Therapeutic Hypothermia After In-hospital Cardiac Arrest: A Critique

Eugene A. Hessel II, MD, FACS

More than 210,000 in-hospital cardiac arrests occur annually in the United States. Use of moderate therapeutic hypothermia (TH) in comatose survivors after return of spontaneous circulation following out-of-hospital cardiac arrest (OOH-CA) caused by ventricular fibrillation or pulseless ventricular tachycardia is recommended strongly by many professional organizations and societies. The use of TH after cardiac arrest associated with nonshockable rhythms and after in-hospital cardiac arrest (IH-CA) is recommended to be considered by these same organizations and is being applied widely. The use in these latter circumstances is based on an extrapolation of the data supporting its use after out-of-hospital cardiac arrest associated with shockable rhythms. The purpose of this article is to review the limitations of existing data supporting these extended application of TH after cardiac arrest and to suggest approaches to this dilemma. The data supporting its use for OOH-CA appear to this author, and to some others, to be rather weak, and the data supporting the use of TH for IH-CA appear to be even weaker and to include no randomized controlled trials (RCTs) or supportive observational studies. The many reasons why TH might be expected to be less effective following IH-CA are reviewed. The degree of neurologic injury may be more severe in many of these cases and, thus, may not be responsive to TH as currently practiced following OOH-CA. The potential adverse consequences of the routine use of TH for IH-CA are listed and include complications associated with TH, interference with diagnostic and interventional therapy, and use of scarce personnel and financial resources. Most importantly, it inhibits the ability of researchers to conduct needed RCTs. The author believes that the proper method of providing TH in these cases needs to be better defined. Based on this analysis the author concludes that TH should not be used indiscriminately following most cases of IH-CA, and instead clinicians should concentrate their efforts in conducting high-quality large RCTs or large-scale, well-designed prospective observation studies to determine its benefits and identify appropriate candidates.

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It is estimated that more than 210,000 in-hospital (IH) cardiac arrests (CA) occur annually in the United States and the rate is increasing. A study by the American Heart Association (AHA) Get with the Guidelines (GWTG)-Resuscitation Investigators of 84,625 in-hospital cardiac arrests in 553 hospitals between 2001 and 2009 reported that only 17% survived to discharge and of the survivors 32.8% had clinically significant neurologic disability and 10.8% had severe neurologic disability. In 79.2% the initial rhythm was nonshockable (ie, asystole or pulseless electrical activity [PEA]), and this percentage increased over the 10-year period. Survival was about one-third as high in patients with nonshockable rhythms (about 12% vs 35%). This has led to the search for methods of improving these terrible results and to early adoption of the use of therapeutic hypothermia (TH) for in-hospital cardiac arrest (IH-CA). One jury of experts representing 5 professional organizations has opined that the term “therapeutic hypothermia” should be discarded in favor of “targeted temperature management” (TTM) although in this paper the former terminology will be used.

Starting in 2003 moderate therapeutic hypothermia (TH) has been recommended strongly by many professional organizations after return of spontaneous circulation (ROSC) for patients who remain comatose after out-of-hospital (OOH) cardiac arrest (CA) because of “shockable rhythms” (ventricular fibrillation [VF] or pulseless ventricular tachycardia [PVT]). These organizations include the International Liaison Committee on Resuscitation; the European Resuscitation Council; the International Consensus on Cardiopulmonary Resuscitation; the American Heart Association (AHA); the National Institute for Health and Clinical Excellence (NICE; www.nice.org.uk/guidance/IP/863/overview); a combined jury of representatives of the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the Societe de Reanimation de Langue Francaise; the Australian Resuscitation Council; the Scandinavian Society of Anaesthesiology and Intensive Care Medicine; and the Canadian Association of Emergency Physicians. Many of these organizations also have recommended that TH be considered after resuscitation from other cardiac rhythms and after in-hospital cardiac arrest (IH-CA), which probably is responsible for the widespread use of TH after CA in circumstances beyond those employed in the initial 2 major randomized controlled trials (RCTs).

The use of TH after IH-CA is based on the laudable effort to improve its poor prognosis (death and poor neurologic function) and extrapolation of the data supporting its use after out-of-hospital cardiac arrest (OOH-CA). Unfortunately, as will be

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reviewed later, even that evidence is weak. This author believes that the evidence does not support the widespread use of TH after IH-CA and that this recommendation needs to be reassessed. The purpose of this article is to identify the limitations of the existing data supporting the use of TH after CA, especially after IH-CA, which often is associated with nonshockable rhythms and of noncardiac etiology, and to suggest possible responses to this limited evidence.

