favoured 33°C rather than 32°C as the lower bound of our recommended temperature range on the basis of the current primary literature.

Practical tip. The chosen target temperature should ideally be maintained during the active temperature management phase. Excessive bradycardia or hemodynamic instability at 33°C might be improved by raising the target temperature to up to 36°C.

What is the benefit of prehospital use of TTM?

Seven randomized clinical trials studied the effect of initiating TTM in the prehospital setting on favourable neurologic outcome or survival only at discharge.[32-38] Most used chilled intravenous fluids. The largest and most rigourous study showed no benefit of prehospital-initiated cooling with chilled intravenous fluids and showed increased hypoxemia and radiographic pulmonary edema in the first 24 hours.[37]

RECOMMENDATION

5. We do not recommend the use of chilled intravenous fluids for prehospital cooling after ROSC (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Because of the lack of evidence, the risk vs benefit of initiating TTM should be individualized when long transport times are anticipated. There is insufficient evidence to provide a recommendation regarding other methods of prehospital cooling.

What is the optimal method of delivering TTM?

TTM may be applied using ice packs, surface gel pads, or cooling blankets, and intravascular catheters circulating cold fluid.[39,40] Newer-generation TTM systems might also incorporate feedback temperature control mechanisms.[41] Significant differences in mortality or neurological outcomes have not been shown in comparisons of surface and intravascular cooling methods in randomized trials[39,42] or in observational studies.[40,43]

RECOMMENDATION

6. We suggest that either surface cooling or intravascular cooling techniques may be used to induce and maintain TTM (Conditional Recommendation; Low-Quality Evidence).

Practical tip. Surface as well as intravascular cooling devices have their own unique advantages and disadvantages. The choice of method should take into account patient variables, equipment availability, and institutional expertise.

What is the optimal duration of TTM and the effect of post-TTM fever?

Up to 50% of patients might develop fever after rewarming from TTM,[44] but the association between postrewarming fever and outcomes remains unclear.[45-48] It has been postulated that the presence of post-TTM fever might cause further central nervous system damage, or might be just a marker of adverse outcomes.[49,50] However, some data suggest the presence of fever is paradoxically associated with improved neurological outcomes.[46]

No randomized clinical trials have defined the optimal duration for TTM. One retrospective study did not report an advantage of 72 hours of TTM compared with 24 hours.[51] The 2 landmark randomized trials of therapeutic hypothermia applied active TTM for either 12 or 24 hours followed by passive warming.[17,20] The TTM trial maintained active temperature management for 28 hours followed by a period of gradual rewarming at 0.5°C/h. Fever control techniques to keep the body temperature below 37.5°C were then implemented in the 33°C as well as in the 36°C group for 72 hours after the index arrest.[19]

RECOMMENDATION

7. We suggest that the cooling temperature selected for TTM be maintained for at least 24 hours (Conditional Recommendation; Very Low-Quality Evidence).
8. We suggest TTM be continued beyond 24 hours from ROSC to prevent fever (temperature > 37.5°C) (Conditional Recommendation; Very Low-Quality Evidence).

Values and preferences. Despite the controversy as to whether the presence of fever is a cause or consequence of cerebral anoxia, we value the potential benefit and low risk of continuing TTM beyond 24 hours for this recommendation.

Adjunctive Angiography and Revascularization After OHCA

Ischemic heart disease is the most frequent cause of OHCA,[52] with acute coronary occlusion causing pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) in many cases.[53-56] Prompt identification and appropriate management of an acute culprit coronary lesion is therefore important. Although large randomized trials of percutaneous coronary intervention (PCI) in patients with acute coronary syndromes have excluded comatose postcardiac arrest patients,[57] case series have shown an association between routine diagnostic coronary angiography and PCI in OHCA survivors with improved survival.[58-66]

Role of coronary angiography in OHCA patients with ST-segment elevation myocardial infarction

The presence of ST-segment elevation in OHCA survivors is associated with an underlying acute coronary occlusion, and current ST-segment elevation myocardial infarction (STEMI) guidelines support primary PCI (PPCI) for OHCA survivors with acute ST-segment elevation on electrocardiogram (ECG).[67] Although comatose OHCA survivors with STEMI have increased long-term mortality relative to other STEMI patients,[68] they do benefit from successful PPCI.[69-71] OHCA survivors with post-ROSC ST-elevation and unsuccessful PPCI have poor long-term survival.[72] No randomized trials have compared PPCI with fibrinolysis for comatose survivors of OHCA with STEMI. Retrospective data suggest fibrinolysis and PPCI are associated with improved rates of hospital discharge and neurological recovery among survivors of OHCA,[73] with a suggestion that PPCI might be superior to fibrinolysis.[74] Importantly, adjunctive fibrinolysis administered as an acute resuscitative intervention for OHCA patients has no clinical benefit and is associated with increased rates of intracranial hemorrhage.[75]

Role of coronary angiography in OHCA survivors without STEMI

Some have proposed that all OHCA survivors without an obvious noncardiac cause of arrest be considered for diagnostic coronary angiography.[76] However, clinical outcomes after routine angiography in patients without STEMI on presentation are mixed, with some studies showing improved survival with routine angiography[23,58,60-66,77] and others showing no benefit.[78,79] In addition, OHCA patients who undergo coronary angiography in observational studies tend to represent a lower-risk population with fewer comorbidities compared with those managed noninvasively.[80] Unselected OHCA populations were also reported to have a lower

prevalence of acute coronary lesions and a reduced survival benefit from revascularization compared with selected post-arrest populations.[81] A strategy of routine angiography for all OHCA survivors has less benefit compared with restricting angiography for selected OHCA patients post-ROSC.[82]

RECOMMENDATION

9. We recommend that in OHCA patients with STEMI, immediate angiography and PPCI be considered when timely access to cardiac catheterization is feasible (Strong Recommendation; Moderate-Quality Evidence).
10. We recommend fibrinolytic therapy in OHCA patients with STEMI if timely PPCI cannot be performed and there are no absolute contraindications to its use[67] (Strong Recommendation; Low-Quality Evidence).

Practical tip. This recommendation recognizes that many OHCA patients with STEMI might not have immediate access to PPCI because of geographic diversity and the proposed hub-and-spoke model of postarrest care. Therefore, reperfusion decisions should be made according to existing local/regional STEMI protocols.

RECOMMENDATION

11. We recommend against the use of fibrinolytic agents as an acute or adjunctive intervention as part of ongoing resuscitative efforts (Strong Recommendation; Moderate-Quality Evidence).
12. We suggest angiography with or without PCI be performed as soon as clinically feasible in patients without ST-elevation after OHCA if there is a high level of suspicion for an underlying ischemic etiology due to an acute coronary lesion, and no major comorbidities or contraindications to invasive angiography (Conditional Recommendation; Moderate-Quality Evidence).

Practical tip. The need for urgent diagnostic coronary angiography and PCI in OHCA survivors without STEMI should incorporate the likelihood of benefit from acute coronary revascularization and the perceived risk of the procedure. Uncertain neurologic status should not be regarded as a contraindication to early invasive assessment after OHCA. No randomized trial has defined the optimal timing for angiography among OHCA survivors without STEMI, but we believe it is reasonable to proceed with angiography for OHCA survivors without STEMI who have a suspected cardiac etiology as soon as it is feasible.

Predicting an acute coronary lesion in OHCA survivors

It is often difficult to predict which patients would benefit from prompt revascularization.[53] However, retrospective data suggest an acute culprit coronary occlusion might be found in up to 50%-70% of postarrest patients,[53-56] supporting risk stratification to select patients who would benefit from adjunctive angiography.

