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Therapeutic Hypothermia After Cardiac Arrest

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Case 1

A 63-year-old man was at home watching television when his roommate noticed him gurgle and lose consciousness. He started cardiopulmonary resuscitation (CPR) and called emergency medical services. The initial rhythm was ventricular fibrillation (VF). A perfusing rhythm was obtained within 15 minutes, but there were repeated episodes of VF requiring multiple defibrillations and repeated episodes of cardiopulmonary resuscitation. With restoration of circulation, he was not responsive. Initial ECG revealed inferior ST-segment elevations. In the emergency department, he required further defibrillations and was then taken for primary coronary intervention. Emergency medical personnel started intravenous iced saline, and ice packs were placed while he was in the emergency department and remained in place during cardiac catheterization. A stent was placed in a thrombotic right coronary artery. On arrival at the cardiac intensive care unit, surface cooling pads were placed, and he received therapeutic hypothermia (TH) for 24 hours, at which point he was rewarmed. He initially remained comatose, but by day 5, he was awake, alert, and interactive. He was discharged home.

Case 2

A 54-year-old woman was found unresponsive by coworkers. It was not clear how long she had been down. Cardiopulmonary resuscitation was started, and an automated external defibrillator recommended no shock. Emergency medical personnel identified asystole as the initial rhythm. After 25 minutes of advanced cardiac life support, a perfusing rhythm was obtained. There were no ischemic changes on the ECG. She was unresponsive on arrival at the emergency department. Computed tomographs of the head and pulmonary arteries were normal. She received TH for 24 hours and, when rewarmed, had no change in her mental status by day 5. Magnetic resonance imaging did not reveal any major abnormalities, but she had incomplete recovery of brainstem

reflexes and bilaterally absent sensory stimulatory evoked potentials. After extensive discussions with her family, continued support was withdrawn, and she expired.

Cardiac arrest (CA) remains one of the most unexpected, dramatic, and life-threatening events in medicine. Survival and neurological recovery vary widely, depending on whether an arrest was witnessed or unwitnessed and the initial cardiac rhythm during resuscitation. Even among patients with successful return of spontaneous circulation (ROSC) who are admitted to an intensive care unit, survival until hospital discharge has historically been <10%.[1] Fortunately, recent data suggest a steady trend toward improved survival. However, in 2009, mortality remained at almost 60%.[2,3]

Improvements in the survival and neurological outcomes of patients with CA have focused on 2 principal areas of treatment. The first is increased education to improve immediate post-CA perfusion via national efforts promoting the 4 links in the chain of survival that include early access to emergency medical care, early cardiopulmonary resuscitation, early defibrillation, and early advanced cardiac life support.[4]

The second area is greater emphasis on postresuscitation care, which includes optimizing oxygenation and ventilation, avoiding hypotension (systolic blood pressure <90 mm Hg), treating immediate precipitants of CA such as acute coronary ischemia, and initiating TH when appropriate.[5] The American Heart Association (Figure 1), the International Liaison Committee of Resuscitation, and the European Resuscitation Council recently published guidelines and recommendations covering the entire spectrum of postresuscitation care.[5–7] This review focuses on the practical aspects of implementing TH, one of the key therapeutic procedures in postresuscitation care.