What is this author’s justification for challenging the recommendations of these many professional organizations? First, because their recommendations largely are based on low quality and low level of evidence and on expert opinion, and second, because this would not be the first time that guidelines generated by prestigious societies have been wrong. Some examples include prophylactic perioperative beta-blockers, prophylactic aprotinin to reduce bleeding after cardiac surgery, intensive insulin therapy, and use of activated protein C (Xigris\textsuperscript{\textregistered}; Eli Lilly, Indianapolis, IN) in severe sepsis.

But if the evidence is weak, then why has the use of TH after cardiac arrest been adopted so rapidly and widely? This likely is due to at least 4 factors: The strong desire to do something to improve the poor outcome after resuscitation from cardiac arrest, the enthusiasm and strong conviction of many investigators, practitioner and hospital competition, and promotion by the “medical-industrial complex.” Hospitals and practitioners have published articles in the lay press “advertising” and promoting their use of this modality, often accompanied by dramatically successful case reports, but exaggerating the scientific evidence of its benefit. This is known as “spin,” which has been explored by Yavchitz et al.\textsuperscript{14}

The scientific hypothesis underlying the use of TH is that postarrest ischemia-reperfusion results in further neurologic injury and cerebral edema\textsuperscript{15,16} and that postischemic hypothermia may minimize these adverse effects.\textsuperscript{15–25} Animal experimental data strongly support the benefits of prophylactic (ie, prearrest) hypothermia.\textsuperscript{24} However, the animal data are weaker and conflicting regarding whether postarrest hypothermia is beneficial. Several animal studies have demonstrated benefit from hypothermia induced during or immediately after resuscitation and even when initiated as long as 1 to 6 hours postresuscitation; however, other animal studies indicate that a delay of implementation of only 15 to 30 minutes may minimize or eliminate any benefit,\textsuperscript{25,26} although other studies are more encouraging.\textsuperscript{27,28} Whether the results in normal animals are applicable to “sick” patients, often with vascular disease, is problematic, and, further, animal data are low on the pyramid of evidence used to support clinical care.

First, the clinical evidence that supports the use of TH after OOH-CA because of “shockable rhythms” must be examined. According to the AHA 2010 guidelines,\textsuperscript{7} this recommendation is supported only by level B evidence consisting of 1 good RCT,\textsuperscript{29} 1 pseudo-randomized trial,\textsuperscript{30} and 2 studies with historical controls.\textsuperscript{31,32} Walters et al.\textsuperscript{33} conducted a systematic review of the evidence supporting the use of TH after CA. They found 77 studies evaluating effects in humans: 40 were uncontrolled observational studies, 15 were nonrandomized trials using historic controls, and 9 were nonrandomized trials using concurrent controls. They found only 5 independent RCTs (and no more have been found since this study was published). Unfortunately, all 5 RCTs had some limitations. These included a relatively small number of patients randomized (275, 77, 54, 42, and 30); the studies varied regarding details, including cardiac arrest rhythms included, how and when the patients were cooled, the depth and duration of cooling, and the primary outcome examined. All had methodologic problems, all had substantial risk of bias, and in all the care teams obviously were unblinded.\textsuperscript{33} The second largest RCT (77 patients) actually only employed pseudo-randomization, and another of the RCTs only was published as an abstract more than 12 years ago. There have been 6 meta-analyses that included data from some or all of these 5 RCTs.\textsuperscript{33–38} Disturbingly, in 3 of these meta-analyses, 2 of their authors were investigators in the RCTs included in the meta-analyses.