Relatively simple risk stratification techniques using clinical variables have been proposed to identify patients who might benefit from urgent angiography.[83] Clinical variables that have been associated with the presence of underlying culprit coronary artery disease (CAD) in OHCA survivors include diabetes mellitus, a history of preexisting CAD, and ST depression on the post-ROSC ECG.[84] The initial post-ROSC ECG might also help to identify the likelihood of culprit CAD; the presence of ST-segment elevation or dynamic ST-segment depression has a high positive predictive value for culprit CAD in OHCA survivors.[60,85,86] However, the absence of ST-segment deviation, a nonspecific wide QRS complex, or left bundle branch block pattern have limited sensitivities and negative predictive values in selected cohorts of OHCA patients who undergo emergent angiography.[87-89]

Cardiac biomarkers post-ROSC have not been helpful in decision-making for urgent angiography; troponins have a relatively poor sensitivity and specificity for predicting acute occlusive events in the OHCA population.[90] However, higher peak troponin levels (particularly in association with ST-elevation) appear to correlate with the presence of culprit CAD in OHCA patients.[91]

RECOMMENDATION

13. We recommend that the clinical likelihood of an acute ischemic etiology from an acute coronary lesion be taken into account to help guide the use and timing of angiography in the OHCA patient (Strong Recommendation; Low-Quality Evidence).
14. We recommend that troponin measurements should not be used to predict the presence of an acute coronary lesion, nor to guide decisions regarding urgent coronary angiography in the immediate postarrest period (Strong Recommendation; Low-Quality Evidence).

Practical tip. A history of angina, congestive heart failure, diabetes, or CAD, and the presence of ST-elevation or depression, a wide QRS, or new left bundle branch block are variables that have been proposed to help identify OHCA survivors in whom angiography might be of benefit.[83]

Combined TTM and coronary angiography in OHCA survivors

Observational studies have shown that the concomitant use of TTM with PPCI for STEMI is technically feasible and not associated with a significant delay to reperfusion, nor with worsened neurological outcomes related to antiplatelet and antithrombotic-mediated intracranial bleeding.[92-94] Additionally, nonrandomized trials have reported improved survival and neurologic outcomes when PPCI is performed concurrently with TTM among postarrest patients.[95] Although there are isolated case reports of stent thrombosis with the combination

of TTM and PPCI, this strategy has been reported to be safe in larger series with few thrombotic events.[96]

RECOMMENDATION

15. We suggest that TTM be initiated along with angiography in comatose patients if both are required concurrently (Conditional Recommendation; Low-Quality Evidence).

Practical tip. TTM initiation should be considered as soon as clinically feasible in all postarrest patients who require revascularization. However, the use of TTM should never delay the process of revascularization. Individual care providers should choose a system and algorithm that would be best suited to their institutional needs when initiating concomitant angiography and TTM for postarrest patients.

Critical Care Aspects of Management of the Postarrest Patient

The postcardiac-arrest syndrome, characterized by ischemia-reperfusion-mediated cerebral injury, myocardial dysfunction, multiorgan failure, and systemic inflammatory response, is associated with significant morbidity and mortality.[97,98] Clinical outcomes and organ dysfunction in the OHCA patient might be further exacerbated by impaired cerebral autoregulation, microcirculatory failure, hypotension, carbon dioxide and oxygen disturbances, and pyrexia.[99]

Treatments that minimize the factors associated with ischemia-reperfusion injury and postcardiac-arrest syndrome might improve survival and neurologic recovery.[100,101]

Measuring body temperature

Randomized data on comparisons of different methods of measuring body temperature in OHCA survivors are not available. A small observational study showed temperature assessments with nasopharyngeal and bladder probes were similar to temperatures obtained from a pulmonary artery catheter.[102] However, the intraoperative anaesthesia data suggest that esophageal temperature monitoring is the most reliable method compared with a pulmonary artery catheter gold standard.[103] Nonrandomized data from the cardiac surgery literature suggest that true brain temperature is better reflected by tympanic and bladder temperature monitoring as opposed to temperature assessments using a pulmonary artery catheter.[104] Therefore, a recommendation cannot be made regarding the optimal method of measuring body and brain temperature in the setting of TTM for the survivors of OHCA.

RECOMMENDATION

16. We suggest continuous temperature monitoring during hypothermia induction, maintenance, and rewarming phases. However, there is insufficient evidence to recommend a preferred measurement location or technique (Conditional Recommendation; Very Low-Quality Evidence).

Sedation and analgesics

Sedation and analgesics are routinely used in patients who undergo TTM.[105] Intravenous medications are administered with the goal of reducing pain, anxiety, and shivering as well as improving patient comfort. A validated sedation monitoring scale such as the Richmond Agitation-Sedation Scale (RASS) allows for goal-directed medication titration in all intubated post-OHCA patients with the goal of reducing the duration of mechanical ventilation (MV) and associated complications.[106,107] There are no high-quality data on sedation and analgesic choices for patients who undergo TTM and specific agents cannot be recommended. A systematic review of sedation protocols published in TTM trials noted variability in medication preference but identified midazolam and fentanyl as the most commonly used.[105] Shorter-acting medications might allow for a shorter duration of MV and less confounding of the neurologic examination in the OHCA patient after TTM.[108] Propofol and fentanyl were recently reported to be effective in TTM patients[109] and a small randomized trial reported that the use of propofol and remifentanil allowed for earlier extubation decisions to be made compared with longer-acting midazolam and fentanyl.[110]

RECOMMENDATION

17. We suggest that OHCA patients managed with TTM receive analgesic and sedation medications titrated according to a validated sedation scoring tool with the goal of optimizing patient comfort, minimizing anxiety or agitation, and reducing MV duration (Conditional Recommendation; Very Low-Quality Evidence).

Use of neuromuscular blocking agents

Neuromuscular blocking agents can be used to treat shivering in patients who undergo TTM.[105,111] However, use of these agents might be associated with intensive care unit-acquired weakness, altered neurologic examinations, and masking of seizures or myoclonus. Furthermore, it has been postulated that shivering patients might have less anoxic brain injury and more intact central neurologic pathways and that shivering might be an independent predictor of favourable neurological outcomes.[112] There are no randomized data available regarding the use of neuromuscular blocking agents in OHCA patients and observational studies have shown conflicting results regarding the safety and efficacy of these agents in this population.[113,114]

Shivering can be treated without neuromuscular blocking agents using a structured approach. An observational study described a stepwise strategy that included skin counter-warming, acetaminophen, or intravenous magnesium followed by the addition of dexmedetomidine, opioids, or propofol. This protocol enabled the management of most OHCA survivors who underwent TTM without requiring paralytic agents.[111]

RECOMMENDATION

18. We suggest using a stepwise approach for the prevention and treatment of shivering in patients who undergo TTM starting with skin counterwarming, acetaminophen, or intravenous magnesium. For persistent shivering, opioids, propofol, or dexmedetomidine should be attempted before initiating neuromuscular blocking agents (Conditional Recommendation; Very Low-Quality Evidence).

Values and preferences. Our recommendation places higher value on the potential risks of using neuromuscular blocking agents over the potential benefits of treating or preventing shivering in patients who undergo TTM.