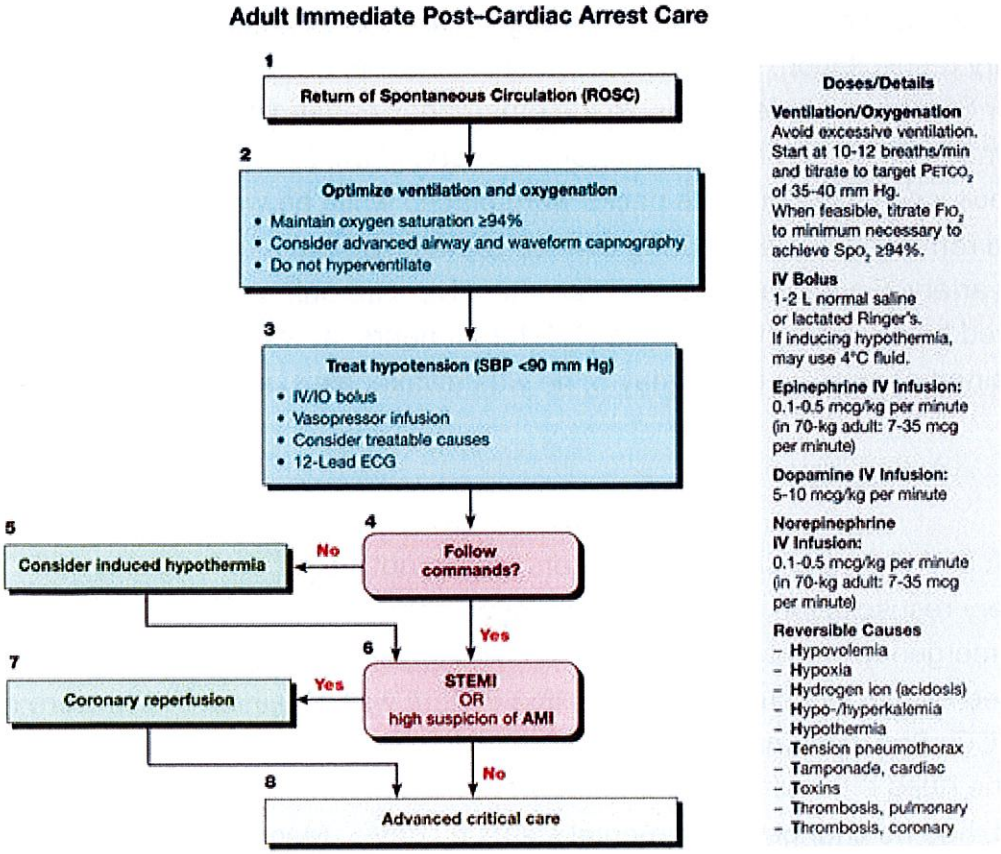

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Figure 1. American Heart Association post–cardiac arrest care algorithm. Reprinted from Peberdy et al.[5]

Anoxia, Reperfusion, and the Role for Hypothermia

Damage from cerebral anoxia comes in stages. Within seconds of anoxia, important cerebral activities are compromised, and within minutes, glucose and ATP are depleted and cells begin to lose structural integrity, leading to mitochondrial damage and loss of calcium hemostasis.[8] Increased levels of intracellular calcium and sustained stimulation by excess release of the excitatory neurotransmitter glutamate precipitate immediate cellular necrosis or eventual programmed cell death (apoptosis). Restoration of adequate oxygenation, which in the case of CA corresponds to reperfusion, limits ongoing anoxic injury. However, it does not blunt continued cellular damage and death resulting from reperfusion injury, which occurs over the subsequent hours and days after successful resuscitation. During reperfusion injury, reoxygenation promotes high concentrations of reactive oxygen species, which, when coupled with other inflammatory processes, further exacerbate endothelial dysfunction, vasomotor dysregulation, edema, tissue-level hypoxia despite adequate arterial oxygenation, and subsequent neurological damage.

Hypothermia tempers the post-CA syndrome inflammatory cascade and aborts activated programmed cell death pathways by reducing the release of excitatory amino acids and free radicals and by minimizing the intracellular consequences of excitotoxin exposure.[8] Moreover, hypothermia decreases cerebral metabolic rate of oxygen, cerebral blood volume, and intracranial pressure, thereby improving the oxygen supply-and-demand mismatch.

Clinical Evidence for TH

Two studies published simultaneously in 2002 reported the clinical benefit of TH compared with standard therapy in a total of 352 patients who were comatose after successfully resuscitated VF arrest.[9,10] In both studies, 12 to 24 hours of TH improved neurological outcomes; in the larger study, it reduced mortality by >25%. On the basis of these 2 studies, TH is now considered standard of care in the treatment of patients successfully resuscitated from a ventricular tachycardia (VT/VF) arrest and is recommended as a reasonable option for patients with CA from a nonshockable rhythm. Given the small size of these 2 studies, the differences in protocols, the inclusion of patients with VF only, and the absence of any subsequent well-powered randomized trials of TH, many recommendations on the specifics of TH implementation are based on observational studies and expert opinion.