The best and the largest RCT was a multicenter (9) European study from the Hypothermia After Cardiac Arrest (HACA) study group.\textsuperscript{39} In this study 273 patients were randomized, and markedly better incidences of favorable neurologic outcome (55% v 39%, relative risk [RR] 1.4, number needed to treat [NNT] 6; p = 0.009) and favorable 6-month survival (deaths 41% v 55%, RR 0.74, NNT 7; p = 0.02) were observed in those receiving TH after witnessed out-of-hospital (predominantly) CA caused by a shockable rhythm. But even this study had significant limitations, as identified by Nielsen et al.\textsuperscript{37} These included baseline differences between the groups, the fact that not all outcomes were reported, that the authors did not define the withdrawal policy (which was not standardized and, therefore, exposed the study to risk of bias), that the study was terminated prematurely without predefined criteria, that baseline coma was not reported, that it was highly selective in terms of patients included (only included 7% of those screened), and, finally, that the investigators did not limit hyperthermia in the control group. Between 8 and 36 hours after ROSC the average temperature in the control group was above 37°C, whereas the patients in the therapeutic group were hypothermic (Fig 1). A similar observation was noted in the retrospective observational study reported by Testori and colleagues\textsuperscript{39} (Fig 2). This is particularly disturbing because animal studies\textsuperscript{40} and several observational clinical studies have reported that even modest degrees of hyperthermia are associated with worse survival and neurologic outcome in victims of cardiac arrest.\textsuperscript{40–45} In a prospective observational study of the neurologic outcome of 151 patients with ROSC after cardiac arrest, Zeiner and colleagues observed that 49% had favorable neurologic recovery at 6 months.\textsuperscript{45} They reported that favorable recovery was associated with a lower highest temperature during the first 48 hours (37.7°C v 38.3°C). For each degree Celsius higher than 37°C the risk of unfavorable neurologic recovery increased, with an odds ratio of 2.6 times (95% CI 1.2–4.1).\textsuperscript{45}

The other highly cited and next largest RCT (77 patients) supporting the use of TH was the Australian study reported by Bernard et al.\textsuperscript{30} They observed a higher incidence of good neurologic outcome (49% v 26%, RR 1.85, NNT 4; p = 0.046) and a lower mortality at discharge (51% v 68%, RR 0.76, NNT 6; p = 0.145) in unresponsive patients receiving TH after return of spontaneous circulation (ROSC) after OOH-CA because of ventricular fibrillation (VF). But this study
also had a number of limitations, including that it employed pseudo-randomization (ie, assignment based on day of the month—even day received one management, odd day the other), the study was quite small (77 patients total), it was obviously unblinded, there was an unexplained unequal number of patients in the 2 groups (43 hypothermia v 34 controls), and an apparently unplanned interim analysis was conducted that led to an extension of the study because the initial difference in outcome was not statistically significant. Furthermore, the better neurologic outcome (incidence of “good outcome”) (49% v 26%) was only barely statistically significant (p = 0.046) and was very fragile, whereas their observed lower mortality at discharge (51% v 68%) was not statistically significant (p = 0.145). As P. J. Devereaux of the Department of Clinical Epidemiology and Biostatistics at the McMaster University has emphasized, small RCTs are at risk of being very fragile. By this he refers to the risk that 1 or 2 different patient outcomes would change the conclusion of a RCT. He recommends calculating the fragility index, which is the minimum number of changes in patient outcomes required in

![Fig 1. Temperature in hypothermic and control groups. Note that the patients in the control group were hyperthermic after the 8th hour to the 40th hour, whereas those in the hypothermic group were below 37 C. (Modified from Figure 1 in Hypothermia after cardiac arrest study group. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest.29 Used with permission.)](image)

![Fig 2. Temperature in hypothermic and control groups. Note that the patients in the control group were hyperthermic after the 12th to the 48th hour while those in the hypothermic group were below 37 C. (Modified from Figure 2 in Testori et al.39 Used with permission.)](image)
a trial to change the result of the trial from being statistically significant to insignificant. If a trial is hinging on 1 or 2 such outcomes, clinicians should be cautious in interpreting the results. In analyzing the neurologic outcome reported from the Australian trial, the fragility index was 1 (ie, if either 1 fewer patient in the hypothermia group had a poor outcome or 1 more patient in the control group had a good outcome, the differences in outcome between the 2 groups would no longer be statistically significant, despite the low NNT numbers quoted by the authors). Finally, in their own conclusions the authors acknowledged that “treatment assignment was not blinded, and there is the possibility that some aspects of care differed between the groups” and they recommended that “further studies are required to confirm these findings and determine the optimal duration of hypothermia.”

In their previously mentioned systematic review of RCTs of hypothermia for post-cardiac arrest, Nielsen et al27 conducted a meta-analysis of the two trials with the least risk of bias (ie, the HACA trial29 and the Laurent trial35), and reported that the observed reduced mortality [RR 0.92 (95% confidence interval (CI) 0.56-1.51)] and improved neurologic outcome [RR 1.24 (95% CI 0.76-2.0)] were not statistically significant. After their review of all of the available RCTs these authors concluded that “while the available randomized trials suggest a possible beneficial effect of mild induced hypothermia after cardiac arrest the results are still inconclusive and associated with non-negligible risks of systematic and random errors. Using GRADE-methodology, we conclude that the quality of evidence is low. Our findings demonstrate that clinical equipoise exists and that large well designed randomized trials with low risk of bias are needed.”

