

General Clinical Practice Update

Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology Clinical Practice Update on Optimal Post Cardiac Arrest and Refractory Cardiac Arrest Patient Care

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ABSTRACT

Survival to hospital discharge among patients with out-of-hospital cardiac arrest (OHCA) is low and important regional differences in treatment practices and survival have been described. Since the 2017 publication of the Canadian Cardiovascular Society's position statement on OHCA care, multiple randomized controlled trials have helped to better define optimal post cardiac arrest care. This working group provides updated guidance on the timing of cardiac catheterization in patients with ST-elevation and without ST-segment elevation, on a revised temperature control strategy targeting normothermia instead of hypothermia, blood pressure, oxygenation, and ventilation parameters, and on the treatment of rhythmic and periodic electroenceph-

RÉSUMÉ

La survie des patients ayant subi un arrêt cardiaque hors de l'hôpital (ACHH) demeure faible à la sortie de l'hôpital et d'importantes différences régionales dans les pratiques de traitement et les taux de survie ont été décrites. Depuis la publication en 2017 de l'énoncé de position de la Société cardiovasculaire du Canada sur les soins de l'ACHH, les nombreux essais contrôlés randomisés ont contribué à mieux définir les soins optimaux après l'arrêt cardiaque. Notre groupe de travail fournit des directives actualisées : sur le moment opportun du cathétérisme cardiaque des patients ayant un sus-décalage du segment ST et n'ayant pas de sus-décalage du segment ST ; qui reposent sur une stratégie révisée de régulation de la température

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

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 interdisciplinary experts on this topic. 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.

alography patterns in patients with a resuscitated OHCA. In addition, prehospital trials have helped craft new expert opinions on antiarrhythmic strategies (amiodarone or lidocaine) and outline the potential role for double sequential defibrillation in patients with refractory cardiac arrest when equipment and training is available. Finally, we advocate for regionalized OHCA care systems with admissions to a hospital capable of integrating their post OHCA care with comprehensive on-site cardiovascular services and provide guidance on the potential role of extracorporeal cardiopulmonary resuscitation in patients with refractory cardiac arrest. We believe that knowledge translation through national harmonization and adoption of contemporary best practices has the potential to improve survival and functional outcomes in the OHCA population.

The international annual incidence of out-of-hospital cardiac arrest (OHCA) is 41-111 per 100,000 persons.¹⁻³ The estimated survival to hospital discharge among patients treated for an OHCA is low (5%-15%), but important international, regional, medical treatment, and socioeconomic variations have been described that might be, in part, due to differences in prehospital responses and hospital-based clinical practices.^{2,4-8} Despite quality of care and public health initiatives, it remains uncertain whether OHCA survival rates are improving in all regions.⁸⁻¹⁰ Collectively, this suggests that continued widespread adoption of best practices is required to improve OHCA outcomes.

The Canadian Cardiovascular Society (CCS) first post cardiac arrest care position statement published in 2017 made comprehensive recommendations for the in-hospital management of patients with resuscitated cardiac arrest. These recommendations were largely on the basis of results of observational studies or randomized controlled trials (RCTs) with important methodological limitations.¹¹ Multiple large, multicentre RCTs have since been published that have advanced our understanding of hospital-based care of patients with a resuscitated OHCA. In addition, new RCTs have tested regionalized OHCA care delivery models and treatment strategies for refractory prehospital cardiac arrest. This CCS clinical practice update (CPU), endorsed by Canadian Cardiovascular Critical Care Society (CANCARE) and the Canadian Association of Interventional Cardiology (CAIC-ACCI), provides expert opinion on best practices of OHCA care (Table 1).

Methods and Scope

This document was developed as a CPU in accordance with the published CCS framework.¹² The writing group members identified a set of clinical or therapeutic OHCA questions and performed comprehensive literature searches limited to RCTs or prespecified secondary analyses of RCTs that were published after the 2017 CCS OHCA position statement (2017 to August 2023).¹¹ Observational studies

axée sur la normothermie plutôt que l'hypothermie; la pression artérielle, les paramètres d'oxygénation et de ventilation; et sur le traitement des activités rythmiques et périodiques en électroencéphalographie chez les patients réanimés après l'ACHH. De plus, les essais en milieu préhospitalier ont favorisé l'élaboration de nouveaux avis d'experts sur les stratégies antiarythmiques (amiodarone ou lidocaïne) et ont montré le rôle potentiel de la double défibrillation séquentielle des patients ayant subi un arrêt cardiaque réfractaire lorsque l'équipement et la formation sont disponibles. Finalement, nous préconisons les systèmes de soins régionalisés de l'ACHH grâce à des admissions dans un hôpital capable d'intégrer leurs soins post-ACHH à des services en cardiologie complets sur place et nous fournissons des précisions sur le rôle potentiel de la réanimation cardiopulmonaire extracorporelle des patients ayant subi un arrêt cardiaque réfractaire. Nous croyons que l'application des connaissances par l'harmonisation nationale et l'adoption de pratiques exemplaires contemporaines ont le potentiel d'améliorer la survie et les résultats fonctionnels de la population ayant subi un ACHH.

were not included in the expert opinions. Primary topic leads performed literature searches and drafted initial expert opinions. The committee revised and provided feedback during weekly teleconferences. All expert opinions were ungraded and derived by consensus.

Post Cardiac Arrest Care

Role and timing of coronary angiography during post cardiac arrest care

i) Coronary angiography in patients with OHCA who present with STEMI. The timing of coronary angiography in comatose OHCA survivors depends largely on the presence or absence of ST-segment elevation on initial electrocardiograms (ECGs) (Fig. 1). Early revascularization of ST-segment elevation myocardial infarction (STEMI) might reduce the risk of hemodynamic decompensation, mechanical cardiac complications, and recurrent arrhythmias.¹¹ As such, the 2017 CCS post cardiac arrest position statement recommended immediate coronary angiography and primary percutaneous coronary intervention (PCI), or fibrinolytic therapy in settings where timely primary PCI was not available for resuscitated patients with OHCA who present with a STEMI.¹¹ Despite minimal data on comatose survivors of OHCA from STEMI reperfusion trials, the totality of the data support emergent revascularization in this patient population. Neurological injury is a meaningful competing risk but reliable neuroprognostication is not possible immediately after OHCA. Therefore, evidence-based STEMI reperfusion therapy as part of post-arrest care is reasonable.¹³

Expert Opinion: In patients with STEMI who do not purposefully respond to verbal commands after a resuscitated OHCA, timely reperfusion therapy at the time of presentation is indicated with immediate coronary angiography and primary PCI, or fibrinolytic therapy in settings where timely primary PCI is not available.

Table 1. Summary of consensus expert opinions for patients with out-of-hospital resuscitated cardiac arrest

Post cardiac arrest care metric	New or revised	2017 CCS position statement ¹¹	2024 Expert opinions
Timing of coronary angiography	R	- 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) - We recommend fibrinolytic therapy in OHCA patients with STEMI if timely PPCI cannot be performed and there are no absolute contraindications to its use (Strong Recommendation; Low-Quality Evidence)	In patients with STEMI who do not purposefully follow verbal commands after a resuscitated OHCA, timely reperfusion at the time of presentation therapy is indicated with immediate coronary angiography and PPCI, or fibrinolytic therapy in settings where timely PPCI is not available
	R	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)	In patients who are comatose after a resuscitated OHCA without ST-segment elevation on the initial ECG, delaying coronary angiography might be considered unless high-risk cardiovascular features are present such as hemodynamic instability, high-risk ischemic ECG changes, or recurrent, or unstable ventricular arrhythmias believed to be related to ongoing ischemia
Temperature control	R	We suggest that TTM be initiated along with angiography in comatose patients if both are required concurrently (Conditional Recommendation; Low-Quality Evidence)	It is reasonable to initiate temperature control as soon as possible after hospital arrival and not in the prehospital environment
	R	- We recommend that TTM be used in unresponsive OHCA survivors with an initial shockable rhythm after ROSC (Strong Recommendation; Low-Quality Evidence) - 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)	In patients who do not purposefully respond to verbal commands after a resuscitated OHCA with an initial shockable rhythm, it is reasonable to target a core temperature target of $\leq 37.5^{\circ}\text{C}$
	R	- We suggest TTM be used in unresponsive OHCA survivors with an initial nonshockable rhythm after ROSC (Conditional Recommendation; Very Low-Quality Evidence) - 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)	In patients who do not purposefully respond to verbal commands after a resuscitated OHCA with an initial non-shockable rhythm, it is reasonable to target a core temperature target of $\leq 37.5^{\circ}\text{C}$
	R	- 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) - 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)	In patients who do not purposefully respond to verbal commands after a resuscitated in-hospital cardiac arrest with an initial shockable or nonshockable rhythm, it is reasonable to target a core temperature target of $\leq 37.5^{\circ}\text{C}$
	R	- We suggest that the cooling temperature selected for TTM be maintained for at least 24 hours (Conditional Recommendation; Very Low-Quality Evidence) - We suggest TTM be continued beyond 24 hours from ROSC to prevent fever (temperature $> 37.5^{\circ}\text{C}$; Conditional Recommendation; Very Low-Quality Evidence)	In patients who do not purposefully respond to verbal commands after resuscitated cardiac arrest, it is reasonable to continue temperature control for at least 72 hours
Blood pressure targets	R	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)	Targeting a MAP ≥ 65 mm Hg is acceptable in resuscitated comatose survivors of OHCA
Oxygenation targets	R	We suggest oxygen therapy be titrated to a PaO₂ between 60 and 200 mm Hg in OHCA patients (Conditional Recommendation; Low-Quality Evidence)	It is reasonable to target a PaO ₂ between 68 and 105 mm Hg in the early phase of care for comatose patients with resuscitated out-of-hospital cardiac arrest. Emphasis should be placed on avoiding hypoxemia (PaO ₂ < 68 mm Hg) and excessive hyperoxemia (PaO ₂ > 195 mm Hg)
Ventilation targets	R	We suggest that, in patients who undergo MV after OHCA, ventilation should target normocapnia (PaCO₂ 35-45 mm Hg; Conditional Recommendation; Low-Quality Evidence)	In patients who require mechanical ventilation after a resuscitated OHCA, it is reasonable to target normocapnia (PaCO ₂ 35-45 mm Hg)
Routine antibiotic prophylaxis	N		In patients who are intubated after a cardiac arrest, antibiotics should be reserved for patients with clinically suspected or confirmed bacterial pneumonia