Indications and Contraindications for TH

Initial Rhythm

Current AHA practice guidelines recommend TH with a goal temperature of 32°C to 34°C for 12 to 24 hours in patients successfully resuscitated after CA as a Class I recommendation if the arrest is from VT/VF and as Class IIb recommendation for CA from other nonshockable rhythms.[5] The

European Resuscitation Council guidelines for resuscitation recommend TH for all comatose survivors of CA regardless of initial rhythm, although the guidelines acknowledge a lower level of evidence for TH in patients with a CA from nonshockable rhythms (Table).[7]

Table. Summary of Practice Guideline Recommendations for Therapeutic Hypothermia

American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (2010)[5]
Comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32°C–34°C (89.6°F–93.2°F) for 12 to 24 h (*Class I; Level of Evidence: B*). Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole (*Class IIb; Level of Evidence: B*).Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C [89.6°F]) after resuscitation from cardiac arrest during the first 48 h after ROSC (*Class III; Level of Evidence: C*).
European Resuscitation Council Guidelines for Resuscitation (2010)[7]
Use of therapeutic hypothermia should include comatose survivors of cardiac arrest associated initially with nonshockable rhythms and shockable rhythms. The lower level of evidence for use after cardiac arrest from nonshockable rhythms is acknowledged.
International Liaison Committee on Resuscitation (2008)[6]
Therapeutic hypothermia should be part of a standardized treatment strategy for comatose survivors of cardiac arrest.

ROSC indicates return of spontaneous circulation; and VF, ventricular fibrillation.

Whether to initiate TH in patients whose initial rhythm was not VT or VF arrest remains one of the most vexing clinical decisions because the benefit of TH remains uncertain in this population. Overall, patients with non-VT/VF arrest have much worse prognoses compared with patients with VT/VF arrest, either because they tend to have more comorbidities or simply because the nonshockable rhythms indicate a more prolonged period of nonperfusion.[2] TH in patients with ROSC after a nonshockable CA should be considered on a case-by-case basis, taking into account the cause of arrest, time until cardiopulmonary resuscitation and ROSC, and underlying comorbidities.

Defining Comatose

TH is indicated for patients who remain comatose after ROSC. However, the definition of comatose varies between studies and further complicates the question of who is eligible for TH. Rather than using strict cut points based on quantitative criteria (such as the Glasgow Coma Scale), current recommendations are that TH be considered for any patient who after ROSC fails to meaningfully respond to verbal commands. This definition will likely include many patients who may not otherwise

be considered comatose but who may still suffer significant neurological damage that could be limited by TH.

Contraindications

There are few true contraindications for TH. Medical conditions in which the risk may be excessive include documented intracranial hemorrhage, severe hemorrhage leading to exsanguination, hypotension refractory to multiple vasopressors, severe sepsis, and pregnancy. Given that most patients from CA die of neurological consequences for which TH is the only proven beneficial therapy, the decision to withhold TH must be weighed carefully.

Initiation of TH

There are 4 stages of TH: initiation, maintenance, rewarming, and return to normothermia (Figure 2).[8] TH should be initiated as soon as possible after the ROSC with a target temperature of 32°C to 34°C. There is a 20% increase in mortality for every hour of delay in the initiation of TH.[11] There are multiple methods to induce and maintain TH. Ice bags and cooling blankets are simple and effective but difficult to titrate to a target temperature. Temperature-regulated surface and endovascular devices that circulate cold water allow easier temperature control during the maintenance phase and prevent rapid temperature changes during rewarming.[12] Several liters of cooled intravenous saline will promptly decrease temperatures by 1°C within 30 minutes,[13] will help prevent postresuscitation hypotension, and can be delivered by first responders or emergency department personnel. Our institution uses a combination of ice packs and standard cooling blankets for rapid initiation of TH with a transition to a temperature-regulated surface cooling device to maintain target temperatures through maintenance and rewarming.[14] During the maintenance phase, temperature fluctuations should be minimized to <0.5°C.

