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Interpreting the Results of the Targeted Temperature Management Trial in Cardiac Arrest

Kees H. Polderman, MD, PhD,[1] and Joseph Varon, MD, PhD[2–4]

The targeted temperature management (TTM) trial, which found that cooling to 33°C after witnessed cardiac arrest (CA) conferred no benefits compared with 36°C, has led to much debate in the hypothermia community. This article discusses what lessons can be drawn. The TTM trial achieved far better outcomes in controls than any previous randomized controlled trial (RCT) or any nonrandomized study where no fever control was applied. On the other hand, rates of good outcomes in the hypothermia group were somewhat lower than in previous RCTs and most nonrandomized studies. The TTM authors conclude that benefits of temperature management are derived exclusively from fever control and that further lowering of temperature confers no benefit. Indeed, without doubt, the TTM trial demonstrates the crucial importance of strict fever control after CA and that this provides sufficient neuroprotection for some patients. However, we argue that the hypothermia intervention was executed suboptimally (possibly inadvertent selection bias; late start of cooling, up to 4 hours after ROSC; slow cooling rates, 10 hours to target temperature; more rapid rewarming than previous studies; and some other issues). This could explain high rates of good outcomes in controls and lower-than-expected rates in patients cooled to 33°C compared with previous randomized and nonrandomized studies. Outside of two previous RCTs, the use of hypothermia after CA is supported by hundreds of animal experiments, evidence from 46 before–after studies and large registries, and indirect supporting evidence from 7 RCTs in newborns with neonatal asphyxia. In addition, one RCT found improved outcomes with 32°C compared with 34°C. It remains to be explained why the TTM results so completely contradict previous studies in this field. These issues should be thoroughly discussed before changes in guidelines and protocols are made. Ending or modifying hypothermia treatment after CA should require the strongest possible evidence.

The publication of the targeted temperature management (TTM) trial, which reported that cooling to 33°C after witnessed cardiac arrest (CA) conferred no benefits compared with 36°C (Nielsen *et al.*, 2013a), has led to a number of heated discussions within the hypothermia community (Varon and Polderman, 2014). The conclusions of the TTM study were criticized by several authors, including the undersigned (Holzer *et al.*, 2014; Polderman and Varon, 2014; Polderman and Varon, 2015). A recent editorial by some of the TTM authors dealt with some of these criticisms and clarified some of the initial ideas that led to the TTM trial (Wise *et al.*, 2014).

The main results of TTM are usually interpreted as showing that benefits of therapeutic hypothermia (TH) are derived exclusively from controlling fever; that is, the TTM trial demonstrates that in previous studies the effect of systemic hypothermia induction was due to strict fever management, not to hypothermia itself. In other words, fever control is effective in preventing postanoxic brain injury, but induction of TH confers no additional benefits beyond highly effective fever management. This is a reasonable hypothesis as numerous studies have shown that fever is highly destructive in patients with all types of neurologic injuries (Polderman, 2008), including those with postanoxic injuries following a cardiac arrest (CA) (Zeiner *et al.*, 2001; Suffoletto *et al.*, 2009). Without any doubt, the TTM trial demonstrates the benefits of strict fever control in mitigating postanoxic injuries in some CA patients. The question is whether there are additional benefits from lower temperatures, that is, TH rather than normothermia, in some patients. Animal experiments very strongly suggest that this is the case, that is, fever control prevents some damage, but hypothermia does have additional benefits (Polderman, 2009). The TTM trial results challenge this notion.