Optimal oxygenation targets

Oxygen therapy might play a critical role in restoring normal oxygen tension and oxygen delivery in OHCA patients. However, hyperoxia (a partial pressure of oxygen [PaO_2] $\geq$ 200 mm Hg) might exacerbate the formation of oxygen free radicals, a putative mechanism for post-ROSC neuronal injury.[115,116] Hyperoxia reduces cerebral blood flow and energy metabolism, increases cerebrovascular resistance, as well as increases hippocampal degeneration, cerebellar inflammation, and lipid oxidation.[117-121] Although there are no randomized trials with clinical end points of oxygen in the OHCA population, several meta-analyses of observational studies reported that hyperoxia is associated with increased mortality.[122-126] A large multicentre study reported each 100-mm Hg increase in PaO_2 was associated with a 24% increase in mortality.[126] Similar associations have been reported for hypoxia (PaO_2 < 60 mm Hg).[124,127] These studies are limited by the use of a single arterial blood gas reading within the first 24 hours to ascertain arterial oxygen tension.

RECOMMENDATION

19. We suggest oxygen therapy be titrated to a PaO_2 between 60 and 200 mm Hg in OHCA patients (Conditional Recommendation; Low-Quality Evidence).

Values and preferences. Target oxygenation recommendations are derived from human observational analyses that reported increased mortality with hypoxia as well as hyperoxia. Together with the adverse hyperoxia outcomes reported for myocardial infarction, heart failure, and other critical illnesses, we believe that it is reasonable to avoid hypoxia as well as hyperoxia in patients with an OHCA.[122,128,129]

Ventilation targets

The partial pressure of carbon dioxide ($PaCO_2$) is commonly deranged in mechanically ventilated comatose OHCA survivors.[130,131] Hyperventilation-induced hypocapnia (often defined as $PaCO_2$ < 35 mm Hg) reduces cerebral blood flow and increases cerebral ischemia.[132-134] Hypocapnia has been consistently associated with in-hospital mortality in the adult OHCA population.[124,131,135-137] In contrast, hypoventilation-induced hypercapnia (often defined as $PaCO_2$ > 45 mm Hg) is associated with increased cerebral flow and cerebral oxygenation as well as increased intracranial blood volume and intracranial pressure.[133,134] However, retrospective cohort studies in adult OHCA populations have reported conflicting associations between mild hypercapnia and in-hospital mortality.[124,131,137,138]

RECOMMENDATION

20. We suggest that, in patients who undergo MV after OHCA, ventilation should target normocapnia ($PaCO_2$ 35-45 mm Hg) (Conditional Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation is on the basis of the known adverse outcomes associated with ventilator-associated hypocapnia. Although the association of mild hypercapnia with clinical outcomes is not clear, we believe it is reasonable to target normocapnia.

Serum lactate measurements

Serum lactate levels are frequently measured in critically ill patients and initially elevated levels correlate with severity of shock and risk of mortality from multiorgan failure in these populations.[139,140] Initial post-OHCA lactate concentrations correlate with global tissue hypoxia during circulatory arrest and the presence of persistent post-ROSC shock. Early serum lactate levels > 12 mmol/L in OHCA survivors are independently associated with poor neurological outcomes.[141] Furthermore, OHCA survivors with better neurological outcomes have faster observed initial 24-hour lactate clearance rates compared with nonsurvivors or those with poor neurological outcomes.[141] Although there are no universally accepted definitions of lactate clearance, observational studies have reported better outcomes among OHCA patients with lactate levels < 2.5 mmol/L at 6 hours and $\geq$ 50% clearance over the first 12 hours after ROSC.[142-144]

RECOMMENDATION

21. We suggest that serial serum lactate levels be followed every 4-6 hours in the post-OHCA period for at least 24 hours (Conditional Recommendation; Low-Quality Evidence).

Practical tip. Although observational data have linked initially elevated lactate levels and decreased lactate clearance with poor outcomes, it remains unclear whether specific therapy targeted toward decreasing serum lactate levels improves OHCA patient outcomes. Failure to achieve lactate clearance targets should prompt careful reassessment to identify and treat ongoing shock.

Mean arterial pressure targets

Hypotension, defined as a systolic blood pressure < 90-100 mm Hg or a mean arterial pressure (MAP) < 65 mm Hg, has been associated with increased mortality among OHCA survivors in the first 6 hours post-ROSC.[145-149] However, higher doses of vasopressors to maintain MAP goals during post-ROSC care are also associated with higher mortality.[145,146,150] MAP values associated with good neurological outcomes in observational studies of post-OHCA patients range from 76 mm Hg to 115 mm Hg.[147,148,151,152] Two small studies that targeted early goal-directed post-OHCA MAPs > 65 mm Hg and 80-100 mm Hg, respectively, reported a trend toward improved outcomes compared with historical controls.[100,153]

RECOMMENDATION

22. We suggest a MAP target of at least 65 mm Hg be maintained in OHCA patients, using intravenous fluids, vasopressors, and/or inotropes as necessary (Conditional Recommendation; Low-Quality Evidence).

    Values and preferences. Our recommendations are on the basis of observational studies that have reported higher mortality rates associated with hypotension.

Central venous pressure monitoring and goals

The invasive assessment of intravascular blood volume is commonly practiced in the management of critically ill patients because excessive fluid administration has been associated with increased edema, acute kidney injury, and potentially increased mortality.[97,100]

There are no randomized clinical trials to guide clinicians regarding an optimal central venous pressure (CVP) in the OHCA population. Nevertheless, low CVP trends in patients with hypotension, poor urine output, or elevated serum lactate levels might help identify relative hypovolemia. Comparatively, a persistently elevated CVP might help identify pathologies such as cardiac tamponade, tension pneumothorax, or acute right ventricular infarction/failure.[97]

RECOMMENDATION

23. We suggest that all hemodynamically unstable OHCA patients have CVP monitoring, without a specific minimum value recommendation, to help guide management efforts (Conditional Recommendation; Very Low-Quality Evidence).

Practical tip. A CVP range of 8-12 mm Hg is the most commonly cited target in the intensive care unit literature. However, the optimal CVP goal remains unclear for OHCA patients. Furthermore, CVP hemodynamic trends are likely of greater clinical importance than a single absolute value.

Optimal hemoglobin transfusion trigger

A large randomized clinical trial on transfusion thresholds in critically ill patients showed comparable outcomes among patients randomized to a lower hemoglobin transfusion trigger of 70 g/L vs 100 g/L.[154] Guidelines for patients after an acute coronary syndrome have suggested that transfusion of red blood cells be considered at a hemoglobin concentration of ≤ 80 g/L in patients with unstable cardiac symptoms.[155] The optimal hemoglobin level in post-OHCA patients has not been well studied, although observational cohort studies in OHCA patients have reported good neurologic outcomes with hemoglobin concentrations ranging from 86 g/L to 123 g/L.[156,157]

RECOMMENDATION

24. We suggest transfusion of red blood cells for a hemoglobin concentration of 80 g/L in patients after OHCA (Conditional Recommendation; Very Low-Quality Evidence).

    Values and preferences. This recommendation recognizes the inability to assess active cardiac symptoms in patients who undergo TTM and the high prevalence of coronary disease and acute coronary syndrome associated with OHCA in whom a hemoglobin concentration ≥ 80 g/L is recommended.

Prophylactic antiarrhythmic drugs

The use of antiarrhythmic drugs during the initial resuscitation for OHCA patients has been evaluated in a limited number of trials.[158-160] The largest of these randomized trials enrolled 3026 patients in the setting of OHCA with resistant VF or pulseless VT, and reported that neither amiodarone nor lidocaine administered at the time of initial resuscitation improved survival or favourable neurologic outcome at hospital discharge vs placebo. Both agents were superior compared with placebo in the subgroup of patients who had a witnessed OHCA.[159]

The clinical benefit of either continuing antiarrhythmic drugs used for the original arrest procedure or prophylactically starting them among OHCA patients who survive to hospital admission remains unclear. In one observational study that evaluated lidocaine vs no lidocaine in 1721 patients resuscitated from OHCA a significant reduction in the recurrence of VF/VT, but with no accompanying difference in survival was reported.[161]

RECOMMENDATION

25. We suggest prophylactic antiarrhythmic medications early in the hospital course in patients with recurrent episodes of VF/VT, nonsustained episodes of VT, or a high burden of ventricular ectopy (Conditional Recommendation; Very Low-Quality Evidence).