Seizure treatment	N		In patients with resuscitated OHCA who remain comatose with electroencephalographic seizures with a continuous, nonsuppressed EEG background, treatment with antiseizure and sedative medications is reasonable, especially if no other indicators of poor prognosis are present
GPDs	N		Patients with resuscitated OHCA who remain comatose with GPDs on EEG are unlikely to benefit from GPD suppression
Refractory cardiac arrest	New or revised	2017 CCS position statement ¹¹	2024 Expert opinions
Antiarrhythmic drug selection	N		In patients with an OHCA who remain in VF or pVT after 1 or more defibrillation attempts, either amiodarone or lidocaine may be administered, particularly in patients with witnessed arrest
Defibrillation strategies	N		In patients with OHCA refractory (defined as no termination after 3 shocks) shockable rhythm, double sequential or vector change defibrillation, when equipment and training is available, can be considered
eCPR	N		eCPR should not be routinely used, but may be considered in highly selected patients with refractory cardiac arrest (> 5-15 minutes) with limited comorbidities and a witnessed cardiac arrest with a targeted cardiac arrest to cannulation time of < 60 minutes
	N		eCPR can be considered in centres with established VA-ECMO programs and formalized integrated eCPR clinical pathways
	N		If eCPR is considered, the target arrest to cannulation time is < 60 minutes and the target hospital arrival to cannulation time is < 30 minutes
Systems of care	New or revised	2017 CCS position statement ¹¹	2024 Expert opinions
	R	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)	Patients with ROSC after an OHCA who do not have a STEMI should be transported to the nearest ED. After initial evaluation and stabilization, it is reasonable to consider admission to a hospital capable of integrating their post-OHCA care with comprehensive on-site cardiovascular, neurology, critical care, and secondary prevention services depending on local geographic resources

CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; eCPR, extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation; ED, emergency department; EEG, electroencephalogram; GPD, generalized periodic discharge; MAP, mean arterial pressure; MV, mechanical ventilation; N, new; OHCA, out-of-hospital cardiac arrest; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; pVT, pulseless ventricular tachycardia; R, revised; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction; TTM, targeted temperature management; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation.

ii) Coronary angiography in patients with OHCA without a STEMI. The efficacy and safety of immediate vs delayed coronary angiography in comatose survivors of OHCA without ST-segment elevation has been examined in 6 multi-centre RCTs (Supplemental Table S1).¹³⁻¹⁸ In the **Coronary Angiography After Cardiac Arrest (COACT)** trial 552 patients with OHCA without ST-segment elevation and a shockable rhythm were randomized to immediate vs delayed coronary angiography (median time from arrest to coronary angiography was 2 and 122 hours, respectively).¹³ There was no significant difference in survival at 90 days for immediate vs delayed angiography (64.5% and 67.2%). In the **Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-hospital Cardiac Arrest Without ST-segment Elevation (TOMAHAWK)** trial 554 patients with OHCA from a suspected coronary origin with either shockable or nonshockable rhythm were randomized to immediate vs delayed coronary angiography (median time from arrest to coronary angiography was 3 and 47 hours).¹⁴ Overall survival at 30 days did not differ significantly for the 2 strategies (46.0% with immediate and 54.0% with delayed angiography; $P = 0.06$). A meta-analysis of the 6 RCTs performed to date showed no significant difference in survival with a good neurological outcome, duration of mechanical ventilation, or intensive care length of stay with early (with trial definitions ranging from immediately after to within 2 hours of randomization) vs delayed coronary angiography.¹⁹ Several factors might account for the lack of benefit of early angiography in OHCA survivors without ST-segment elevation. These include the heterogenous population in the included studies, the relatively low incidence of acute unstable culprit coronary lesions found in this cohort (13.6%–46.9% of coronary angiograms),¹⁹ and the competing risk of death from severe neurological dysfunction, which might not be modulated by early coronary angiography.

Although routine early coronary angiography is not beneficial in comatose survivors of OHCA without STEMI, patient subgroups at high risk of adverse events warrant consideration for immediate angiography.

These include patients with cardiogenic shock, high-risk ischemic ECG changes, or recurrent unstable ventricular arrhythmias believed to be related to ongoing ischemia.

Expert Opinion: In patients who are comatose after a resuscitated OHCA without ST-segment elevation on the initial ECG, delaying coronary angiography may be considered unless high-risk cardiovascular features are present such as hemodynamic instability, high-risk ischemic ECG changes, or recurrent, or unstable ventricular arrhythmias believed to be related to ongoing ischemia.

Temperature control

For the purposes of this CPU, temperature control is defined as active regulation of temperature after cardiac arrest. Animal models and early RCTs have suggested that lowering core body temperature after return of spontaneous circulation (ROSC) after cardiac arrest might improve neurological outcomes and survival. The 2017 CCS position statement suggested that “targeted temperature management” be considered for all unresponsive post-ROSC patients with a recommended target temperature of 33°C–36°C for at least 24 hours.¹¹ Several RCTs, summarized in Table 2, have subsequently evaluated different temperature control targets, durations, and populations, providing additional evidence to guide clinical practice. The degree of neurological impairment required to initiate temperature control is not universally defined and inclusion criteria used in RCTs vary. The Targeted Temperature Management 2 (TTM2) trial defined “unconscious” as the inability to obey verbal commands.²⁰ The 2017 CCS position

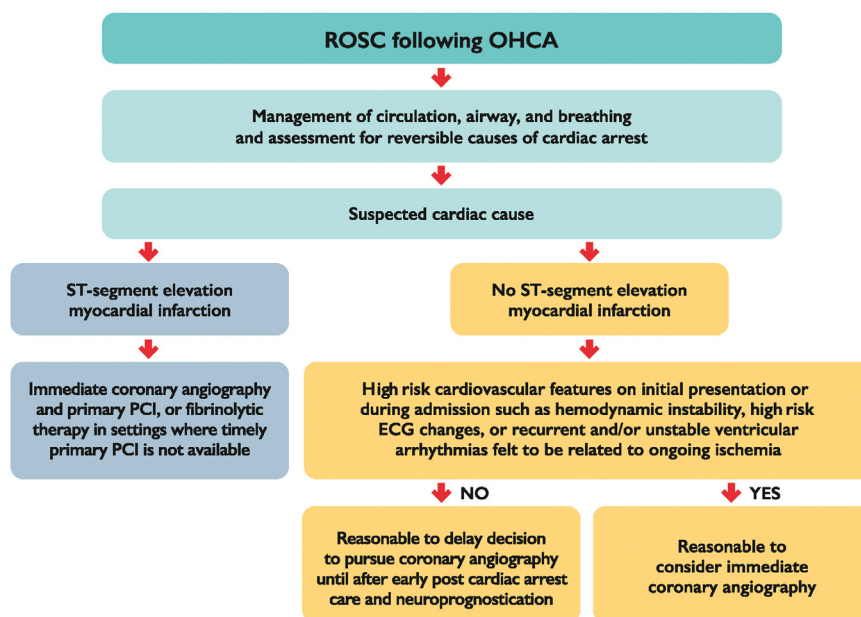
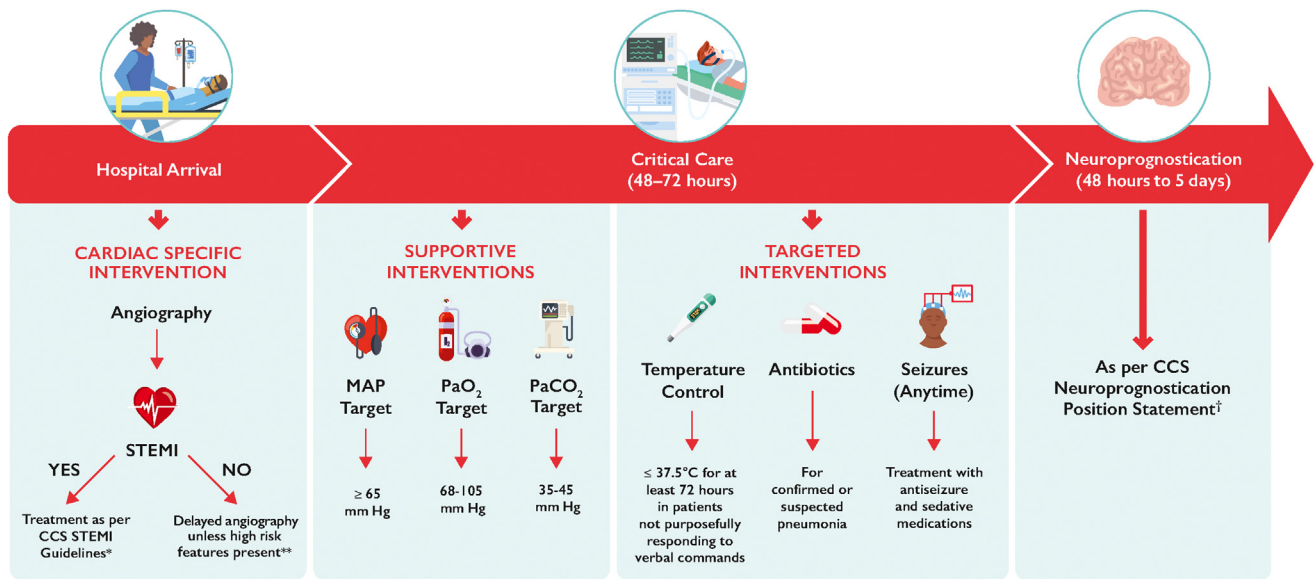