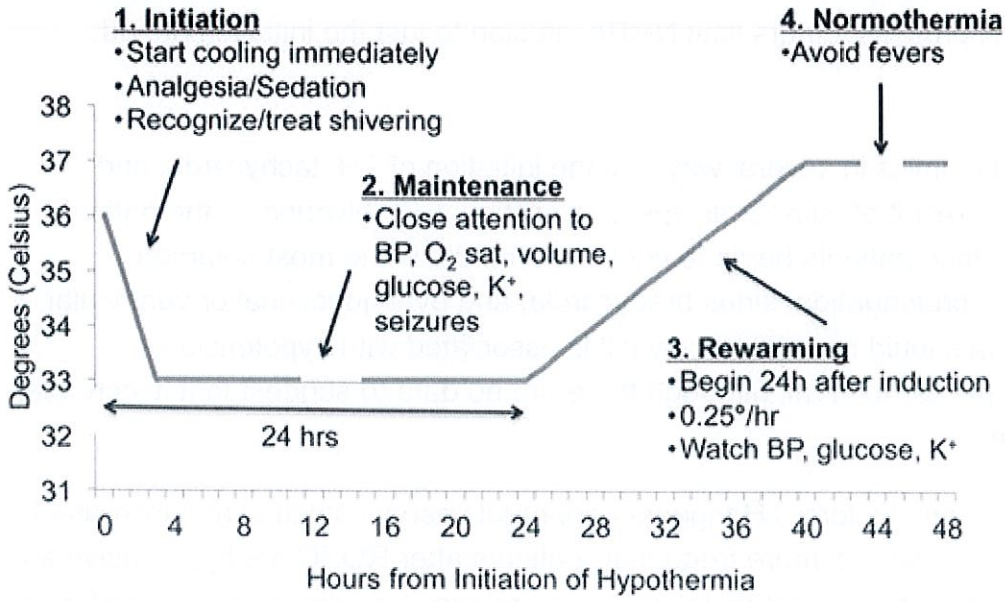

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Figure 2. Phases of hypothermia. BP indicates blood pressure; K^+, serum potassium concentrations; O_2 sat, oxygen saturation; and SBP, systolic blood pressure.

Physiological Consequence and Complications of TH

Shivering

All patients receiving TH should receive low-dose, continuous infusions of both a sedative and an analgesic agent to prevent any potentially painful sensation or discomfort and to suppress shivering. Preference should be given to agents with short half-lives (eg, propofol or midazolam for sedatives and fentanyl or hydromorphone for analgesia) because hypothermia reduces the clearance of most sedatives, analgesics, and neuromuscular blockade agents (NMBAs). This strategy will facilitate neurological assessments after return to normothermia.

Shivering, a natural reaction to cooling, occurs in most patients receiving TH. Shivering should be recognized early and treated aggressively because it increases the metabolic rate and prevents or delays achieving target temperature. Shivering typically occurs during changes in temperature, between 35°C and 37°C. Once a patient achieves the target temperature of 32°C to 34°C, shivering is less common. Nonpharmacological techniques that raise cutaneous temperatures such as wrapping the face, hands, and feet with warm blankets or even placing a warming blanket over the torso are effective at preventing shivering. Magnesium sulfate may raise the shivering threshold, so we give an initial 4-g bolus to all patients receiving TH.[15] If shivering persists, rapid uptitration of anesthetics with analgesic boluses is effective, although some patients require NMBAs to completely suppress shivering. We have found that selective use of NMBA boluses (3 doses of cisatracurium 0.15 mg/kg IV every 10 minutes) is often effective and allows patients to achieve target temperature without a continuous NMBA infusion. Some centers use continuous NMBAs in all patients during the entire TH process; others limit NMBA infusion to just the initiation period.

Hemodynamics

Hypothermia affects hemodynamics in several ways. At the initiation of TH, tachycardia and hypertension may occur as a result of cutaneous vasoconstriction and shivering as the patient attempts to conserve heat. Once patients begin to cool, bradycardia is the most common arrhythmia, together with PR prolongation, sinus bradycardia, and even junctional or ventricular escape rhythms. Bradycardia should be treated only if it is associated with hypotension. Hypothermia also prolongs the QT interval, although there are no data to suggest that it increases the risk of torsade de pointes.

Blood pressure depends on many factors. TH triggers peripheral vasoconstriction and increased systemic vascular resistance. However, more frequently, patients after ROSC are hypotensive as a result of vasodilatation from a postresuscitation inflammatory release and direct cardiac dysfunction from ischemia (either global or regional). Hypotension should be aggressively reversed to avoid cerebral hypotension and recurrent hypoperfusion.[16] On the basis of data from patients with intracranial hemorrhage, a mean arterial pressure should be maintained higher than typically

required in order to reduce vasoconstriction and to improve cerebral perfusions, with mean arterial pressure goals of 80 to 100 mm Hg. Hypotension occurs frequently during rewarming. When required, the decision to initiate and the choice of pressors should be based on the individual hemodynamic requirements of the patient.

Patients who have ROSC and any degree of vasoplegia are effectively intravascularly depleted and usually require a significant volume of resuscitation with several liters of saline. Targeting a goal central venous pressure of at least 10 to 12 mm Hg often prevents hypotension and reduces vasopressor requirements.

If significant dysrhythmias or hemodynamic instability develops, patients should be treated with standard medical procedures. If the instability persists and TH is thought either to be the cause of the instability (eg, profound bradycardia) or to potentially be worsening the instability (eg, bleeding), the target goal temperature can be increased to 34°C to 35°C (93°F to 95°F) at a rate of 0.25°C (0.5°F) per hour. The full TH protocol often can be completed at a slightly higher target temperature.