    Values and preferences. This recommendation is on the basis of expert opinion and places a high weight on the potential for hypoxia and hypotension from recurrent cardiac arrests.

Regional Systems of Care for OHCA

Many critical conditions such as STEMI and trauma have realized significant improvements in care quality and patient outcomes after the implementation of regional systems of care.[162] International societies have advocated for similar regionalized systems of care for the OHCA population to make the coordination, implementation, and assessment of best care practices for OHCA patients possible, from the prehospital setting through to hospital discharge.[163]

Significant improvements in survival among > 41,000 OHCA patients have been observed by the Resuscitation Outcomes Consortium between 2006 and 2010.[6] Multiple international quality improvement initiatives have also reported improved OHCA survival by implementing and optimizing best care practices such as bystander and professional cardiopulmonary resuscitation (CPR), dispatch assisted CPR, automated external defibrillator application, and TTM within care systems.[6,163,164] Public health efforts to integrate and improve adherence to evidence-based OHCA care have been associated with increased use of bystander CPR and use of automated external defibrillators leading to increased survival.[3,165] Similar improvements in mortality were observed where postarrest patients were preferentially transported to designated cardiac arrest centres capable of performing PCI and TTM.[166]

We encourage regions to leverage the infrastructure of existing high-acuity systems of care (including STEMI, trauma, and/or stroke) and that regional health care administrators work with emergency medical service and hospital multidisciplinary medical leadership committees to tailor the following OHCA care system recommendations to their local health care environment.

RECOMMENDATION

26. We recommend adoption of "best practice" protocols and treatment pathways for OHCA patients from the prehospital setting through to hospital discharge (Strong Recommendation; Low-Quality Evidence).

Consideration for the OHCA care environment

Higher annual case volumes, defined at the hospital or physician level, have been consistently associated with improved patient outcomes in STEMI, PPCI, MV, and critical care.[167-170] Observational studies have reported increased survival to hospital discharge for OHCA patients treated at large tertiary hospitals with high volumes of cardiac arrest patients.[135,171-177] Additionally, studies have reported improved survival when patients were transported to centres with PCI capabilities and designated critical care units.[178,179]

We believe that optimal care of OHCA survivors might be improved by improving timely access to similarly specialized centres capable of caring for OHCA patients from the prehospital setting through to hospital discharge. Ideally such centres would have timely access to expertise important for the care of an OHCA survivor (intensive care cardiology, cardiac surgery, electrophysiology, neurology, and intensive care medicine) and to technologies such as 24/7 PCI, neurological imaging, and TTM among others.

RECOMMENDATION

27. We recommend that clinicians who care for OHCA survivors ensure timely access to appropriate specialized post-ROSC care as needed, such as cardiology, PCI, cardiac surgery, electrophysiology, neurology, and intensive care consultation (Strong Recommendation; Low-Quality Evidence).

Overall Perspective

These guidelines were developed to address a variety of complex topical issues to help guide inpatient care of OHCA survivors. In particular, we proposed that the application of an OHCA care bundle encompassing several aspects of in-hospital care be used for the care of the postarrest patient.

We strongly recommended the use of TTM as opposed to no TTM in the postarrest population with an initial shockable rhythm. Our TTM recommendations diverge significantly from recently published guidelines[15] because of important differences in the interpretation of the TTM trial.[19] Specifically, we recommended a target temperature range from 33°C to 36°C in line with recommendations from the International Liaison Committee on Resuscitation and the European Resuscitation Council[14,99] rather than 32°C-34°C.[15]

We emphasized the role of reperfusion therapy in OHCA patients with STEMI as well as the importance of coordinating TTM with coronary angiography, and made recommendations on the use of diagnostic angiography when the post-ROSC ECG is not diagnostic for STEMI. We made recommendations regarding optimizing important hemodynamic, ventilatory, and biochemical parameters in the OHCA population. Finally, we made strong recommendations to develop and implement best care practices and pathways and ensure timely access to appropriate specialized care.

Space considerations have not allowed us to address the extremely complex and difficult issues of neuroprognostication and end of life decision-making for OHCA survivors for whom it is believed that a state of clinical futility has been reached. We recognize that this remains an evolving and highly controversial topic that merits further study and clinical perspective.

Future Directions and Challenges

This document provides recommendations on the basis of available evidence about comprehensive care of the postarrest patient as part of a postarrest care bundle (Fig. 2). However, there are many knowledge gaps in our understanding of how