Figure 1. Timing of coronary angiography during post cardiac arrest care. ECG, electrocardiogram; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation.

Table 2. Summary of randomized trials that targeted different temperatures and trials that assessed the duration of active temperature control

Trial (enrollment)	Target temperature trials				Temperature duration trials	
	TTM2 ²⁰ (2021) (n = 1861)	CAPITAL CHILL ³⁰ (2021) (n = 367)	HACA In-Hospital ³² (2022) (n = 242)	HYPERION ³¹ (2019) (n = 581)	TTH48 ³³ (2017) (n = 351)	BOX ³⁴ (2023) (n = 789)
Intervention	Mild hypothermia (33°C) vs normothermia (≤ 37.5°C)	Moderate hypothermia (31°C) vs mild hypothermia (34°C) for 24 hours	Mild hypothermia (32°C- 34°C) vs normothermia (≤ 37.5°C)	Mild hypothermia (33°C) vs normothermia (36.5°C-37.5°C)	Mild hypothermia (33°C) 24 vs 48 hours	Mild hypothermia (36°C) for 24 hours followed by 12 vs 48 hours of fever prevention (total 36 vs 72 hours)
Age, years	62	61	72	67 (median)	60	62
Male sex, n (%)	1477 (79)	298 (81)	152 (64)	373 (64)	295 (83)	636 (81)
Initial shockable rhythm, n (%)	1371 (74)	316 (86)	57 (24)	0	312 (88)	665 (84)
Location, n (%)						
OHCA	1861 (100)	367 (100)	0 (0)	422 (73)	351 (100)	789 (100)
IHCA	0 (0)	0 (0)	235 (97)	159 (27)	0 (0)	0 (0)
Witnessed arrest, n (%)	1702 (91)	309 (84)	166 (73)	547 (94)	322 (92)	672 (85)
Median time to ROSC, minutes	25	21	16 (mean)	18	20.5	21
Total follow-up duration	180 days	180 days	180 days	90 days	180 days	90 days
Primary outcome (<i>P</i> value)	All-cause death, 50% vs 48% (NS)	All-cause mortality or poor neurological outcome, 48.4% vs 45.4% (NS)	All-cause mortality, 72.5% vs 71.2% (NS)	Survival with a favourable neurological outcome (CPC 1-2) in 33°C, 10.2% vs 5.7% (0.04)	Favourable neurological outcome (CPC 1-2), 64% vs 69% (NS)	All-cause death or discharge with severe cerebral disability or coma, 32.3% vs 33.6% (NS)
Secondary outcomes (<i>P</i> value)	- Moderately severe disability 55% vs 55% (NS) - Hemodynamically significant arrhythmia in 33°C, 24% vs 17% (< 0.001)	- All-cause mortality at 180 days, 43.5% and 41% (NS) - Longer median ICU-LOS in 31°C, 10 vs 7 days (0.004)	- In-hospital mortality, 62.5% vs 57.6% (NS) - Favourable neurological outcome (CPC 1-2) at 180 days, 22.5% vs 23.7% (NS)	- All-cause death at 90 days of 81.3% vs 83.2% (NS) - No differences in adverse events among groups	- All-cause death at 6 months of 34% vs 27% (NS) - More patients with hypotension in the 48-hour group, 62% vs 49% (0.013)	- All-cause death at 90 days of 29.5% vs 30.3% (NS) - MoCA at 3 months of 26 and 27 (NS)

BOX, Blood Pressure and Oxygenation Targets in Post Resuscitation Care; CAPITAL CHILL, Mild vs Moderate Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest Patients; CPC, cerebral performance category; HACA In-Hospital, Hypothermia After In-Hospital Cardiac Arrest; HYPERION, Therapeutic Hypothermia After Cardiac Arrest in Non-Shockable Rhythm; ICU-LOS, intensive care unit length-of-stay; IHCA, in-hospital cardiac arrest; MoCA, Montreal Cognitive Assessment; NS, not significant; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTH48, Time-Differentiated Therapeutic Hypothermia 48; TTM2, Targeted Temperature Management 2.



* Wong et al. Can J Cardiol 2019;35:107-132.

† Fordyce et al. Can J Cardiol 2023;39:366-380.

** High risk features include hemodynamic instability, high risk ischemic ECG changes, or recurrent and/or unstable ventricular arrhythmias.

Figure 2. Summary of contemporary hospital-based best care practices for patient with a resuscitated cardiac arrest. CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; MAP, mean arterial pressure; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; STEMI, ST-segment elevation myocardial infarction. *Wong et al.⁷⁶ †Fordyce et al.⁵¹ **High-risk features include hemodynamic instability, high-risk ischemic ECG changes, or recurrent and/or unstable ventricular arrhythmias.

statement used the term “unresponsive,” which was defined as “the absence of purposeful response to verbal commands.”¹¹

Temperature control can be achieved using intravascular/invasive methods or external surface cooling devices. Substudies of the **Targeted Temperature Management at 33°C After Cardiac Arrest (TTM)** trial and the **Time-Differentiated Therapeutic Hypothermia 48 (TTH48)** showed no mortality or neurological outcome differences between strategies.^{21,22} However, 1 RCT showed higher bleeding complication rates associated with endovascular cooling.²³ We advocate that all patients who undergo temperature control should receive continuous core temperature monitoring. In-hospital temperature control and management best practices are summarized in [Figure 2](#).

i) Timing of temperature control initiation. It has been postulated that prehospital cooling might reduce the time to achieve temperature targets and reduce the potential for early neurological damage. However, this strategy has been associated with more complications and/or no benefit compared with in-hospital initiation of temperature control. The **Rapid Infusion of Cold Normal Saline (RINSE)** trial used a 2-L cold saline infusion vs standard of care during prehospital cardiac arrest in 1198 patients. The cold saline group had lower rates of ROSC (41.2% vs 50.6%), a higher incidence of acute pulmonary edema, and no improvement in survival to discharge (10.2% vs 11.4%).²⁴ In the **Initiation of Cooling by Emergency Medical Services to Promote the Adoption of In-hospital Therapeutic Hypothermia in Cardiac Arrest Survivors (ICEPACS)** trial 585 patients were randomized to prehospital cooling with ice packs and cold saline initiated 5 minutes after

ROSC vs standard of care and showed no difference in the secondary outcome of survival with good neurological function (29.3% vs 25.1%).²⁵ In the **Prehospital Resuscitation Intranasal Cooling Effectiveness Survival Study (PRINCESS)** trial 677 patients were randomized to prehospital transnasal evaporative cooling vs standard of care and showed no differences in survival with good neurological outcome at 90 days (16.6% vs 12.5%).²⁶

Expert Opinion: It is reasonable to initiate temperature control as soon as possible after hospital arrival and not in the prehospital environment.

ii) Temperature targets. The 2017 CCS position statement recommended a temperature control range of 33°C-36°C on the basis of the TTM trial, the **Hypothermia After Cardiac Arrest (HACA)** study, and the study from Bernard et al.²⁷⁻²⁹ The TTM trial showed no difference in all-cause mortality in 950 patients randomized to mild hypothermia temperature control targets (33°C vs 36°C). Since 2017, several RCTs have helped further refine optimal temperature control targets. The largest and most methodologically robust trial of temperature control in patients with OHCA is the TTM2 trial, which randomized 1900 patients (72% shockable and 28% nonshockable rhythms, 90% witnessed arrest, 78% bystander cardiopulmonary resuscitation [CPR], 40% STEMI) to mild hypothermia (33°C for 28 hours followed by controlled rewarming to 37°C until 40 hours) or normothermia (maintenance of temperature at 37.5°C for 40 hours with active cooling initiated only if the temperature reached 37.8°C).²⁰ After the 40-hour intervention period both groups continued with a common normothermia strategy with a

target temperature between 36.5°C and 37.7°C for 72 hours after randomization. There was no difference in the primary outcome of 6-month all-cause death (50.3% vs 48.2%), or the secondary outcome of a poor neurological function, defined as a score of 4–6 on the modified Rankin scale (55.4% vs 55.3%), among the treatment strategies. No differences in treatment effect were noted in predefined subgroups including shockable vs nonshockable rhythms or time to ROSC < 25 minutes. Adverse events were similar among the groups except for a greater incidence of hemodynamically significant arrhythmias in the mild hypothermia arm (23.9% vs 16.5%). Trial strengths included size, protocolization of withdrawal of life-sustaining therapy, and neurological outcome assessments by trained assessors. However, the greater proportion of witnessed OHCA with bystander-initiated CPR compared with many population-based registries might limit its generalizability. In the Mild vs Moderate Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest Patients (CAPITAL CHILL) trial 367 patients with OHCA (86% shockable, 33% STEMI) were randomized to mild (34°C) vs moderate (31°C) hypothermia and no difference in 180-day all-cause mortality or poor neurological outcome (45.4% vs 48.4%) was shown, suggesting no benefit to moderate hypothermia.³⁰ Notably, there are no trials that have compared normothermia/fever prevention with a fever treatment approach.