Interestingly, in their recently published editorial, the authors indicate that their initial aim was to compare 32–34°C

[1]The CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.
[2]Department of Acute and Continuing Care, The University of Texas Health Science Center at Houston, Houston, Texas.
[3]Department of Medicine, The University of Texas Medical Branch at Galveston, Galveston, Texas.
[4]Department of Critical Care Services, University General Hospital, Houston, Texas.

with *no* temperature control (Wise *et al.*, 2014). They changed their strategy, according to the editorial, because it was ''*considered infeasible*'' as ''*failing to control fever would have been unacceptable to many clinicians*.'' If the original aim was indeed to challenge the importance of temperature control after CA *per se*, this would explain the apparent reluctance by some TTM authors to unequivocally state that strict temperature control should remain central to the treatment of patients with posthypoxemic injuries. However, whatever else one can say about the TTM trial, in the final design, strict temperature control was applied in all patients, and the consequences of no temperature control were not addressed. Moreover, to our knowledge, no study where no temperature management was applied has ever reported good outcome rates above 35%, whereas studies using strict temperature management (usually TH 32–33°C) routinely found favorable outcome rates above 50% (Polderman, 2008; Polderman and Varon, 2015). To be sure, the TTM trial had fairly good outcomes in both groups: 47.8% (222/464) in the 36°C group and 46.5% (218/469) in the 33°C group. However, these findings certainly do not justify completely abolishing strict temperature management after CA.

However, does the TTM trial prove that there are no additional benefits of cooling to temperatures lower than 36°C? In the TTM patient population, this was certainly the case. However, we and others have argued that this conclusion should not apply to all patients with CA (Holzer *et al.*, 2014; Polderman and Varon, 2014; Rittenberger and Callaway, 2014; Polderman and Varon, 2015).

The TTM authors have claimed on numerous occasions and in numerous articles (Nielsen *et al.*, 2010, 2011a, 2011b, 2012, 2013b; Walden *et al.*, 2011; Lilja *et al.*, 2013;), including in the above-mentioned editorial (Wise *et al.*, 2014), that use of TH after CA was based on only two trials with limited inclusion criteria. However, this ignores evidence from 47 before–after studies, a 5317 patient registry reporting 6.6% lower mortality after introduction of TH, and indirect supporting evidence from 7 randomized controlled trials (RCTs) in newborns with neonatal asphyxia (Polderman, 2008; van der Wal *et al.*, 2011; Polderman and Varon, 2015). It is also often, erroneously, claimed that none of the previous RCTs have applied fever management in controls (Nielsen *et al.*, 2010, 2011a, 2011b, 2012, 2013a; Walden *et al.*, 2011;); this is true for one of the pivotal studies (the hypothermia after cardiac arrest [HACA] trial), but the smaller of the two key RCTs *did* apply fever control in controls (at a target of 37°C, actual maximum temperature 37.4°C) (Bernard *et al.*, 2002).

We and others have repeatedly challenged the lengthy time to target temperature (10 hours from return of spontaneous circulation [ROSC]) and the rewarming rates of 0.5°C/h in the TTM trial, much faster than in previous trials. The authors have stated that this rewarming rate was chosen in keeping with current guidelines (Wise *et al.*, 2014). However, the guidelines actually stress that rewarming should be slow (Nolan *et al.*, 2010; Peberdy *et al.*, 2010); they recommend a warming rate of 0.25°C/h (Nolan *et al.*, 2010; Peberdy *et al.*, 2010) with a *maximum* of 0.5°C/h (Nolan *et al.*, 2010); this upper limit was based not on an interpretation of scientific evidence, but on a survey of clinical practice (Arrich, 2007), which did not directly address the issue of rewarming. The relevant literature on this subject clearly shows potential harm with rapid rewarming (Polderman, 2009; Polderman and Herold, 2009; Povlishock *et al.*, 2009). Not one study, in humans or animals, suggests any benefits from rapid warming (Polderman, 2009; Polderman and Herold, 2009). In fact, this issue was raised repeatedly when the TTM protocol was being developed—but the authors chose, against the advice of many experts in the field (disclosure–including one of us, K.H.P.), for unclear reasons (other than absence of direct evidence from RCTs in this specific patient category) to use the absolute maximum that the guidelines allowed.