Although the evidence from these RCTs is perhaps flawed and somewhat weak, it must be acknowledged that it has been supported (with little contradictory evidence) by many observational studies. Fifteen of these (12 using historical controls and 3 concurrent controls) recently were reviewed by Delhaye et al.21 All reported favorable effect on neurologic outcome and none observed improved survival or neurologic outcome [ICUs] or procedure rooms); 41% were unwitnessed, and 87%

Table 1. Nonrandomized Comparison of Therapeutic Hypothermia for In-Hospital Cardiac Arrest

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Reference</th>
<th>Study Type</th>
<th>Patients (n)</th>
<th>Hospital Survival %</th>
<th>Good Neuro Outcomes %</th>
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<td>Hospital</td>
<td>Good Neuro Outcomes</td>
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<tr>
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<td>52</td>
<td>Retrospective historic Beth Israel</td>
<td>17</td>
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<td>53</td>
<td>Multicenter prospective observational USA</td>
<td>214</td>
<td>8102</td>
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</table>

Abbreviations: C, control group (did not receive therapeutic hypothermia); n, number; TH, received therapeutic hypothermia.
These negative findings do not prove the lack of benefit of TH for IH-CA, especially in certain subsets of patients, but in the opinion of the authors of this study (and of the accompanying editorial by Nielsen and Friberg27) they indicate the need for high-quality controlled studies of the use of TH in this population of patients.

It is perhaps relevant to note that in a survey of more than 84,000 patients who experienced in-hospital cardiac arrests in more than 500 hospitals monitored between 2000 and 2009 by the American Heart Association (AHA) Get with the Guidelines (GWTG)–Resuscitation Investigators, a significant improvement in survival was noted, increasing from 13.7% to 22.3%, as well as a reduction in the incidence of significant neurologic disability, decreasing from 32.9% to 28.1%.2

A survey by this same group of investigators of more than 67,000 patients who had ROSC after in-hospital cardiac arrest in these hospitals between 2003 and 2009 reported that TH only was used in 2% of these patients and the target temperature of 32°C to 34°C was not achieved in 44% of those so treated.59 Fugate et al35 also noted a decline in the mortality from CA between 2001 and 2009 during which TH was not widely employed. These data cast doubt on the role TH played in the observed improvement of outcome over this period and suggest that other factors (eg, more prompt diagnosis, higher quality CPR, and improved other components of postarrest care) may account for this improvement. This observation emphasizes the limitations of studies employing historic controls or even concurrent nonrandomized controls.

There are reasons to anticipate that TH might be less effective for “survivors” (ie, ROSC) of IH-CA. These include the fact that more than 75% are due to nonshockable rhythms (eg, PEA or asystole); IH-CA often is due to hemorrhage, respiratory insufficiency, or pulmonary embolism (instead of primary arrhythmias or an acute coronary event); and patients with IH-CA are often “sicker” and have more co-morbidities. Girotra et al2 listed the pre-existing conditions in patients who suffered IH-CA: 44% had respiratory insufficiency, 29% hypotension, 20% heart failure, 17% sepsis, 15% pneumonia; 58% were in an ICU, 31% on mechanical ventilation, and 29% were receiving intravenous vasopressors. Larken et al57 reported similar rates of pre-existing adverse conditions in patients experiencing IH-CA. In declining to recommend use of therapeutic hypothermia for IH-CA, the aforementioned jury from 5 societies explained that their distinction between IH-CA and OOH-CA was a reflection that out-of-hospital patients are generally well or at least physiologically well compensated before cardiac arrest, whereas hospitalized patients are heterogeneously ill.3