In the Therapeutic Hypothermia After Cardiac Arrest in Non-Shockable Rhythm (HYPERION) trial 584 resuscitated patients with cardiac arrest with nonshockable rhythms (80% asystole, 94% bystander witnessed arrests, 70% bystander performed CPR) were randomized to mild hypothermia (33°C) or normothermia (37°C) for 24 hours. HYPERION included patients with in-hospital cardiac arrest (IHCA) and OHCA (72.6%).³¹ The primary outcome (90-day survival with favourable neurological outcome, defined as cerebral performance category [CPC] of 1 or 2) occurred more frequently in the mild hypothermia group compared with the normothermia group (10.2% vs 5.7%), but there was no difference in all-cause mortality (81.3% vs 83.2%). The study had several limitations: a concern regarding its generalizability (2139 of 2723 patients screened for eligibility did not meet inclusion criteria [eg, moribund condition, hemodynamic instability, late presentation, long no- or low-flow times]), the reliability of neurological status assessments done in telephone interview, and a low fragility index of 1 (a change of only 1 event would result in a loss of statistical significance). In contrast to the HYPERION results, a prespecified subgroup analysis of 490 patients in the TTM2 trials with nonshockable rhythm showed no heterogeneity in treatment effect.²⁰ Thus, there are insufficient data to support a target temperature of 33°C as an alternative temperature target in patients with OHCA with nonshockable rhythm and targeting a uniform temperature ($\leq 37.5^\circ\text{C}$) might reduce institutional protocol complexities.

In the Hypothermia After In-Hospital Cardiac Arrest (HACA In-Hospital) trial 249 patients with IHCA (70% non-shockable, 65% cardiac etiology, 73% witnessed) were randomized to mild hypothermia (32°C–34°C) vs normothermia (target $\leq 37.5^\circ\text{C}$).³² No difference was observed in the incidence of all-cause mortality (72.5% vs 71.2%) or favourable neurological outcome (22.5% vs 23.7%) between groups at 180 days. These results were consistent for IHCA

patients with shockable and nonshockable rhythms. However, the study was underpowered and 25% of patients in the hypothermic arm did not reach their intended target temperature. The subgroup with the least RCT evidence is IHCA with a shockable rhythm. In this trial, 24% of patients had a shockable rhythm. A prespecified subgroup analysis of patients with shockable and nonshockable rhythms showed no difference for mild hypothermia compared with normothermia.³² Because of the limitation of IHCA literature and lack of clear benefit of a strategy beyond targeted normothermia, there is insufficient evidence to support alternative temperature targets in this patient cohort.

Expert Opinion: In patients who do not purposefully respond to verbal commands after a resuscitated OHCA with an initial shockable rhythm, it is reasonable to target a core temperature target of $\leq 37.5^\circ\text{C}$.

Expert Opinion: In patients who do not purposefully respond to verbal commands after a resuscitated OHCA with an initial nonshockable rhythm, it is reasonable to target a core temperature target of $\leq 37.5^\circ\text{C}$.

Expert Opinion: In patients who do not purposefully respond to verbal commands after a resuscitated IHCA with an initial shockable or nonshockable rhythm, it is reasonable to target a core temperature target of $\leq 37.5^\circ\text{C}$.

iii) Duration of temperature control. Early mild hypothermia trials protocolized a temperature intervention duration of 12–36 hours.^{27–29} In the TTH48 trial 355 patients with resuscitated OHCA were randomized to 24 vs 48 hours of mild hypothermia (33°C) and showed no difference in the rates of favourable neurological outcomes at 6 months.³³ However the 48-hour arm had a greater incidence of hypotension and longer median intensive care length-of-stay. In the Blood Pressure and Oxygenation Targets in Post Resuscitation Care (BOX) trial 789 unconscious resuscitated patients with OHCA were randomized to 36 vs 72 hours of fever prevention and also showed no difference in all-cause death within 90 days (29.5% vs 30.3%) or discharge with severe cerebral impairment or coma at 90 days (32.3% vs 33.6%).³⁴ Finally, the TTM2 trial protocolized temperature control for 72 hours.²⁰ Although there are few data to support the use of temperature control beyond 72 hours, secondary brain injury from increased intracranial pressure and fever-mediated injury might persist beyond this time. Therefore, maintaining temperature control beyond the durations tested in existing randomized trials might be reasonable.

Expert Opinion: In patients who do not purposefully respond to verbal commands after resuscitated cardiac arrest, it is reasonable to continue temperature control for at least 72 hours.

Blood pressure targets in comatose survivors of cardiac arrest

Adequate cerebral oxygen delivery is an important consideration to mitigate brain injury after OHCA. Mean arterial pressure (MAP), urine output, and serum lactate levels are readily available surrogates of end organ perfusion that are associated with clinical outcomes in critically ill patients. MAP target recommendations for post cardiac arrest care have been traditionally on the basis of observational studies and/or

extrapolation of clinical trials on other critical illnesses. However, OHCA is a distinctive critical illness phenotype characterized by severe neurological injury and a post cardiac arrest syndrome, in which patients with impaired cerebrovascular autoregulation might require higher MAP for adequate cerebral perfusion.³⁵

The 2017 CCS post cardiac arrest position statement suggested a MAP target of ≥ 65 mm Hg in comatose survivors of OHCA.¹¹ Three RCTs have since examined the efficacy and safety of higher MAP targets during post cardiac arrest care.³⁶⁻³⁸ The BOX trial randomized 789 patients to a MAP target of 77 mm Hg or 63 mm Hg and showed no significant difference in the primary outcome of death or severe neurological dysfunction at 90 days (33.8% vs 32.1, respectively; $P = 0.56$).³⁶ Acute kidney injury requiring renal replacement therapy, neuron-specific enolase concentrations at 48 hours, or median cognitive assessment scores at 3 months were also similar. In the Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients (NEUROPROTECT) trial 112 patients were randomized to conventional care (MAP ≥ 65 mm Hg) or a goal-directed hemodynamic strategy consisting of a MAP of 85-100 mm Hg and a mixed venous oxygen saturation of 65%-75%.³⁷ A goal-directed hemodynamic strategy did not reduce the primary outcome of severity of anoxic brain injury on magnetic resonance imaging. In the Carbon Dioxide, Oxygen and Mean Arterial Pressure After Cardiac Arrest and Resuscitation (COMACARE) trial 123 patients were randomized to a MAP target of 65-85 mm Hg or 80-100 mm Hg and no difference was shown in the primary outcome of neuron-specific enolase concentration at 48 hours.³⁸ Higher MAP targets were feasible and safe in all studies but required higher doses of vasoactive agents. A limitation in the design of existing trials is that the optimal MAP after OHCA might vary from patient to patient and be largely dependent on the presence or absence of cerebrovascular dysregulation. In addition, in the BOX trial, the mean difference in MAP was 11 mm Hg (which was below the expected 14 mm Hg) and the higher MAP target of 77 mm Hg was well below the estimated threshold required to maintain adequate cerebral perfusion in the presence of cerebrovascular dysregulation.^{36,39} Despite some limitations, these new data do not support changes to the previously suggested MAP target of ≥ 65 mm Hg.

Expert Opinion: Targeting a MAP of ≥ 65 mm Hg is acceptable in resuscitated comatose survivors of OHCA.

Optimal oxygenation targets

The 2017 CCS position statement post arrest position statement suggested titrating partial pressure of arterial oxygen (PaO_2) levels to between 60 mm Hg and 200 mm Hg.¹¹ However, the available evidence was limited to observational data. Two randomized trials (BOX and Reduction of Oxygen After Cardiac Arrest [EXACT]) and a prespecified secondary analysis of the TTM2 trial have subsequently examined oxygenation targets in patients with resuscitated OHCA.