The authors have addressed this issue by stating that actual rewarming rates in the TTM trial were only 0.36°C ± 0.13°C/h (Wise *et al.*, 2014), which they assess is comparable to the HACA trial. However, the HACA trial used passive, not active, rewarming at a maximum of 0.25°C/h (HACA study group, 2002); in addition, the actual rewarming rate in the TTM trial cannot be accurately determined because graphs showing the temperatures are cut off at 36 hours, before temperatures in the two study groups had equalized (Nielsen *et al.*, 2013a; Wise *et al.*, 2014); at this point in time, the two groups still had a temperature difference of ± 0.7°C (although with temperatures in the 33°C group rapidly rising). For comparison, the HACA trial article shows temperature development for 48 hours—the point where temperatures of the treatment groups converge. The authors so far have not clarified this issue by publishing, in their recent editorial or elsewhere, a more complete set of temperature data.

It would be interesting to see, for example, if any rebound hyperthermia occurred in the 33°C group after rewarming. This is important because it has been shown that post-hypothermia fever is associated with a 14% absolute increase in mortality after out-of-hospital CA (Bro-Jeppesen *et al.*, 2013). In other words, fever can be more harmful after a treatment with hypothermia. Of note, the article by Jeppesen and associates was performed in the largest enrolling center of the TTM trial.

We have questioned enrolment rates in the TTM trial–extremely high (66%) in relative terms, low (1 patient/month/center) in absolute terms. Based on these numbers, we raised the possibility of selection bias (Polderman and Varon, 2014; Polderman and Varon, 2015). In a recent publication addressing some of these criticisms, the authors explain the high enrollment percentage by hard work from participating sites (Wise *et al.*, 2014). However, it seems hard to envisage how this can be a complete explanation as sites enrolling for previous and subsequent studies were without doubt also working hard to enroll patients. The low absolute number (on average one patient per center per month enrolled based on the numbers provided in the TTM article) is explained by the authors as follows: it took 9 months to get a majority of sites online, and the median enrollment rate was 21 patients (Wise *et al.*, 2014). However, when using these numbers to revise our calculations, the average number of patients rises from 1 patient to 1½ enrolled per center per month*; this does not meaningfully affect our calculations and conclusions or the risk of selection bias.

The authors have performed a truly Herculean task in completing this study, which has many significant strengths

*Calculated as follows: Trial period 2 years and 2 months, minus 9 months (the time to get a majority of centers online according to the TTM authors) = 15 months; using the median number of 21 patients enrolled per center as indicated by the TTM authors (Wise *et al.*, 2014): 21/15 months = 1.4 patient/month/center enrolled.

(Polderman and Varon, 2014; Polderman and Varon, 2015). They deserve great praise for this endeavor. Their results clearly demonstrate that strict fever control is a sufficient degree of temperature management in many patients after CA. Their study raises important questions, including what is the appropriate temperature and duration of temperature management after CA. However, in contrast to the authors, we do not believe that they have proven that 36°C should now become the default target temperature in most or all patients with witnessed CA. Animal studies clearly indicate additional effects from inducing hypothermia, beyond the effects of controlling fever (Polderman, 2008; Polderman, 2009); in most experiments studying postischemic injuries to the brain or heart, there is a more or less linear dose–response relationship between temperature and tissue injury. There is also some clinical evidence supporting this; for example, a randomized clinical trial by Lopez and coworkers, published in Circulation in 2012, shows significantly improved outcomes in patients cooled to 32°C after witnessed VT/VF CA compared with patients who were cooled to 34°C (Lopez *et al.*, 2012).