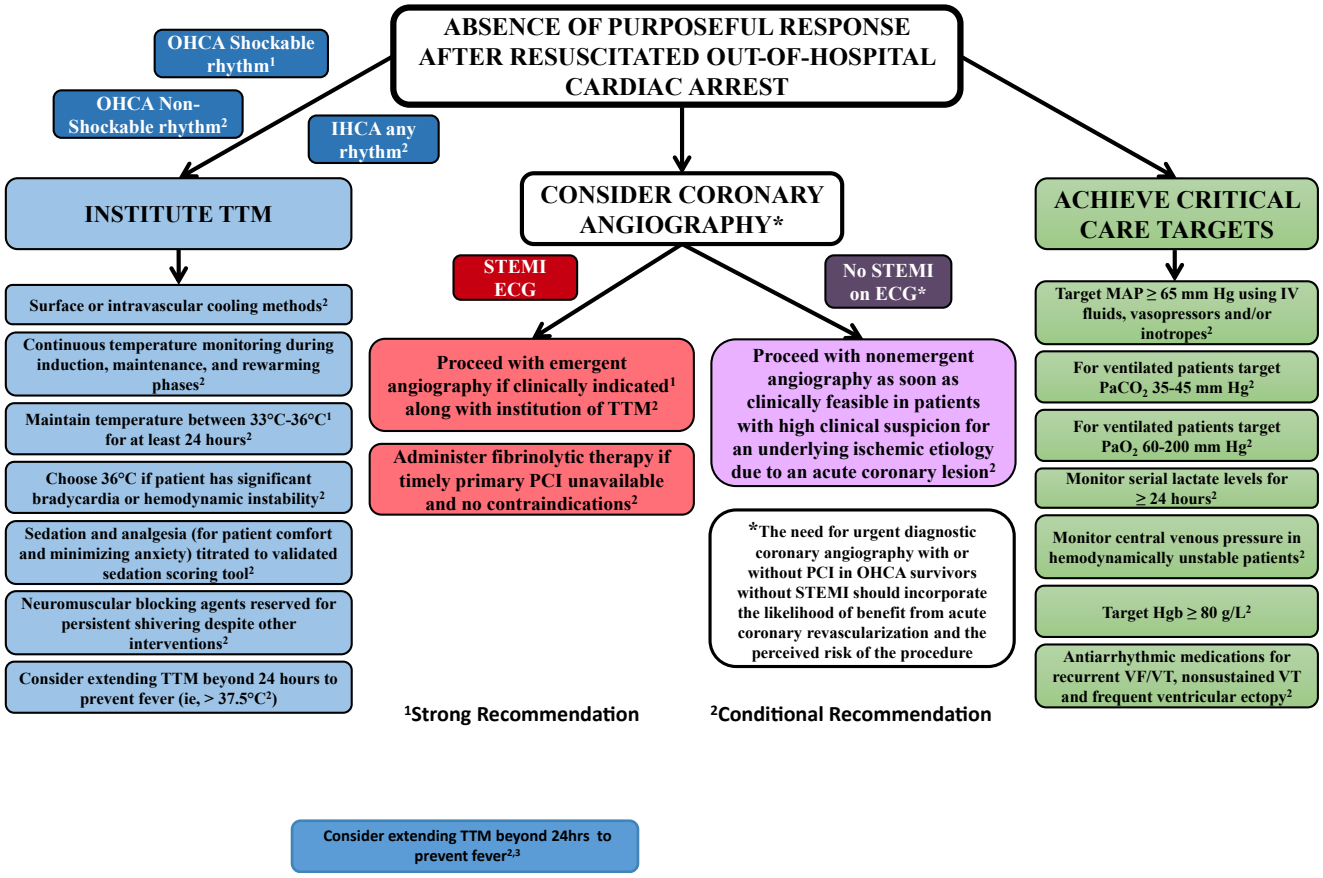

Figure 2. Summary of recommendations for optimal in-hospital care of the postarrest patient. ECG, electrocardiogram; Hgb, hemoglobin; IHCA, in hospital cardiac arrest; MAP, mean arterial pressure; OHCA, out of hospital cardiac arrest; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TTM, targeted temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

to best care for these complex patients. Research in care and management of OHCA survivors continues to evolve and future studies (Table 1) might clarify or change our present recommendations on the basis of the uncertainties of currently available nonrandomized trials.

Conclusions

Survivors of OHCA are a diverse population with a high risk of mortality and neurological morbidity. An integrated post-ROSC care system and the timely adoption of contemporary in-hospital best care practices have the potential to

Table 1. Selected ongoing clinical trials on in-hospital management of OHCA survivors

Trial	Trial ID number*	Population	Comparator/control	Primary end point
TTM				
CAPITAL CHILL	NCT02011568	Comatose OHCA survivors older than 18 hours of age	Moderate (31°C) vs mild (34°C) TTM using an endovascular cooling device	Death and poor neurological outcome at 6 months
Angiography				
PEARL	NCT02387398	OHCA survivors older than 18 years of age with a suspected cardiac etiology but without STEMI on post-ROSC ECG	Early (<120 minutes) angiography vs no early angiography after admission to the emergency room	Efficacy and safety at 6 months (efficacy: LV function and neurological status; safety: rearrest, bleeding, pulmonary edema, hypotension, renal insufficiency, and pneumonia)

CAPITAL CHILL, Mild Versus Moderate Therapeutic Hypothermia in Out-of-hospital Cardiac Arrest Patients; ECG, electrocardiogram; LV, left ventricular; OHCA, out of hospital cardiac arrest; PEARL, A Pilot Randomized Clinical Trial of Early Coronary Angiography Versus No Early Coronary Angiography for Post-Cardiac Arrest Patients Without ECG ST-Segment Elevation; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction; TTM, targeted temperature management.

*ID numbers taken from www.ClinicalTrials.gov.

improve survival in this vulnerable population. We believe that our recommendations can serve as a practical template to model the in-hospital care of cardiac arrest patients.

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References

1. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010;81:1479-87.
2. Chan PS, McNally B, Tang F, Kellermann A. CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 2014;130:1876-82.
3. Malta Hansen C, Kragholm K, Pearson DA, et al. Association of bystander and first-responder intervention with survival after out-of-hospital cardiac arrest in North Carolina, 2010-2013. JAMA 2015;314:255-64.
4. Nakahara S, Tomio J, Ichikawa M, et al. Association of bystander interventions with neurologically intact survival among patients with bystander-witnessed out-of-hospital cardiac arrest in Japan. JAMA 2015;314:247-54.
5. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:63-81.
6. Daya MR, Schmicker RH, Zive DM, et al. Out-of-hospital cardiac arrest survival improving over time: results from the Resuscitation Outcomes Consortium (ROC). Resuscitation 2015;91:108-15.
7. Fordyce CB, Wang TY, Chen AY, et al. Long-term post-discharge risks in older survivors of myocardial infarction with and without out-of-hospital cardiac arrest. J Am Coll Cardiol 2016;67:1981-90.
8. Kragholm K, Wissenberg M, Mortensen RN, et al. Return to work in out-of-hospital cardiac arrest survivors: a nationwide register-based follow-up study. Circulation 2015;131:1682-90.
9. van Diepen S, Abella BS, Bobrow BJ, et al. Multistate implementation of guideline-based cardiac resuscitation systems of care: description of the HeartRescue project. Am Heart J 2013;166:647-653.e2.
10. Nolan JP, Soar J. Post resuscitation care—time for a care bundle? Resuscitation 2008;76:161-2.
11. Canadian Cardiovascular Society. Framework for application of GRADE in CCS Guideline and Position statement development. Available at: http://www.ccs.ca/images/Guidelines/Dev_proces/CCS_GRADE_Framework_June2015.pdf. Accessed September 16, 2015.
12. Williams GR Jr, Spencer FC. The clinical use of hypothermia following cardiac arrest. Ann Surg 1958;148:462-8.
13. Nunnally ME, Jaeschke R, Bellingan GJ, et al. Targeted temperature management in critical care: a report and recommendations from five professional societies. Crit Care Med 2011;39:1113-25.
14. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:2448-56.
15. Howes D, Gray SH, Brooks SC, et al. Canadian guidelines for the use of targeted temperature management (therapeutic hypothermia) after cardiac arrest: a joint statement from the Canadian Critical Care Society (CCCS), Canadian Neurocritical Care Society (CNCCS), and the Canadian Critical Care Trials Group (CCCTG). Resuscitation 2016;98:48-63.
16. Monsieurs KG, Nolan JP, Bossaert LL, et al. European Resuscitation Council guidelines for resuscitation 2015: section 1. Executive summary. Resuscitation 2015;95:1-80.
17. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest [erratum in 2002;346:1756]. N Engl J Med 2002;346:549-56.
18. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005;46:432-7.
19. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 2013;369:2197-206.
20. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
21. Nielsen N, Wetterslev J, al-Subaie N, et al. Target temperature management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. Am Heart J 2012;163:541-8.
22. Doshi P, Patel K, Banuelos R, et al. Effect of therapeutic hypothermia on survival to hospital discharge in out-of-hospital cardiac arrest secondary to nonshockable rhythms. Acad Emerg Med 2016;23:14-20.
23. Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: Insights from a large registry. Circulation 2011;123:877-86.
24. Lundbye JB, Rai M, Ramu B, et al. Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. Resuscitation 2012;83:202-7.
25. Mader TJ, Nathanson BH, Soares WE 3rd, Coute RA, McNally BF. Comparative effectiveness of therapeutic hypothermia after out-of-hospital cardiac arrest: insight from a large data registry. Ther Hypothermia Temp Manag 2014;4:21-31.
26. Perman SM, Grossestreuer AV, Wiebe DJ, et al. The utility of therapeutic hypothermia for post-cardiac arrest syndrome patients with an initial nonshockable rhythm. Circulation 2015;132:2146-51.
27. Testori C, Sterz F, Behringer W, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. Resuscitation 2011;82:1162-7.
28. Vaahersalo J, Hiltunen P, Tiainen M, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med 2013;39:826-37.
29. Nichol G, Huszti E, Kim F, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013;84:620-5.
30. Lopez-de-Sa E, Rey JR, Armada E, et al. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. Circulation 2012;126:2826-33.

31. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study results. J Gen Intern Med 2002;17:469-76.

32. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation 2010;122:737-42.