Further, the diagnosis of CA is in-hospital often delayed in these patients. Between 12% and 48% of IH-CA are unwitnessed.53,58-62 It is worse at night and when patients are on the general wards.53 Jones-Crawford et al59 reported that between 35% and 43% of IH-CA associated with PEA and asystole were unwitnessed. This obviously should not be the case if the patient is in the operating room or in an ICU. Wallmuller et al63 observed that noncardiac causes of IH-CA rarely presented with ventricular fibrillation and were associated with longer times to ROSC and that noncardiac etiology and nonshockable rhythms were associated with worse outcome. It is conceivable that “survivors” of IH-CA, especially if postoperative, may be more prone to the complications of TH. Finally, the poor outcome after IH-CA is less likely to be due to neurologic injury. In a retrospective review of the mode of death after admission for ROSC after CA, Laver et al reported that the cause of death in those experiencing OOH-CA was neurologic in 68% (cardiovascular in 23% and multiorgan failure in 9%); whereas in those after IH-CA the cause of death was neurologic in only 23%, while the majority (51%) were due to multiorgan failure and 26% were cardiovascular.61 In a study of CA in children, Moler et al65 observed similar findings: The cause of death was neurologic in 69% of OOH-CAs but in only 20% of IH-CAs.

The fact that the vast majority of IH-CAs are due to nonshockable rhythms (eg, PEA or asystole)—81% in the last year of the recent study of IH-CA— is also worrisome. Several observational studies have noted that the percent survival and good neurologic outcome in patients who received TH is much lower in those with nonshockable compared with shockable rhythms.66-68 Oddo et al attributed this to the longer duration of time to ROSC observed in the non-VT group.66 There is no high-level evidence (eg, large well-conducted RCTs) demonstrating improved outcome with use of TH in those experiencing cardiac arrest as a result of nonshockable rhythms (either out-of-hospital or in-hospital). What evidence there is consists of 2 small RCTs and a number of observational studies using either historical or concurrent nonrandomized controls (Table 2). Kim et al79 and Sandroni et al80 provided recent reviews and meta-analyses of these and other studies reporting on the effectiveness of TH after CA presenting with nonshockable rhythms. Two small RCTs (combined total of 22 patients in each arm of the studies) observed a non–statistically significant improvement in 6-month survival. Fifteen nonrandomized observational studies (4 with concurrent controls and 11 with historical controls) compared 546 patients receiving TH with 1,038 who did not. Of 12 studies, 10 reported no statistically significant difference and 2 reported improved survival with use of TH. In aggregate there was a 12% decrease in mortality with use of TH. In 13 studies, 12 reported no statistical difference and 1 reported improved incidence of good neurologic outcome with use of TH. In aggregate there was a statistically insignificant 5% increase in percent of patients with a good neurologic outcome in the TH groups. Thus, there is a suggestion of benefit with use of TH but the magnitude was much less than seen in patients with shockable rhythms, and because of the low quality of the evidence (GRADE) the authors indicated the need for high-quality RCTs to confirm any benefit while acknowledging that conducting such a trial would be difficult because of logistical and ethical constraints. Interestingly, Meaney et al reported that during IH-CA it is common for initial nonshockable rhythms to transition to VF/VT and that the outcomes in these patients are dismal.56 As mentioned earlier, although the nature of the neurologic injury in these patients is presumably the same as after shockable rhythms, TH hypothermia may be less effective in these patients because the severity of the neurologic injury is likely greater because nonshockable rhythms often are encountered in patients with pre-existing cardiorespiratory failure with hypotension and hypoxia, resulting in pre-existing cerebral
Table 2. Effect of Therapeutic Hypothermia on Patients After Cardiac Arrest Associated With Nonshockable Rhythms

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Ref</th>
<th>Type of Control Design</th>
<th>Characteristics</th>
<th>Site &amp; Years of Study</th>
<th>Location of Arrest</th>
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<th>Hospital Survival (%)</th>
<th>Good Neuro Outcome (%)</th>
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Abbreviations: both, OOH and in-hospital; C, controls (ie, no TH); Conc, concurrent; Hx, historical; NS, not significant; OOH, out-of-hospital; P, prospective; R, retrospective; RCT, randomized control trial; S, significant; SS, statistical significance; TH, therapeutic hypothermia.

* Survival at time of hospital discharge unless otherwise stated in comments.
† At hospital discharge unless otherwise noted in comments.
‡ Outcome at 6 months.
§ Per Fisher’s exact test by author of this essay.
‖ Outcome at 1 year.
¶¶ Raw data not in primary reference but authors stated that these outcomes were not different in the 2 groups.
ischemia, and because resuscitation is often more difficult and prolonged for these nonshockable rhythms and more commonly followed by postresuscitation shock.