It remains to be explained why the TTM trial so completely contradicts all previous studies in this field. Stating that previous studies had exclusion criteria limiting generalizability (Nielsen *et al.*, 2013a; Wise *et al.*, 2014) does not suffice as the majority of patients enrolled in the TTM trial met the inclusion criteria from previous trials. As mentioned above, favorable outcome rates in patients with witnessed VT/VF CA have routinely exceeded 50% in studies using TH. For example, a recently published large RCT compared outcomes with prehospital cooling using large volumes of refrigerated saline with rapid in-hospital cooling (Kim *et al.*, 2014). This study, which enrolled a total of 1364 patients, found no benefits of prehospital cooling, but the rates of favorable outcomes in patients with witnessed VT/VF arrest were 57.5% and 61.9%, respectively—an absolute difference of more than 10% compared with either arm of the TTM group. The TTM trial achieved far better outcomes in controls than any previous RCT or any nonrandomized study where no fever control was applied. On the other hand, rates of favorable outcomes in the TH group (46.5%) were lower than in previous RCTs (48.8% in the Bernard trial, 55.2% in the HACA trial) and lower than the intervention groups in most nonrandomized studies (average of 53.1%: Polderman and Varon, 2015). One can interpret this as lack of efficacy of TH compared with fever control, as the authors have done; however, one could also argue that these results show the crucial importance of fever control, whereas the TH intervention was not optimal (late start, slow cooling rate, rapid rewarming, a possibility of inadvertent selection bias, and some other problems discussed in more detail elsewhere: Polderman and Varon, 2015), which could explain the lower rate of favorable outcome in the hypothermia group compared with previous studies.

Finally, it is a misconception that maintaining a core temperature of 36°C would be somehow easier than a core temperature of 32°C or 33°C. The shivering response is likely to be much more pronounced around 36°C than around 32°C (Dill and Forbes, 1941; Fay, 1959; Polderman, 2009; Polderman and Herold, 2009) and thus the likelihood of accidentally slipping into febrile territory will be much greater. In keeping with this, in the TTM trial, the number of patients with shivering was higher, not lower, in the 36°C group compared with the 33°C group (34% vs. 30%, $p = \text{NS}$ [not significant]).

We conclude that further studies are needed to determine what the optimal core temperature should be for patients following witnessed and unwitnessed CA. One of us (K.H.P.) is involved in organizing a trial that intends to compare very rapid cooling to 32.0°C for a period of 48 hours, followed by slow rewarming (over 24 hours) to maintaining 36.0°C for 72 hours, followed by a minimum of 2 days of strict fever control (36.5°C) in both groups. Hopefully, additional studies with different variations on temperature management will be performed elsewhere.

It is highly likely that the optimal temperature and optimal duration of temperature management will vary per patient and will depend on a myriad of factors, such as duration of the arrest and subsequent anoxia/hypoxia, bystander cardiopulmonary resuscitation (CPR), hypotension following the arrest, subsequent blood pressure and ventilator management, pre-existing condition, age, and gender. Some patients would have good outcomes without any temperature management; many others can benefit from strict fever management alone, as the TTM trial proves. However, based on physiology and the evidence discussed above, the effects of temperature management are highly likely to be dose-dependent with additional effects of hypothermia above and beyond just fever control in at least some patients and not just the most severely injured ones (Polderman and Varon, 2015).

Perhaps in the future, we will be able to identify which patients need which degree of temperature management based on the severity of the initial injury and aided by tools, such as biomarkers, electroencephalogram, thermal imaging, regional monitoring of brain oxygenation, and others. However, at the present time, there is unfortunately no way to identify these patients with sufficient accuracy. We therefore recommend continuing to cool most patients to 32–33°C rather than 36.0°C, at this time, pending the results of future studies.

In summary, even if we uncritically accept the results of the TTM trial, this does not justify ignoring core temperature or tolerating temperatures at or above 37.0°C. Of note, temperature can almost never be adequately controlled with acetaminophen or NSAIDs alone (Polderman, 2009).

Studies using TH in witnessed CA routinely report >50% favorable outcome rates; studies without temperature management never came close to this number, the Kim study being just one recent example. Ending or modifying hypothermia treatment after CA should require the strongest possible evidence.

Disclosure Statement

Neither of the authors has a relevant conflict of interest to declare.

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Address correspondence to:
Kees H. Polderman, MD, PhD
The CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center
Department of Critical Care Medicine
University of Pittsburgh School of Medicine
3550 Terrace Street
Scaife Hall/6th Floor
Pittsburgh, PA 15261

E-mail: k.polderman@tip.nl; poldermankh@upmc.edu