33. Bernard SA, Smith K, Cameron P, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. Crit Care Med 2012;40:747-53.

34. Castren M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010;122:729-36.

35. Debaty G, Maignan M, Savary D, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. Intensive Care Med 2014;40:1832-42.

36. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta Anaesthesiol Scand 2009;53:900-7.

37. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA 2014;311:45-52.

38. Kim F, Olsufka M, Longstreth WT Jr, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation 2007;115:3064-70.

39. Deye N, Cariou A, Girardie P, et al. Endovascular versus external targeted temperature management for patients with out-of-hospital cardiac arrest: a randomized, controlled study. Circulation 2015;132:182-93.

40. Tomte O, Draegni T, Mangschau A, et al. A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. Crit Care Med 2011;39:443-9.

41. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med 2009;37:1101-20.

42. Pittl U, Schratter A, Desch S, et al. Invasive versus non-invasive cooling after in- and out-of-hospital cardiac arrest: a randomized trial. Clin Res Cardiol 2013;102:607-14.

43. Oh SH, Oh JS, Kim YM, et al. An observational study of surface versus endovascular cooling techniques in cardiac arrest patients: a propensity-matched analysis. Crit Care 2015;19:85.

44. Cocchi MN, Boone MD, Giberson B, et al. Fever after rewarming: incidence of pyrexia in postcardiac arrest patients who have undergone mild therapeutic hypothermia. J Intensive Care Med 2014;29:365-9.

45. Winters SA, Wolf KH, Kettinger SA, et al. Assessment of risk factors for post-rewarming "rebound hyperthermia" in cardiac arrest patients undergoing therapeutic hypothermia. Resuscitation 2013;84:1245-9.

46. Lee BK, Song KH, Jung YH, et al. The influence of post-rewarming temperature management on post-rewarming fever development after cardiac arrest. Resuscitation 2015;97:20-6.

47. Bro-Jeppesen J, Hassager C, Wanscher M, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation 2013;84:1734-40.

48. Bouwes A, Robillard LB, Binnekade JM, et al. The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest. Resuscitation 2012;83:996-1000.

49. De Deyne C. Post-cooling fever in post-cardiac arrest patients: post-cooling normothermia as part of target temperature management? BMC Emerg Med 2015;15(suppl 1):A8.

50. Leary M, Grossestreuer AV, Iannacone S, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation 2013;84:1056-61.

51. Lee BK, Lee SJ, Jeung KW, et al. Outcome and adverse events with 72-hour cooling at 32 degrees C as compared to 24-hour cooling at 33 degrees C in comatose asphyxial arrest survivors. Am J Emerg Med 2014;32:297-301.

52. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Clin Invest 2005;115:2305-15.

53. Larsen JM, Ravkilde J. Acute coronary angiography in patients resuscitated from out-of-hospital cardiac arrest—a systematic review and meta-analysis. Resuscitation 2012;83:1427-33.

54. Redfors B, Ramunddal T, Angeras O, et al. Angiographic findings and survival in patients undergoing coronary angiography due to sudden cardiac arrest in western Sweden. Resuscitation 2015;90:13-20.

55. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997;336:1629-33.

56. Steinhaus DA, Vittinghoff E, Moffatt E, et al. Characteristics of sudden arrhythmic death in a diverse, urban community. Am Heart J 2012;163:125-31.

57. Noc M. Urgent coronary angiography and percutaneous coronary intervention as a part of postresuscitation management. Crit Care Med 2008;36:S454-7.

58. Bergman R, Hiemstra B, Nieuwland W, et al. Long-term outcome of patients after out-of-hospital cardiac arrest in relation to treatment: a single-centre study. Eur Heart J Acute Cardiovasc Care 2016;5:328-38.

59. Dumas F, Bougouin W, Geri G, et al. Emergency percutaneous coronary intervention in post-cardiac arrest patients without ST-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv 2016;9:1011-8.

60. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv 2010;3:200-7.

61. Geri G, Dumas F, Bougouin W, et al. Immediate percutaneous coronary intervention is associated with improved short- and long-term survival after out-of-hospital cardiac arrest. Circ Cardiovasc Interv 2015;8:e002303.

62. Kim MJ, Ro YS, Shin SD, et al. Association of emergent and elective percutaneous coronary intervention with neurological outcome and survival after out-of-hospital cardiac arrest in patients with and without a history of heart disease. Resuscitation 2015;97:115-21.

63. Sideris G, Voicu S, Yannopoulos D, et al. Favourable 5-year post-discharge survival of comatose patients resuscitated from out-of-hospital cardiac arrest, managed with immediate coronary angiogram on admission. Eur Heart J Acute Cardiovasc Care 2014;3:183-91.

64. Vyas A, Chan PS, Cram P, et al. Early coronary angiography and survival after out-of-hospital cardiac arrest. Circ Cardiovasc Interv 2015;8:e002321.

65. Wijesekera VA, Mullany DV, Tjahjadi CA, Walters DL. Routine angiography in survivors of out of hospital cardiac arrest with return of spontaneous circulation: a single site registry. BMC Cardiovasc Disord 2014;14:30.

66. Zanuttini D, Armellini I, Nucifora G, et al. Impact of emergency coronary angiography on in-hospital outcome of unconscious survivors after out-of-hospital cardiac arrest. Am J Cardiol 2012;110:1723-8.

67. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-425.

68. Siudak Z, Birkemeyer R, Dziewierz A, et al. Out-of-hospital cardiac arrest in patients treated with primary PCI for STEMI. Long-term follow up data from EUROTRANSFER registry. Resuscitation 2012;83:303-6.

69. Liu HW, Pan W, Wang LF, et al. Impact of emergency percutaneous coronary intervention on outcomes of ST-segment elevation myocardial infarction patients complicated by out-of-hospital cardiac arrest. Chin Med J (Engl) 2012;125:1405-9.

70. Lim HS, Stub D, Ajani AE, et al. Survival in patients with myocardial infarction complicated by out-of-hospital cardiac arrest undergoing emergency percutaneous coronary intervention. Int J Cardiol 2013;166:425-30.

71. Garot P, Lefevre T, Eltchaninoff H, et al. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. Circulation 2007;115:1354-62.

72. Zimmermann S, Flachskampf FA, Alff A, et al. Out-of-hospital cardiac arrest and percutaneous coronary intervention for ST-elevation myocardial infarction: long-term survival and neurological outcome. Int J Cardiol 2013;166:236-41.

73. Richling N, Herkner H, Holzer M, et al. Thrombolytic therapy vs primary percutaneous intervention after ventricular fibrillation cardiac arrest due to acute ST-segment elevation myocardial infarction and its effect on outcome. Am J Emerg Med 2007;25:545-50.

74. Koeth O, Zahn R, Bauer T, et al. Primary percutaneous coronary intervention and thrombolysis improve survival in patients with ST-elevation myocardial infarction and pre-hospital resuscitation. Resuscitation 2010;81:1505-8.

75. Bottiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. N Engl J Med 2008;359:2651-62.

76. Geri G, Dumas F, Cariou A. Should we perform a coronary angiography in all cardiac arrest survivors? Curr Opin Crit Care 2014;20:273-9.

77. Kern KB, Lotun K, Patel N, et al. Outcomes of comatose cardiac arrest survivors with and without ST-segment elevation myocardial infarction: importance of coronary angiography. JACC Cardiovasc Interv 2015;8:1031-40.

78. Kleissner M, Sramko M, Kohoutek J, Kautzner J, Kettner J. Impact of urgent coronary angiography on mid-term clinical outcome of comatose out-of-hospital cardiac arrest survivors presenting without ST-segment elevation. Resuscitation 2015;94:61-6.