In the BOX trial 789 OHCA survivors were randomized to a restrictive (PaO_2 68-75 mm Hg) or liberal (PaO_2 98-105 mm Hg) oxygenation strategy for up to 5 days post-randomization or until removal of the arterial catheter.⁴⁰

There were no significant differences in the composite primary end point of all-cause mortality or hospital discharge with severe disability or coma at 90 days for the restrictive and liberal oxygenation arms (32.0% vs 33.9%, respectively). The incidence of adverse events was similar among the 2 groups. It should be noted that the restrictive and liberal arms were within the “normoxia” range, which might explain the lack of difference among the 2 groups.

In the EXACT trial the effect of a lower peripheral O_2 saturation target among OHCA survivors in a prehospital setting was assessed.⁴¹ Unfortunately, the trial was stopped prematurely due to enrollment difficulties related to COVID-19 and was therefore underpowered. A lower peripheral O_2 saturation target of 90%-94% in a prehospital setting after OHCA did not improve survival to hospital discharge compared to a target of 98%-100%.

Finally, a prespecified secondary analysis of the TTM2 trial measured the PaO_2 in 1418 patients for 72 hours post randomization.⁴² Compared with normoxia, hypoxemia ($\text{PaO}_2 < 69$ mm Hg) and hyperoxemia ($\text{PaO}_2 > 195$ mm Hg) were significantly associated with mortality in a “U shaped” relationship. However, neither hypoxemia nor hyperoxemia were shown to be associated with worse neurological outcome. Increased time exposure to hyperoxemia was associated with an increased risk of 6-month mortality. It is noteworthy that BOX and the TTM2 subanalysis enrolled OHCA populations with high rates of shockable rhythms and bystander CPR, which might reduce the external validity of the trial results.

Expert Opinion: It is reasonable to target a PaO_2 between 68 and 105 mm Hg in the early phase of care for comatose patients with resuscitated OHCA. Emphasis should be placed on avoiding hypoxemia ($\text{PaO}_2 < 68$ mm Hg) and excessive hyperoxemia ($\text{PaO}_2 > 195$ mm Hg).

Partial pressure of arterial carbon dioxide targets

The partial pressure of arterial carbon dioxide (PaCO_2) is a regulator of cerebrovascular blood flow.⁴³ Although hypercapnia increases cerebrovascular blood flow, might improve cerebral oxygen saturations, and attenuates neuron-specific enolase release, observational studies have shown an inconsistent link between hypercapnia and improved clinical outcomes.⁴³⁻⁴⁷ In contrast, hypocapnia might reduce cerebral blood flow and has been associated with increased in-hospital mortality in patients with resuscitated OHCA and ROSC, but high-quality RCTs are lacking.^{43,46}

In the Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME) trial adult patients with resuscitated OHCA from a presumed cardiac (or unknown) cause with ROSC ≥ 20 minutes and a Full Outline of Unresponsiveness (FOUR) score < 4 , were randomly assigned to mild hypercapnia (PaCO_2 50-55 mm Hg) or normocapnia (PaCO_2 35-45 mm Hg) target PaCO_2 ranges for 24 hours.⁴⁸ Patients with a ROSC to screening time > 180 minutes and unwitnessed asystole were excluded. The study protocolized deep sedation for 24 hours with no adjustment of PaCO_2 or pH. The study enrolled 1700 patients and showed no difference in favourable neurological outcomes at 6 months in the mild hypercapnia arm (43.5%) compared with the normocapnia arm (44.6%). Similarly, there was no significant

difference in 6-month all-cause mortality (48.2% vs 45.9%) or adverse events. During the 24-hour intervention period, the mild hypercapnia group required more neuromuscular blockade use and had a lower pH, but the MAP was similar in both groups. Weaknesses of the trial include the unblinded design, missing outcomes in 7.6% of participants, and non-protocolized withdrawal of life-sustaining therapy.

Expert Opinion: In patients who require mechanical ventilation after a resuscitated OHCA, it is reasonable to target normocapnia (PaCO₂ 35–45 mm Hg).

Routine antibiotic prophylaxis for aspiration pneumonia

Infectious complications are common in comatose patients with resuscitated OHCA, with pneumonia rates as high as 50% in RCT populations.^{20,27} However, most deaths after cardiac arrest result primarily from severe anoxic brain injury, cardiovascular failure, or multiorgan dysfunction and not infectious causes. Therefore, it is unclear if a strategy of prophylactic antibiotics will improve overall outcomes in the OHCA population.

A small, randomized pilot study previously showed no improvement in postresuscitation pneumonia or other clinical outcomes with the use of prophylactic antibiotics in this population.⁴⁹ In the more recent Antibiotherapy During Therapeutic Hypothermia to Prevent Infectious Complications (ANTHARTIC) trial 194 patients with resuscitated OHCA, who presented initially with a shockable rhythm and underwent targeted temperature management (32°C–34°C), were randomly assigned to empiric antibiotic therapy (amoxicillin-clavulanate for 2 days) or placebo.⁵⁰ The primary outcome of ventilator-associated pneumonia during the first 7 days of hospitalization was significantly lower in the antibiotic prophylaxis group (19.2% vs 33.7%). However, patient-centred outcomes such as 28-day mortality, favourable neurological outcome, intensive care unit length of stay, or ventilator-free days were similar in both groups. Therefore, at present, the evidence does not support routine prophylactic antibiotic use after OHCA to improve patient-centred outcomes.

Expert Opinion: In patients who are intubated after a cardiac arrest, antibiotics should be reserved for patients with clinically suspected or confirmed bacterial pneumonia.

Treatment of seizures and high-risk electroencephalography patterns

Post cardiac arrest seizures and rhythmic and periodic electroencephalography (EEG) patterns (RPP), especially generalized periodic discharge (GPD) might be associated with a poor neurological prognosis.⁵¹ Whether suppression of these patterns improves outcomes remains unclear. Moreover, studies have reported good outcomes in patients treated for status epilepticus post OHCA provided no other unfavourable prognostic indicators were present.⁵² To further investigate this question, in the Treatment of Electroencephalographic Status Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial 172 comatose OHCA survivors with RPP on continuous EEG monitoring were randomized to stepwise antiseizure and sedation-based suppression for at least 48 hours or standard of care.⁵³ Complete suppression was achieved in 56% in the antiseizure arm and in 2% in the control arm. At 3 months, no differences in poor CPC scores of 3–5

(90% vs 92%) or mortality (80% vs 82%) were reported in the intervention and control groups, respectively. The study has several important considerations that preclude generalization to all patients with RPPs and seizures. The study was open-label, which might have influenced medical therapies and withdrawal of life support decisions. Mortality was high in both groups and mostly related to withdrawal of life support (including 7.5% within 24 hours postarrest) because of perceived poor prognosis suggesting the potential for positive verification bias. GPDs (considered a highly malignant pattern)⁵¹ were documented in 79% of the patients, 57% had myoclonus, and > 30% who underwent somatosensory evoked potentials had bilaterally absent bilateral N20s, suggesting that many of the RPP patterns being treated were epiphenomena of established severe hypoxic ischemic brain injury. Only 21% had non-GPD patterns and less than half of these patients had seizures. In a prespecified subgroup analysis, a nonsignificant trend toward better outcomes among patients with seizures was observed in the intervention arm.

Expert Opinion: In patients with resuscitated OHCA who remain comatose with electroencephalographic seizures with a continuous, nonsuppressed EEG background, treatment with antiseizure and sedative medications is reasonable, especially if no other indicators of poor prognosis are present.

Expert Opinion: In patients with resuscitated OHCA who remain comatose with GPDs on EEG are unlikely to benefit from GPD suppression.

Refractory Cardiac Arrest Treatment

The trials presented in this section were all conducted in the prehospital phase of care. Although patients were not enrolled after hospital admission, the strategies presented for refractory prehospital cardiac arrest interventions might also translate to the hospital phase of care. An approach to refractory cardiac arrest is summarized in [Figure 3](#).

Antiarrhythmic drug selection for patients with a refractory cardiac arrest with a shockable rhythm

Ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) refractory to external defibrillation is associated with decreased survival in patients with OHCA.⁵⁴ Small trials initially reported that the administration of amiodarone, compared with lidocaine or placebo, was associated with higher rates of ROSC and survival to hospital admission.^{55,56} However, the trials did not address whether amiodarone or lidocaine improved survival to hospital discharge or survival with favourable neurological outcomes. In the Amiodarone, Lidocaine, or Placebo Study (ALPS) study 3026 patients with an OHCA with shock-refractory VF or pVT after one or more defibrillation attempts were randomized to initial amiodarone (300 mg [150 mg in patients < 100 pounds] intravenous bolus), lidocaine (120 mg [60 mg in patients < 100 pounds] intravenous bolus), or placebo.⁵⁷ There was no significant difference among the groups in the primary outcome of survival to hospital discharge (24.4%, 23.7%, and 21.0%, respectively). The trial might have been underpowered because the overall and treatment-related survival differences reported in the 3 groups were less than previously estimated. The incidence of the secondary outcome of survival with favourable neurological function (defined as a modified Rankin score of ≤ 3) was also