Perhaps relevant to this discussion are the findings of a recent retrospective analysis of 2,524 patients experiencing perioperative (ie, intraoperative or during the first 24 hours postoperatively) IH-CA.81 This study observed that these patients had a better survival rate (32%) and rate of good neurologic outcome (20%) compared with the general populations of patients experiencing IH-CA despite the fact that 76% of these perioperative patients had nonshockable rhythms (but as with previous studies, patients with nonshockable rhythms had worse outcomes).81 Whether these findings have relevance to the potential benefits (or lack thereof) of TH in this particular population of IH-CA remains to be studied.

Finally, as emphasized by many others, basing guidelines for medical practice on a single RCT or a few small RCTs or even lower level evidence can be misleading.82–85 As mentioned earlier, there are many examples of single-center trials or single RCTs or even several small RCTs that subsequently have been found to be wrong. An example was the introduction and wide promulgation of intensive insulin therapy/tight glucose control based on a large RCT (1,548 patients, more than 5 times greater than the largest RCT of TH),86 which subsequently has been refuted.87–89 Regarding the challenges of relying on published research to guide clinical care, the sobering commentaries by J. P. A. Ioannidis90 and James Penston91,92 are worth reviewing.

Clearly, different authors reviewing these data regarding use of TH after CA have reached different conclusions. Walters et al in their systematic review concluded, “The extrapolation of the data from OOH-CA associated with shockable rhythms to other cardiac arrests (e.g., other initial rhythms, in-hospital arrests and cardiac arrests in children)...seems reasonable but is supported by only lower level data. There is need for randomized controlled trials...in these other groups.”93 Such reservations have been expressed by others,53,54,79,80,93 but not everyone agrees94–96 and many authorities continue to enthusiastically support its widespread use.21–23,97–100

But even if there is no high-level evidence (eg, large, well-conducted RCTs) supporting the use of TH for OOH-CA associated with initial nonshockable rhythms, nor for IH-CA caused by any rhythm, what is the harm in applying TH because it might help? There are a number of reasons. These include the potential complications of TH, which may be more likely in patients with IH-CA. These include infection, pneumonia, sepsis, hemodynamic instability, arrhythmias, hyperglycemia, coagulopathy, bleeding, electrolyte abnormalities, polycythemia, seizures, and altered drug metabolism, which have been reviewed by a number of authors and studies.13,21,22,94,101–104 Although in most of these studies the incidence of these complications, except for bleeding, infection, and hyperglycemia, are not significantly higher in patients subjected to TH nor associated with adverse outcomes, these complications and the other pathophysiologic responses to TH demand careful surveillance and management.105 But reassuringly, a recent large RCT comparing targeted temperature management of 33°C versus 36°C in patients experiencing OOH-CA observed no difference in incidence of serious adverse events or causes of death with the lower targeted temperature.105

The possible adverse effect of bleeding in post-CA surgical patients is unknown but of some concern.96,106 In some other circumstances hypothermia has been associated with worse outcomes, such as in sepsis,107 colon and rectal surgery,108 and pediatric traumatic brain injury.109 Other potential adverse consequences of initiating TH in these patients after CA are that employment of therapeutic hypothermia complicates other care (eg, angiography, interventional cardiology), although there have been many reports that coronary angiography and percutaneous coronary interventions (PCI) can be used successfully in patients receiving TH without apparent complications and they may even be associated with improved survival and better neurologic recovery.97,100,111 Other potential adverse consequences of implementing TH are that it is expensive, labor intensive, and diverts hospital resources (including staff, ICU beds, and money) and that it may give a false sense of hope for family (conversely, failure to use TH may suggest to the family that the hospital or physicians are not providing optimal care [because they probably have heard about TH in lay press or on the Internet]). Most importantly, the adoption of use of TH for IH-CA inhibits the ability to conduct badly needed RCTs. It becomes nearly impossible to conduct such studies in the face of widely accepted opinion of its benefit by the medical profession (and the public). Such an attitude regarding the use of pulmonary artery catheters delayed the conducting of good RCTs of their use for about 15 years after concerns were first raised about their benefit.