79. Dankiewicz J, Nielsen N, Annborn M, et al. Survival in patients without acute ST elevation after cardiac arrest and association with early coronary angiography: a post hoc analysis from the TTM trial. Intensive Care Med 2015;41:856-64.

80. Casella G, Carinci V, Cavallo P, et al. Combining therapeutic hypothermia and emergent coronary angiography in out-of-hospital cardiac arrest survivors: Optimal post-arrest care for the best patient. Eur Heart J Acute Cardiovasc Care 2015;4:579-88.

81. Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. Emergency coronary angiography in comatose cardiac arrest patients: do real-life experiences support the guidelines? Eur Heart J Acute Cardiovasc Care 2012;1:291-301.

82. Reynolds JC, Rittenberger JC, Toma C, Callaway CW. Post Cardiac Arrest Service. Risk-adjusted outcome prediction with initial post-cardiac arrest illness severity: implications for cardiac arrest survivors being considered for early invasive strategy. Resuscitation 2014;85:1232-9.

83. Waldo SW, Chang L, Strom JB, et al. Predicting the presence of an acute coronary lesion among patients resuscitated from cardiac arrest. Circ Cardiovasc Interv 2015;8:e002198.

84. Aurore A, Jabre P, Liot P, et al. Predictive factors for positive coronary angiography in out-of-hospital cardiac arrest patients. Eur J Emerg Med 2011;18:73-6.

85. Anyfantakis ZA, Baron G, Aubry P, et al. Acute coronary angiographic findings in survivors of out-of-hospital cardiac arrest. Am Heart J 2009;157:312-8.

86. Radsel P, Knafelj R, Kocjancic S, Noc M. Angiographic characteristics of coronary disease and postresuscitation electrocardiograms in patients with aborted cardiac arrest outside a hospital. Am J Cardiol 2011;108:634-8.

87. Sideris G, Voicu S, Dillinger JG, et al. Value of post-resuscitation electrocardiogram in the diagnosis of acute myocardial infarction in out-of-hospital cardiac arrest patients. Resuscitation 2011;82:1148-53.

88. Zanuttini D, Armellini I, Nucifora G, et al. Predictive value of electrocardiogram in diagnosing acute coronary artery lesions among patients with out-of-hospital-cardiac-arrest. Resuscitation 2013;84:1250-4.

89. Staer-Jensen H, Nakstad ER, Fossum E, et al. Post-resuscitation ECG for selection of patients for immediate coronary angiography in out-of-hospital cardiac arrest. Circ Cardiovasc Interv 2015;8:e002784.

90. Dumas F, Manzo-Silberman S, Fichet J, et al. Can early cardiac troponin I measurement help to predict recent coronary occlusion in out-of-hospital cardiac arrest survivors? Crit Care Med 2012;40:1777-84.

91. Voicu S, Sideris G, Deye N, et al. Role of cardiac troponin in the diagnosis of acute myocardial infarction in comatose patients resuscitated from out-of-hospital cardiac arrest. Resuscitation 2012;83:452-8.

92. Dumas F, White L, Stubbs BA, Cariou A, Rea TD. Long-term prognosis following resuscitation from out of hospital cardiac arrest: role of percutaneous coronary intervention and therapeutic hypothermia. J Am Coll Cardiol 2012;60:21-7.

93. Callaway CW, Schmicker RH, Brown SP, et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. Resuscitation 2014;85:657-63.

94. Grasner JT, Meybohm P, Caliebe A, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. Crit Care 2011;15:R61.

95. Stub D, Hengel C, Chan W, et al. Usefulness of cooling and coronary catheterization to improve survival in out-of-hospital cardiac arrest. Am J Cardiol 2011;107:522-7.

96. Chisholm GE, Grejs A, Thim T, et al. Safety of therapeutic hypothermia combined with primary percutaneous coronary intervention after out-of-hospital cardiac arrest. Eur Heart J Acute Cardiovasc Care 2015;4:60-3.

97. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350-79.

98. Stub D, Bernard S, Duffy SJ, Kaye DM. Post cardiac arrest syndrome: a review of therapeutic strategies. Circulation 2011;123:1428-35.

99. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202-22.

100. Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation 2009;80:418-24.

101. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29-39.

102. Knapik P, Rychlik W, Duda D, et al. Relationship between blood, nasopharyngeal and urinary bladder temperature during intravascular cooling for therapeutic hypothermia after cardiac arrest. Resuscitation 2012;83:208-12.

103. Strapazzon G, Procter E, Paal P, Brugger H. Pre-hospital core temperature measurement in accidental and therapeutic hypothermia. High Alt Med Biol 2014;15:104-11.

104. Camboni D, Philipp A, Schebesch KM, Schmid C. Accuracy of core temperature measurement in deep hypothermic circulatory arrest. Interact Cardiovasc Thorac Surg 2008;7:922-4.

105. Chamorro C, Borrallo JM, Romera MA, Silva JA, Balandin B. Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. Anesth Analg 2010;110:1328-35.

106. De Jonghe B, Cook D, Appere-De-Vecchi C, et al. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med 2000;26:275-85.

107. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983-91.

108. Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. Neurocrit Care 2011;15:113-9.

109. May TL, Seder DB, Fraser GL, et al. Moderate-dose sedation and analgesia during targeted temperature management after cardiac arrest. Neurocrit Care 2015;22:105-11.

110. Bjelland TW, Dale O, Kaisen K, et al. Propofol and remifentanil versus midazolam and fentanyl for sedation during therapeutic hypothermia after cardiac arrest: a randomised trial. Intensive Care Med 2012;38:959-67.

111. Choi HA, Ko SB, Presciutti M, et al. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. Neurocrit Care 2011;14:389-94.

112. Nair SU, Lundbye JB. The occurrence of shivering in cardiac arrest survivors undergoing therapeutic hypothermia is associated with a good neurologic outcome. Resuscitation 2013;84:626-9.

113. Lascarrou JB, Le Gouge A, Dimet J, et al. Neuromuscular blockade during therapeutic hypothermia after cardiac arrest: observational study of neurological and infectious outcomes. Resuscitation 2014;85:1257-62.

114. Salciccioli JD, Cocchi MN, Rittenberger JC, et al. Continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients. Resuscitation 2013;84:1728-33.

115. Dell'Anna AM, Lamanna I, Vincent JL, Taccone FS. How much oxygen in adult cardiac arrest? Crit Care 2014;18:555.

116. Globus MY, Busto R, Lin B, Schnippering H, Ginsberg MD. Detection of free radical activity during transient global ischemia and recirculation: effects of intraischemic brain temperature modulation. J Neurochem 1995;65:1250-6.

117. Douzinas EE, Patsouris E, Kypriades EM, et al. Hypoxaemic reperfusion ameliorates the histopathological changes in the pig brain after a severe global cerebral ischaemic insult. Intensive Care Med 2001;27:905-10.

118. Floyd TF, Clark JM, Gelfand R, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. J Appl Physiol (1985) 2003;95:2453-61.

119. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest 1948;27:484-92.

120. Liu Y, Rosenthal RE, Haywood Y, et al. Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome. Stroke 1998;29:1679-86.

121. Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. Stroke 2007;38:1578-84.

122. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2014;18:711.

123. Elmer J, Scutella M, Pullalarevu R, et al. The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med 2015;41:49-57.

124. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, et al. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit Care 2015;19:348.

125. Kilgannon J, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-71.

126. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. Circulation 2011;123:2717-22.

127. Bellomo R, Bailey M, Eastwood GM, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care 2011;15:R90.

128. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart 2010;96:533-8.

129. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment elevation myocardial infarction. Circulation 2015;131:2143-50.