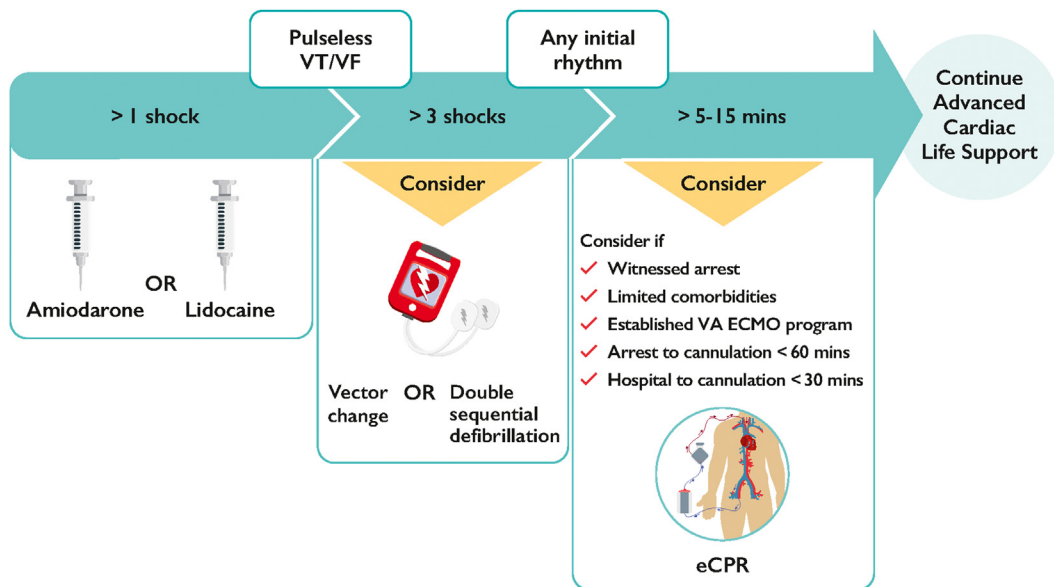


Figure 3. Strategies to potentially improve survival in patients with refractory cardiac arrest. eCPR, extracorporeal cardiopulmonary resuscitation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia.

similar in the amiodarone, lidocaine, and placebo groups (18.8%, 17.5%, 16.6%, respectively). Notably, the survival rate was higher with amiodarone (27.7%) and lidocaine (27.8%) compared with placebo (22.7%) among the 1934 patients with a bystander-witnessed arrest. Other notable pre-specified exploratory outcomes included higher rates of survival to hospital admission, fewer shocks needed to terminate arrhythmias after admission to hospital, a reduced need for CPR during hospitalization among patients who received amiodarone or lidocaine (vs placebo) in the shock-refractory arrest setting, and higher rates of ROSC at emergency department (ED) arrival with patients who received lidocaine compared with placebo. However, these differences did not translate into overall improved survival to hospital discharge or higher rates of favourable neurological outcomes. Also, it remains unclear whether these results can be extrapolated to the IHCA population.

Expert Opinion: In patients with an OHCA who remain in VF or pVT after 1 or more defibrillation attempts, either amiodarone or lidocaine may be administered, particularly in patients with witnessed arrest.

Defibrillation strategies patients with refractory cardiac arrest with shockable rhythms

High-quality compressions and early defibrillation are the only interventions that reduce mortality in patients with VF or pVT. Despite technological advances and public health initiatives, up to 45% of patients with shockable OHCA remain in refractory VF/ventricular tachycardia, typically defined as the absence of ROSC after 3 shocks at 2-minute intervals.^{58,59}

There have been small studies to evaluate different defibrillation strategies in patients with refractory shockable cardiac arrest including anterolateral vs anteroposterior pad placement, the use of paddles vs adhesive pads, or anatomic

chest compression (compressing the chest and left ventricle with pressure in the midchest at the inter nipple line) that showed no clear differences in outcomes.⁶⁰ In addition, 4 RCTs and a systematic review showed no difference in ROSC or mortality in comparisons of monophasic vs biphasic defibrillation.⁶⁰

New strategies such as double sequential defibrillation (2 shocks from 2 separate defibrillators with anterolateral and anteroposterior pad placement) have been postulated to improve defibrillation success by immediately delivering a second shock after the heart is preconditioned by the first. In the **Double Sequential External Defibrillation for Refractory Ventricular Fibrillation (DOSE VF)** trial 405 prehospital patients with refractory VF/ventricular tachycardia (no response to 3 standard shocks) were randomized to double sequential external defibrillation, or a vector change defibrillation (moving from anterolateral to anteroposterior), or standard anterolateral defibrillation.⁵⁹ ROSC rates in the double sequential, vector change, and standard defibrillation arms were 46.4%, 35.4%, 26.5%, respectively. In the intention to treat analysis, double sequential (30.4%) and vector change (21.7%) significantly improved the primary outcome of survival to hospital discharge compared with standard defibrillation (13.3%). Survival with good neurological recovery was only significantly higher with double sequential (27.4%) compared with standard defibrillation (11.2%). Although the study results are encouraging, the trial had several important methodological limitations, which included early termination because of COVID-19, a lower than expected event rate, a low fragility index, a high crossover rate (12.3%), and a per-protocol analysis that showed no outcome differences. Considering the large investment in infrastructure/training, stronger evidence is required to inform large-scale changes in advanced cardiac life support (ACLS). Nevertheless, consideration of these strategies might still be reasonable because of the low risk of the intervention along

with the potential for improved ROSC and patient survival if and when equipment and training is readily available.

Expert Opinion: In patients with OHCA and a refractory (defined as no termination after 3 shocks) shockable rhythm, double sequential or vector change defibrillation, when equipment and training is available, can be considered.

Extracorporeal membrane oxygenation-assisted CPR

With the increasing use of venoarterial extracorporeal membrane oxygenation (ECMO) in patients in cardiogenic shock, there has been a parallel increase of extracorporeal CPR (eCPR) for patients with refractory cardiac arrest. The applications of eCPR restores systemic perfusion thereby allowing time for targeted investigations and therapies. However, eCPR is resource- and cost-intensive, and RCTs of eCPR have yielded conflicting results.

In a small single-centre feasibility study with expedited transport to the ED for eCPR initiation (< 30 minutes from 911 call to ED arrival, for shockable and non-shockable rhythms), none of the 15 patients enrolled survived, including the 5 who received eCPR of whom 3 received eCPR within 30 minutes of arrival to the ED.⁶¹ In the single-centre **Advanced Reperfusion Strategies for Refractory Cardiac Arrest (ARREST)** trial eCPR was evaluated in 30 patients with refractory OHCA with VF refractory to 2 shocks and an anticipated transfer time < 30 minutes.⁶² Exclusion criteria included catheterization lab unavailability or contraindication to emergent angiography, trauma or burn-related injury, drowning, or known overdose. Upon arrival to hospital, patients were randomized to receive eCPR in the catheterization lab or standard ACLS in the emergency room. Survival to hospital discharge was higher with eCPR compared with standard ACLS (42.9% vs 6.7%). Survivors in the eCPR group had favourable functional status (CPC < 2) and modified Rankin score of < 2 up to 6 months post discharge. This trial was terminated early because of the superiority of eCPR and ethical concerns of withholding therapy.

In the Hyperinvasive Approach in Cardiac Arrest trial, an early invasive strategy (eCPR if ROSC was not obtained en route or upon hospital arrival) vs standard ACLS in 256 OHCA patients with shockable and nonshockable rhythms was evaluated.⁶³ Patients were identified by dispatch and randomized in the field via a call with an eCPR centre physician. The study included patients (18-65 years old) with a witnessed arrest of presumed cardiac cause, with a minimum of 5 minutes of ACLS without ROSC. Exclusion criteria included suspected or confirmed pregnancy, stroke, known severe chronic organ dysfunction, and bleeding diathesis or recent intracranial bleeding. The investigators reported no statistically significant difference in survival with good neurological outcome (CPC 1-2) at 180 days for the eCPR (31.5%) and standard treatment (22.0%) arms ($P = 0.09$). The risk of bleeding was higher with eCPR (31.0%) than in the standard group (14.5%). The trial was terminated early because of futility criteria.

In the recent multicentre **Early Initiation of Extracorporeal Life Support in Refractory Out of Hospital Cardiac Arrest (INCEPTION)** trial eCPR (upon hospital arrival) compared with standard ACLS in 160 patients aged 18-70 years with a witnessed cardiac arrest due to a shockable rhythm without

ROSC after > 15 minutes of CPR was evaluated.⁶⁴ The investigators excluded patients with > 60 minutes between initial cardiac arrest to initiation of cannulation, those with advanced comorbidities, or patients who had a valid do not resuscitate order. The investigators reported no significant difference in survival with a favourable neurological outcome (CPC 1-2) at 30 days (20.0% with eCPR vs 16.1% with ACLS; $P = 0.52$). Notably, the median time from initial cannulation to start of ECMO flows were longer in the INCEPTION trial compared with in the ARREST and Prague OHCA trials, potentially reflecting varying experience and logistics among the participating centres.

A summary of patient, prehospital, and hospital-based variables potentially associated with eCPR outcomes is presented in **Table 3**. No RCTs have evaluated eCPR for patients with IHCA.

Expert Opinion: eCPR should not be routinely used, but may be considered in highly selected patients with refractory cardiac arrest (> 5-15 minutes) with limited comorbidities and a witnessed cardiac arrest with a targeted cardiac arrest to cannulation time of < 60 minutes.