Furthermore, even if clinicians opt to employ TH, they really do not know how to implement it optimally.4,54 especially after the more severe neurologic injury that is likely to be present in in-hospital patients and in patients with CA associated with nonshockable rhythms, who, therefore, as suggested earlier, may require more intense TH. Some of the unresolved particulars include the time window of therapeutic effectiveness; the optimal method of inducing and maintaining cooling; optimal temperature; optimal duration of the period of hypothermia; how to rewarm; where and how to measure temperature; proper sedation, analgesia, and muscle relaxation112; need for electroencephalographic (EEG) monitoring; seizure detection and management; management of shivering; optimal hemodynamic goals13; neurologic assessment and how to assess neurologic prognosis14,115; and criteria for and when to withdraw life support. These unknowns do not rule out applying TH but make optimal application problematic. Interestingly, a recent large RCT (1,364 patients) reported no improved survival or neurologic outcome with prehospital induction of cooling compared with starting it in-hospital even though initiation of cooling before hospitalization did lower admission temperature and shortened the time to achieve temperature below 34°C.116

Intriguingly, it may be that simply preventing hyperthermia may be as effective as inducing mild hypothermia after resuscitation from cardiac arrest. Although one porcine study117 and a retrospective chart review118 suggested that TH led to superior outcome than simply avoiding hyperthermia, a recently completed large (about 470 patients in each group) RCT reported that a strategy of preventing hyperthermia produced
comparable results to TH to 33°C. This study compared targeted temperature management (TTM) of 33°C versus 36°C after resuscitation from OOH-CA of presumed cardiac cause. In the 36°C group the mean temperature was kept at 36°C (which resulted in keeping the temperature below 37.2°C in 97.5% of the patients) for 28 hours and then below 37.5°C in all patients in both groups for the next 44 hours. This is the largest RCT of TH to date. The incidence of death and death or poor neurologic function at 180 days were nearly identical in the 2 groups: Death 48% versus 50% in the 36°C versus 33°C groups, and death or poor neurologic function in 52% versus 52% or 54% (depending on the neurologic function scale used) in 36°C versus 33°C groups. About 80% in both groups had shockable initial rhythms. Whether similar results would be observed for patients experiencing nonshockable rhythms or IH-CA is unknown. Also, notably, both groups were actively cooled, and whether limiting cooling to only when it was necessary to keep temperature at or below 37°C would produce comparable outcomes to their 36°C group is speculative and deserves study.

In conclusion, the limitations of the data supporting the use of TH after CA, especially after IH-CA, have been reviewed and the problems associated with continuing this practice until TH can be justified by better data discussed. Clearly the evidence refuting the benefits of TH is as weak or more so than that which supports its use, but it is the tradition of scientific inquiry that a study must meet a higher standard (eg, less than 5% risk of a type-I error) to suggest that an intervention has an effect than the risk of rejecting a possibly effective intervention (ie, a type-II error). This leads this author to the recommendation that TH should not be used indiscriminantly for most patients after resuscitation from IH-CA. Instead of devoting their efforts to implementing an unproven method, clinicians should devote their efforts to determining if it is effective in any or in a particular subset of patients experiencing CA. The latest consensus statement from the American Heart Association on improving survival after IH-CA emphasizes the limitations of extrapolating information from OOH-CA. Although acknowledging the 2010 recommendation that TH be considered after IH-CA, it mentions the potential detrimental effects of TH in this circumstance and the important knowledge gaps that need to be addressed by future research. It is important not to repeat the history of the premature adoption of guidelines based on limited data, only to have to revise them subsequently. One way of accomplishing this is via large, well-designed RCTs. Such a study is underway for IH-CA in children. Granger and Becker, in a recent editorial, highlighted the many unanswered questions regarding TH and emphasized the need for more RCTs while acknowledging the challenges of conducting such trials. Others have emphasized that the conduct of such studies will be costly and logistically difficult and raises ethical concerns. Implementing an RCT comparing no therapy with TH is likely impossible in the presence of the current guidelines and knowledge of the lay public; however, an RCT comparing the use of therapeutic hypothermia with simply rigorously avoiding hyperthermia (ie, keeping temperature at or below 37°C) as was done in the recently reported TTM trial seems entirely feasible and ethically defensible. An alternative to RCTs may be the conduct of large multicenter observational studies/registries with carefully scripted management of patients receiving and not receiving TH, precise description of the patient characteristics, and recording of details of the CA and its management and employment of identical objective outcome assessment. In the meantime, until definitive data are available, it is not unreasonable to consider implementing TTM (32-34°C or keeping the temperature ≤37°C) in patients with IH-CA who fail to regain consciousness and have a good likelihood of favorable response to the use of TH (eg, witnessed CA, especially in the perioperative setting, as a result of reversible causes, in patients without severe preexisting conditions that could have aggravated the neurologic injury or that limit the likelihood of long-term survival.)

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