130. Falkenbach P, Kamarainen A, Makela A, et al. Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation 2009;80:990-3.

131. Roberts BW, Kilgannon JH, Chansky ME, et al. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. Circulation 2013;127:2107-13.

132. Bouzat P, Suys T, Sala N, Oddo M. Effect of moderate hyperventilation and induced hypertension on cerebral tissue oxygenation after cardiac arrest and therapeutic hypothermia. Resuscitation 2013;84:1540-5.

133. Brian JE Jr. Carbon dioxide and the cerebral circulation. Anesthesiology 1998;88:1365-86.

134. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke 1997;28:1569-73.

135. Lee SJ, Jeung KW, Lee BK, et al. Impact of case volume on outcome and performance of targeted temperature management in out-of-hospital cardiac arrest survivors. Am J Emerg Med 2015;33:31-6.

136. Roberts BW, Karagiannis P, Coletta M, et al. Effects of PaCO2 derangements on clinical outcomes after cerebral injury: a systematic review. Resuscitation 2015;91:32-41.

137. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation 2013;84:927-34.

138. Vaahersalo J, Bendel S, Reinikainen M, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med 2014;42:1463-70.

139. Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. J Trauma 1993;35:584-8 [discussion 8-9].

140. Blow O, Magliore L, Claridge JA, Butler K, Young JS. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. J Trauma 1999;47:964-9.

141. Shinozaki K, Oda S, Sadahiro T, et al. Blood ammonia and lactate levels on hospital arrival as a predictive biomarker in patients with out-of-hospital cardiac arrest. Resuscitation 2011;82:404-9.

142. Donnino MW, Miller J, Goyal N, et al. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. Resuscitation 2007;75:229-34.

143. Lee TR, Kang MJ, Cha WC, et al. Better lactate clearance associated with good neurologic outcome in survivors who treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Crit Care 2013;17:R260.

144. Riveiro DF, de Oliveira VM, Braunner JS, Vieira SR. Evaluation of serum lactate, central venous saturation, and venous-arterial carbon dioxide difference in the prediction of mortality in postcardiac arrest syndrome. J Intensive Care Med 2016;31:544-52.

145. Beylin ME, Perman SM, Abella BS, et al. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Intensive Care Med 2013;39:1981-8.

146. Bro-Jeppesen J, Kjaergaard J, Soholm H, et al. Hemodynamics and vasopressor support in therapeutic hypothermia after cardiac arrest: prognostic implications. Resuscitation 2014;85:664-70.

147. Kilgannon JH, Roberts BW, Jones AE, et al. Arterial blood pressure and neurologic outcome after resuscitation from cardiac arrest. Crit Care Med 2014;42:2083-91.

148. Trzeciak S, Jones AE, Kilgannon JH, et al. Significance of arterial hypotension after resuscitation from cardiac arrest. Crit Care Med 2009;37:2895-903 [quiz 904].

149. Young MN, Hollenbeck RD, Pollock JS, et al. Higher achieved mean arterial pressure during therapeutic hypothermia is not associated with neurologically intact survival following cardiac arrest. Resuscitation 2015;88:158-64.

150. Bro-Jeppesen J, Annborn M, Hassager C, et al. Hemodynamics and vasopressor support during targeted temperature management at 33 degrees C versus 36 degrees C after out-of-hospital cardiac arrest: a post hoc study of the target temperature management trial. Crit Care Med 2015;43:318-27.

151. Ameloot K, Meex I, Genbrugge C, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: a prospective observational study. Resuscitation 2015;91:56-62.

152. Wang CH, Huang CH, Chang WT, et al. Optimal blood pressure for favorable neurological outcome in adult patients following in-hospital cardiac arrest. Int J Cardiol 2015;195:66-72.

153. Walters EL, Morawski K, Dorotta I, et al. Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after out-of-hospital cardiac arrest: a feasibility study. Shock 2011;35:360-6.

154. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.

155. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2012;157:49-58.

156. SOS-KANTO study group. Relationship between the hemoglobin level at hospital arrival and post-cardiac arrest neurologic outcome. Am J Emerg Med 2012;30:770-4.

157. Wang CH, Huang CH, Chang WT, et al. Association between hemoglobin levels and clinical outcomes in adult patients after in-hospital cardiac arrest: a retrospective cohort study. Intern Emerg Med 2016;11:727-36.

158. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884-90.

159. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 2016;375:802-3.

160. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999;341:871-8.

161. Kudenchuk PJ, Newell C, White L, et al. Prophylactic lidocaine for post resuscitation care of patients with out-of-hospital ventricular fibrillation cardiac arrest. Resuscitation 2013;84:1512-8.

162. Jollis JG, Roettig ML, Aluko AO, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. JAMA 2007;298:2371-80.

163. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008;300:1423-31.

164. Mooney MR, Unger BT, Boland LL, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. Circulation 2011;124:206-14.

165. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 2013;310:1377-84.

166. Spaite DW, Bobrow BJ, Stolz U, et al. Statewide regionalization of postarrest care for out-of-hospital cardiac arrest: association with survival and neurologic outcome. Ann Emerg Med 2014;64:496-506.e1.

167. Kahn JM, Goss CH, Heagerty PJ, et al. Hospital volume and the outcomes of mechanical ventilation. N Engl J Med 2006;355:41-50.

168. Shahin J, Harrison DA, Rowan KM. Is the volume of mechanically ventilated admissions to UK critical care units associated with improved outcomes? Intensive Care Med 2014;40:353-60.

169. Tu JV, Austin PC, Chan BT. Relationship between annual volume of patients treated by admitting physician and mortality after acute myocardial infarction. JAMA 2001;285:3116-22.

170. Walkey AJ, Wiener RS. Hospital case volume and outcomes among patients hospitalized with severe sepsis. Am J Respir Crit Care Med 2014;189:548-55.

171. Callaway CW, Schmicker R, Kampmeyer M, et al. Receiving hospital characteristics associated with survival after out-of-hospital cardiac arrest. Resuscitation 2010;81:524-9.

172. Carr BG, Goyal M, Band RA, et al. A national analysis of the relationship between hospital factors and post-cardiac arrest mortality. Intensive Care Med 2009;35:505-11.

173. Carr BG, Kahn JM, Merchant RM, Kramer AA, Neumar RW. Inter-hospital variability in post-cardiac arrest mortality. Resuscitation 2009;80:30-4.

174. Cudnik MT, Sasson C, Rea TD, et al. Increasing hospital volume is not associated with improved survival in out of hospital cardiac arrest of cardiac etiology. Resuscitation 2012;83:862-8.

175. Schober A, Holzer M, Hochrieser H, et al. Effect of intensive care after cardiac arrest on patient outcome: a database analysis. Crit Care 2014;18:R84.

176. Shin SD, Suh GJ, Ahn KO, Song KJ. Cardiopulmonary resuscitation outcome of out-of-hospital cardiac arrest in low-volume versus high-volume emergency departments: an observational study and propensity score matching analysis. Resuscitation 2011;82:32-9.

177. Soholm H, Wachtell K, Nielsen SL, et al. Tertiary centres have improved survival compared to other hospitals in the Copenhagen area after out-of-hospital cardiac arrest. Resuscitation 2013;84:162-7.

178. Kajino K, Iwami T, Daya M, et al. Impact of transport to critical care medical centers on outcomes after out-of-hospital cardiac arrest. Resuscitation 2010;81:549-54.

179. Wnent J, Seewald S, Heringlake M, et al. Choice of hospital after out-of-hospital cardiac arrest—a decision with far-reaching consequences: a study in a large German city. Crit Care 2012;16:R164.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2016.10.021.