Expert Opinion: Extracorporeal CPR can be considered in centres with established venoarterial ECMO programs and formalized integrated eCPR clinical pathways.

Expert Opinion: If eCPR is considered, the target arrest to cannulation time is < 60 minutes and the target hospital arrival to cannulation time is < 30 minutes.

Cardiac Arrest Regionalized Systems of Care

A meta-analysis of observational studies showed that patients with OHCA who are admitted to high OHCA volume centres (> 40-100 OHCA cases per year) have lower mortality rates.⁶⁵ In addition, a prospective before and after study in the state of Arizona of OHCA emergency medical services triage to specialized cardiac arrest centres reported improved survival and favourable neurologic outcomes.⁶⁶ International societies have advocated for regionalization of OHCA care including timely transfer to centres capable of comprehensively centralizing OHCA care, but randomized studies were

Table 3. Patient, prehospital, and hospital-based variables potentially associated with eCPR outcomes

Patient variables	Target metrics
Associated with favourable outcomes	Prehospital
• Shockable rhythm • Reversible etiology • Witnessed arrest	• Estimated hospital transfer time < 30 minutes • Operationalized eCPR pathway within EMS • Advance care or critical care paramedics
Associated with poor outcomes	Intrahospital
• Older age • Comorbidities • Prolonged no or low flow time	• Cardiac arrest to eCPR flow time < 60 minutes • eCPR team available for cannulation on arrival • Established VA-ECMO program • Multidisciplinary team

eCPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical services; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

lacking.^{67,68} In the ARREST trial 862 adult patients in London, England with ROSC after an OHCA were randomized to expedited transfer to 1 of 7 catheterization laboratories at a cardiac arrest centre (with intensive care unit and cardiac surgery on-site) or to the geographically closest ED.⁶⁹ Exclusion criteria included STEMI, pregnancy, and do not resuscitate orders. In the cardiac arrest centre group, a greater proportion of patients were admitted to an intensive care unit (80% vs 69%), received mechanical ventilation (86% vs 76%), vasoactive support (72% vs 62%), and underwent coronary angiography 56% vs 37%). The primary end point of 30-day mortality occurred in 63% in the catheterization laboratory/cardiac arrest centre arm and 63% in the standard care arm (risk ratio 1.00; 95% confidence interval, 0.90–1.11; $P = 0.96$). In a subgroup analysis, patients younger than 57 years had a reduced risk of all-cause mortality in the cardiac centre arm and standard care favoured patients 57–71 years of age (P interaction = 0.0029). Limitations of the trial included its major urban setting and ED, which might not be generalizable to rural settings or lower-volume EDs. Second, the cardiac arrest centre criteria did not include the need for on-site ECMO, neurology, specialized electrophysiology studies, or structured neuroprognostication protocols, which might mitigate inappropriate early withdrawal of life-sustaining therapy.⁶⁸

Expert Opinion: Patients with ROSC after an OHCA who do not have a STEMI should be transported to the nearest ED. After initial evaluation and stabilization, it is reasonable to consider admission to a hospital capable of integrating their post-OHCA care with comprehensive on-site cardiovascular, neurology, critical care, and secondary prevention services depending on local geographic resources.

Current Knowledge Gaps and Future Directions

Many of the recent clinical trials in which patients resuscitated from a cardiac arrest were evaluated showed no differences in outcome among treatment groups. Nonetheless, the results are important insofar as they change clinical practice and potentially provide new directions for research in this complex and critically ill group of patients. Yet, many important questions remain unanswered.

The recent temperature control trials have cast doubt on the benefits of therapeutic hypothermia and the pendulum has swung toward normothermia. However, many issues regarding temperature targets remain. First, a temperature ceiling has not been established and an adequately powered trial is needed to determine if treatment of fever is beneficial in these patients. Second, the optimal window for a therapeutic benefit with temperature control remains unknown. Third, it is possible that the optimal temperature control strategy depends on patient or index event characteristics and the individualized risk of hypoxic ischemic brain injury. For this reason, there is a pressing need for better tools to assess the extent of baseline and ongoing brain injury.

Because most trials recruited patients with OHCA, more data are needed on patients with IHCA. New strategies to mitigate in-hospital complications such as infections and delirium are also needed. The recent studies help define appropriate physiological targets for the management of the post cardiac arrest population (eg, MAP, PaO₂, PaCO₂). That

said, will reliable bedside biomarker assays designed to quantitate ongoing brain injury further assist in adjusting these physiological targets on an individual basis?

The recent trials have shown no harm with a delayed cardiac catheterization strategy in patients without STEMI, but these trials excluded conditions such as cardiogenic shock and electrical instability. Trials designed to address these subsets are needed. Double sequential or vector change defibrillation along with antiarrhythmic drug selection in patients with refractory shockable rhythms appear promising, but data on the efficacy and safety in the in-hospital setting are also needed.

A strategy that includes eCPR in highly selected patients with refractory shock has been proposed for centres with advanced cardiac arrest programs. However, eCPR requires extensive resources, and because of the mixed results in the recent trials, this approach will likely be confined to centres equipped with highly skilled dedicated specialized teams. Hence, larger trials using refined inclusion criteria coupled with very fast cannulation times are needed to further define the role of eCPR.

As prognostication literature continues to evolve and show that post-arrest myoclonus and seizures are not uniformly suggestive of a poor prognosis, further direction will be required on how best to manage post-arrest patients with these disorders.

It could be argued that many studies have been negative thus far because we have not been defining different phenotypes and treating them accordingly. Precision medicine is a novel approach that considers patient variability rather than a “one-size-fits-all” approach.⁷⁰ Studies of the benefits of precision medicine using protocols tailored to the individual patient with a resuscitated cardiac arrest should be considered.

Because the trials that explored post-OHCA physiologic targets that are discussed in this CPU were neutral, it is possible that the on-scene OHCA response might be the most important determinant of neurological outcomes. Thus, renewed focus on early bystander CPR and defibrillation together (eg, smartphone-activated bystander responses, smartphone connectivity to dispatch services, automated external defibrillator drone delivery) with improvements in integrating all of the links in the chain of survival (ie, early activation of the emergency medical services, early bystander CPR, rapid defibrillation, early advanced life cardiac support, and integrated post cardiac care)^{71–75} might have the most potential to improve outcomes.

Conclusions

Our understanding of the optimal care of patients with a resuscitated cardiac arrest has been advanced through many of the hospital-based interventions discussed herein, but this has not resulted in improved survival and the outcomes of patients with OHCA remain poor. Nevertheless, the available literature discussed in this CPU has provided additional clarity regarding the use of post arrest management strategies in the prehospital and hospital setting. We have identified a number of key future research priorities for this acute, high risk, and treatment time-sensitive population. Achieving meaningful improvements in survival will also require an integrated multifaceted strategy to link the chain of survival from

bystander recognition, prehospital response, in-hospital care, through to postdischarge care. Finally, recognizing existing regional variations in care, we also advocate for a national knowledge translation initiative focused on education and adoption of contemporary best-care practices outlined in this CCS CPU, which has the potential to mitigate regional disparities and improve patient outcomes.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article because no individual patient was reviewed in the development of this CPU.