Oxygenation/Ventilation

All patients receiving TH require mechanical ventilation with a goal arterial oxygen saturation of 94% to 96%. FiO_2 should be reduced as soon as possible to avoid prolonged oxygen saturations of 100%, which may further exacerbate reactive oxygen production and neurological damage.[17] The ventilatory goal is to maintain normocarbia and to avoid both hyperventilation and hypoventilation.

Glucose Control

Hyperglycemia is common during TH as lower temperatures decrease insulin secretion and increase insulin resistance. Blood glucose should be measured at least hourly during TH to avoid hypoglycemia, especially in patients receiving intravenous insulin, and during rewarming, when glucose levels can fall precipitously. Given these concerns, hyperglycemia typically does not require treatment until glucose levels exceed 200 mg/mL. It is prudent to stop intravenous insulin as soon as glucose levels fall below 200 mg/mL unless the patient has type I diabetes mellitus.

Potassium

Hypothermia will lower serum potassium levels, primarily by promoting inward cellular potassium flux, although hypothermia also induces a mild diuresis with concurrent electrolyte wasting. Serum electrolytes should be measured at regular intervals (every 4–6 hours). Potassium should be repleted to maintain levels above 3.5 mEq/L. Rewarming reverses the potassium flux and increases serum levels, so repletion should be held 4 hours before rewarming begins. In our experience, clinically significant hyperkalemia is unusual in patients with preserved renal function.

Infection

Infections are common in patients who have a CA and particularly in those receiving TH, which suppresses cellular and antibody immunity. Overall, more than two thirds of patients who have ROSC after CA and are treated with TH experience some infectious complication. Pulmonary infections, most likely related to cardiopulmonary resuscitation, emergent intubation, and mechanical ventilation, are most common, followed by bloodstream and catheters infections.

Fortunately, despite a higher risk of infection in TH, infection does not appear to increase mortality.[18,19] Patients who receive TH should have surveillance cultures, and if an infection is suspected, prompt, broad-spectrum antibiotics that cover community- and hospital-acquired pathogens should be initiated.

Rewarming

Rewarming begins 12 to 24 hours after the initiation of cooling. In our institution, we begin after 24 hours, although other institutions begin 24 hours after the target temperature is achieved. The greatest risks during rewarming are hypotension, hyperkalemia, and hypoglycemia. Rewarming should be slow, with a target rate of 0.25°C (0.5°F) every hour until the patient returns to normothermia (37°C [98.6°F]). It will take ≈12 to 16 hours to rewarm. After normothermia is achieved, the goal of therapy is to maintain a temperature of 37°C and to avoid hyperthermia. Post-CA fevers are particularly harmful and associated with worse neurological outcomes. We use the same surface cooling pads to maintain normothermia for an additional 48 hours.

Prognosis After TH

Most patients resuscitated after CA will die of neurological complications.[20] Providing appropriate prognosis after CA remains one of the most challenging aspects of caring for patients who receive TH. It is important to begin the conversation with families early in the hospital course so that they aware of the overall poor prognosis after CA. However, there are few, if any, clinical data that will help guide the discussion during the first few days. Although the evidence is still preliminary, recent data suggest that meaningful neurological recovery in patients who received TH may occur late. Specifically, the often-cited Levy criteria,[21] which rely on a 72-hour neurological assessment after CA, may not be applicable in patients receiving TH and may not be appropriate for gauging prognosis.

Compounding the problem is a lack of sensitive and specific tests to help assess prognosis. Many studies are confounded by a self-fulfilling prophecy: Patients with any perceived poor prognostic indicator are not given the chance of survival. Moreover, most tests are insufficiently powered to adequately exclude a tolerable false-positive rate. Current AHA guidelines recognize this dilemma and recommend that neurological prognostication should be delayed until at least 72 hours after the return to normothermia (ie, ≈5 days after CA),[5] although some have argued that even this is too early, with reports of meaningful neurological recovery weeks after CA.

Neurological testing relies on physical examination, electroencephalography, neuroimaging, sensory stimulatory evoked potentials, and less commonly, biomarkers. The absence of any abnormal finding in these tests alone does not indicate a good prognosis, but the presence of 1 abnormal finding does not automatically indicate a poor outcome. Two abnormal findings, however, such as incomplete recovery of brainstem reflexes and bilaterally absent sensory stimulatory evoked potentials have a higher specificity for poor neurological recovery.[22] Developing validated prognostic tools or scores for neurological recovery in patients receiving TH is one of the most pressing research needs in postresuscitation care.