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References

1. Berdowski J, Berg RA, Tijssen JGP, 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. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update. *Circulation* 2021;143:e254-743.
3. Nishiyama C, Kiguchi T, Okubo M, et al. Three-year trends in out-of-hospital cardiac arrest across the world: second report from the International Liaison Committee on Resuscitation. *Resuscitation* 2023;186:109757.
4. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008;300:1423-31.
5. Girotra S, van Diepen S, Nallamothu BK, et al. Regional variation in out-of-hospital cardiac arrest survival in the United States. *Circulation* 2016;133:2159-68.
6. Sasson C, Magid DJ, Chan P, et al. Association of neighborhood characteristics with bystander-initiated CPR. *N Engl J Med* 2012;367:1607-15.
7. Møller SG, Wissenberg M, Møller-Hansen S, et al. Regional variation in out-of-hospital cardiac arrest: incidence and survival — a nationwide study of regions in Denmark. *Resuscitation* 2020;148:191-9.
8. Buick JE, Drennan IR, Scales DC, et al. Improving temporal trends in survival and neurological outcomes after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes* 2018;11:e003561.
9. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes* 2010;3:63-81.
10. van Diepen S, Girotra S, Abella BS, et al. Multistate 5-year initiative to improve care for out-of-hospital cardiac arrest: primary results from the HeartRescue Project. *J Am Heart Assoc* 2017;6:e005716.
11. Wong GC, van Diepen S, Ainsworth C, et al. Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology position statement on the optimal care of the postarrest patient. *Can J Cardiol* 2017;33:1-16.
12. Canadian Cardiovascular Society: Clinical Practice Updates: Purpose, Processes & Policies. Available at: https://ccs.ca/app/uploads/2021/07/CPU_PurposeProcessPolicies_Jan2020.pdf. Accessed June 5, 2023.
13. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. *N Engl J Med* 2019;380:1397-407.
14. Desch S, Freund A, Akin I, et al. Angiography after out-of-hospital cardiac arrest without ST-segment elevation. *N Engl J Med* 2021;385:2544-53.
15. Elfwen L, Lagedal R, Nordberg P, et al. Direct or subacute coronary angiography in out-of-hospital cardiac arrest (DISCO)—an initial pilot study of a randomized clinical trial. *Resuscitation* 2019;139:253-61.
16. Kern KB, Radsel P, Jentzer JC, et al. Randomized pilot clinical trial of early coronary angiography versus no early coronary angiography after cardiac arrest without ST-segment elevation. *Circulation* 2020;142:2002-12.
17. Hauw-Berlemont C, Lamhaut L, Diehl JL, et al. Emergency vs delayed coronary angiogram in survivors of out-of-hospital cardiac arrest: results of the randomized, multicentric EMERGE trial. *JAMA Cardiol* 2022;7:700-7.
18. Viana-Tejedor A, Andrea-Riba R, Scardino C, et al. Coronary angiography in patients without ST-segment elevation following out-of-hospital cardiac arrest. COUPE clinical trial. *Rev Esp Cardiol (Eng Ed)* 2023;76:94-102.
19. Al Lawati K, Forestell B, Binbraik Y, et al. Early versus delayed coronary angiography after out-of-hospital cardiac arrest without ST-segment elevation—a systematic review and meta-analysis of randomized controlled trials. *Crit Care Explor* 2023;5:e0874.
20. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021;384:2283-94.
21. Glover GW, Thomas RM, Vamvakas G, et al. Intravascular versus surface cooling for targeted temperature management after out-of-hospital cardiac arrest - an analysis of the TTM trial data. *Crit Care* 2016;20:381.
22. De Fazio C, Skrifvars MB, Søreide E, et al. Intravascular versus surface cooling for targeted temperature management after out-of-hospital cardiac arrest: an analysis of the trial. *Crit Care* 2019;23:61.
23. 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.
24. Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline. *Circulation* 2016;134:797-805.
25. Scales DC, Cheskes S, Verbeek PR, et al. Prehospital cooling to improve successful targeted temperature management after cardiac arrest: a randomized controlled trial. *Resuscitation* 2017;121:187-94.

26. Nordberg P, Taccone FS, Truhlar A, et al. Effect of trans-nasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest. *JAMA* 2019;321:1677-85.
27. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197-206.
28. The 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.
29. 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.
30. Le May M, Osborne C, Russo J, et al. Effect of moderate vs mild therapeutic hypothermia on mortality and neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest. *JAMA* 2021;326:1494-503.
31. Lascarrou J-B, Merdji H, Le Gouge A, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. *N Engl J Med* 2019;381:2327-37.
32. Wolfrum S, Roedel K, Hanebutte A, et al. Temperature control after in-hospital cardiac arrest: a randomized clinical trial. *Circulation* 2022;146:1357-66.
33. Kirkegaard H, Søreide E, de Haas I, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest. *JAMA* 2017;318:341-50.
34. Hassager C, Schmidt H, Möller JE, et al. Duration of device-based fever prevention after cardiac arrest. *N Engl J Med* 2023;388:888-97.
35. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. *Circulation* 2008;118:2452-83.
36. Kjaergaard J, Möller JE, Schmidt H, et al. Blood-pressure targets in comatose survivors of cardiac arrest. *N Engl J Med* 2022;387:1456-66.
37. Ameloot K, De Deyne C, Eertmans W, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. *Eur Heart J* 2019;40:1804-14.
38. Jakkula P, Pettilä V, Skrifvars MB, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med* 2018;44:2091-101.
39. Ameloot K, Genbrugge C, Meex I, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop 'one-size-fits-all' hemodynamic targets? *Resuscitation* 2015;90:121-6.
40. Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med* 2022;387:1467-76.
41. Bernard SA, Bray JE, Smith K, et al. Effect of lower vs higher oxygen saturation targets on survival to hospital discharge among patients resuscitated after out-of-hospital cardiac arrest. *JAMA* 2022;328:1818-26.
42. Robba C, Badenes R, Battaglini D, et al. Oxygen targets and 6-month outcome after out of hospital cardiac arrest: a pre-planned sub-analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial. *Crit Care* 2022;26:323.
43. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. *Stroke* 1997;28:1569-73.
44. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: the impact of hypercapnia. *Resuscitation* 2016;102:11-6.
45. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation* 2016;104:83-90.
46. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. *Circulation* 2013;127:2107-13.
47. 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.
48. Eastwood G, Nichol AD, Hodgson C, et al. Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. *N Engl J Med* 2023;389:45-57.
49. Ribaric SF, Turel M, Knafelj R, et al. Prophylactic versus clinically-driven antibiotics in comatose survivors of out-of-hospital cardiac arrest—a randomized pilot study. *Resuscitation* 2017;111:103-9.
50. François B, Cariou A, Clere-Jehl R, et al. Prevention of early ventilator-associated pneumonia after cardiac arrest. *N Engl J Med* 2019;381:1831-42.
51. Fordyce BC, Kramer AH, McCredie V, et al. Neuroprognostication in the post cardiac arrest patient: a Canadian Cardiovascular Society position statement. *Can J Cardiol* 2023;39:366-80.
52. Beretta S, Coppo A, Bianchi E, et al. Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. *Neurology* 2018;91:E2153-62.
53. Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans C, et al. Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. *N Engl J Med* 2022;386:724-34.
54. Berdowski J, ten Haaf M, Tijssen JG, Chapman FW, Koster RW. Time in recurrent ventricular fibrillation and survival after out-of-hospital cardiac arrest. *Circulation* 2010;122:1101-8.
55. 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.
56. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002;346:884-90.
57. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med* 2016;374:1711-22.
58. Holmén J, Hollenberg J, Claesson A, et al. Survival in ventricular fibrillation with emphasis on the number of defibrillations in relation to other factors at resuscitation. *Resuscitation* 2017;113:33-8.
59. Cheskes S, Verbeek PR, Drennan IR, et al. Defibrillation strategies for refractory ventricular fibrillation. *N Engl J Med* 2022;387:1947-56.
60. Faddy SC, Jennings PA. Biphasic versus monophasic waveforms for transthoracic defibrillation in out-of-hospital cardiac arrest. *Cochrane Database Syst Rev* 2016;2:Cd006762.
61. Hsu CH, Meurer WJ, Domeier R, et al. Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest (EROCA): results of a randomized feasibility trial of expedited out-of-hospital transport. *Ann Emerg Med* 2021;78:92-101.

62. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST). *Lancet* 2020;396:1807-16.
63. Belohlavek J, Smalcova J, Rob D, et al. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest. *JAMA* 2022;327:737-47.
64. Suverein MM, Delnoij TSR, Lorusso R, et al. Early extracorporeal CPR for refractory out-of-hospital cardiac arrest. *N Engl J Med* 2023;388:299-309.
65. Goh AXC, Seow JC, Lai MYH, et al. Association of high-volume centers with survival outcomes among patients with nontraumatic out-of-hospital cardiac arrest: a systematic review and meta-analysis. *JAMA Netw Open* 2022;6:e2214639.
66. Spaite DW, Bobrow BJ, Stolz U, et al. Statewide regionalization of post-arrest care for out-of-hospital cardiac arrest: association with survival and neurologic outcome. *Ann Emerg Med* 2014;64:496-506.
67. Nichol G, Aufderheide TP, Eigel B, et al. Regional systems of care for out-of-hospital cardiac arrest. *Circulation* 2010;121:709-29.
68. Sinning C, Ahrens I, Cariou A, et al. The cardiac arrest centre for the treatment of sudden cardiac arrest due to presumed cardiac cause - aims, function and structure. *Eur Heart J Acute Cardiovasc Care* 2020;9(4 suppl):S193-202.
69. Patterson T, Perkins GD, Perkins A. Expedited transfer to a cardiac arrest centre for non-ST-elevation out-of-hospital cardiac arrest (ARREST). *Lancet* 2023;402:1329-37.
70. Shrestha GS, Suarez JI, Hemphill JC. Precision medicine in neurocritical care. *JAMA Neurol* 2018;75:1463-4.
71. Andelius L, Malta Hanse C, Lippert FK, et al. Smartphone activation of citizen responders to facilitate defibrillation in out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2020;76:43-53.
72. Allan KS, O'Neill E, Currie MM, Lin S, Sapp JL, Dorian P. Responding to cardiac arrest in the community in the digital age. *Can J Cardiol* 2022;38:491-501.
73. Rosamond WD, Johnson AM, Bogle BM, et al. Drone delivery of an automated external defibrillator. *N Engl J Med* 2020;383:1186-8.
74. Fordyce CB, Grunau BE, Guan M, et al. Long-term mortality, readmission, and resource utilization among hospital survivors of out-of-hospital cardiac arrest. *Can J Cardiol* 2022;38:1719-28.
75. van Diepen S, Jentzer JC. Linking data through the chain of survival: the potential for better population-based out-of-hospital cardiac arrest epidemiology, process of care, risk prediction, and outcomes. *Can J Cardiol* 2022;38:1729-31.
76. Wong GC, Welsford M, Ainsworth C, et al. 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the acute management of ST-elevation myocardial infarction: focused update on regionalization and reperfusion. *Can J Cardiol* 2019;35:107-32.

Supplementary Material

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