An Integrated Approach to Improve Neurological Recovery

Delivering efficient, coordinated, and effective postresuscitation care requires hospital-wide initiatives, interdisciplinary cooperation, and repeated programs aimed at education and quality improvement. As with any low-frequency, high-complexity procedure, the quality of TH will be improved by the use of established guidelines of care, with standardized-order templates and checklists to ensure that all tasks are completed in a timely fashion. The guideline of care for TH at our institution, summarized in Figure 3, provides a practical, goal-directed algorithm designed by an interdisciplinary task force.

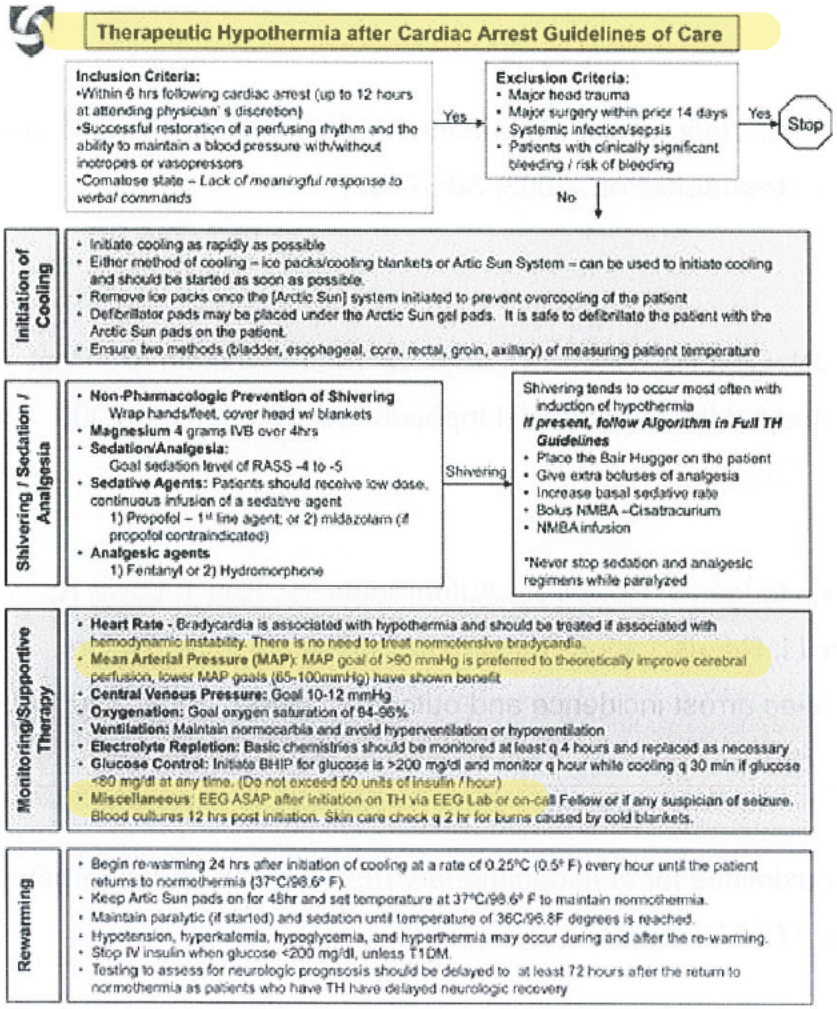

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Figure 3. An example of a hospital-based protocol for therapeutic hypothermia (TH) that summarizes key steps for initiation and implementation of hypothermia. IVB indicates intravenous bolus; NMBA, neuromuscular blocking agent; and T1DM, type 1 diabetes mellitus.

Disclosures

Dr Scirica reports that the Thrombolysis in Myocardial Infarction (TIMI) Study Group, where he works, has received research grants via Brigham and Women's Hospital from Abbott, AstraZeneca, Amgen, Bayer Healthcare, Bristol-Myers Squibb, Daichii Sankyo, Eli Lilly, Eisai, Gilead,

GlaxoSmithKline, Merck (SPRI), Novartis, Pfizer, Roche (Diagnostics), Sanofi Aventis, and Johnson & Johnson. He has served as a consultant for Lexicon, Arena, St. Jude, Gilead, and Eisai.

Footnotes

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