*Temperature Management White Paper*

# Compliance in Targeted Temperature Management: Best Practices in Improving Patient Outcomes

**Abstract**

Therapeutic hypothermia has been widely acknowledged as a proven therapy for neuroprotection in post-resuscitation care. This has led to the inclusion of therapeutic hypothermia as a Class I recommendation in the guidelines of many global medical organizations. However, the publication of the Targeted Temperature Management (TTM) trial has generated many questions and uncertainties regarding post-resuscitation care, which has led to changes in clinical practice for many healthcare facilities, despite TTM remaining a Class I recommendation. This whitepaper is a discussion of the results from these changes and the impact on clinical practice as well as patient outcomes.

**Key Takeaways**

1) In late 2018, four large registry studies totaling nearly 100,000 patients from 837 hospitals published reports of suboptimal use of therapeutic hypothermia resulting in decreased survival since the TTM trial.
2) Since the TTM trial was published, treatment of up to 60% of patients was in non-compliance with the evidence-based practice guidelines, as indicated by the ROC registry. Similar studies showed the same tendency in non-compliance, which resulted in a decrease in survival (34% in the CARES registry, 46% in the ANZICS-CORE registry).
3) Better patient survival is associated with the use of a standardized therapeutic hypothermia protocol, IVTM, and emergency coronary angiography, as demonstrated by the HACORE registry (30-day survival of 73% in HACORE vs. in-hospital survival of 56% in the TTM trial).

**Abbreviations**

ILCOR: International Liaison Committee on Resuscitation
IVTM: Intravascular temperature management
OHCA: Out-of-hospital cardiac arrest
TH: Therapeutic hypothermia
TTM: Targeted temperature management

**Background**

Therapeutic hypothermia has emerged as an innovative, cardiocerebral resuscitation therapy that both improves survival and mitigates unfavorable neurological outcomes in cardiac arrest survivors. Two seminal trials[1,2] and subsequent endorsements by the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association led to a flourish of translational research related to TH. In 2002 two randomized clinical trials reported that inducing hypothermia (32°C –34°C for 12–24 hours) in comatose patients after resuscitation from out-of-hospital cardiac arrest (OHCA) improved survival and neurologic function[1,2]. Multiple global organizations developed and disseminated guidelines for therapeutic hypothermia (TH) in patients resuscitated from cardiac arrest based on these trials[3-5].

In the following decade (from 2003 to 2013), guidelines were gradually adopted and incorporated into clinical practice. In 2010 the American Heart Association (AHA) issued a first-time Class I recommendation:

> Unconscious adult patients with ROSC after out of-hospital cardiac arrest should be cooled to 32°C – 34°C for 12 to 24 hours[6].

In late 2013, a large multicenter randomized controlled trial (RCT) called the Targeted Temperature Management (TTM) trial compared target temperatures controlled to 33°C or 36°C in OHCA. There was no significant difference between the two groups for either survival or neurological outcomes. The TTM trial achieved far better outcomes in the control group (36°C) than any previous RCT or any nonrandomized study where no fever control was applied, despite several weaknesses and methodological flaws that could have influenced the outcomes[8]. The key message from the trial is that temperature management remains an important component of post resuscitation care in the unconscious cardiac arrest population[9].

This finding led to changes in international cardiac arrest guidelines. In 2015, both AHA and the International Liaison Committee on Resuscitation (ILCOR) updated 2015 guideline to Class I to include TH for both shockable, non-shockable and in-hospital arrest patients. The guidelines also expanded the temperature range between 32°C to 36°C, which suggests that more patients would benefit from temperature management and therapeutic hypothermia[9,10].

**TTM trial impacts clinical practice and patient outcome**

It is important to distinguish between the use of TH and TTM. TH refers to the active cooling of patients to a temperature of 32-34°C, while TTM refers to the general temperature management strategies in a target temperature between 32°C to normothermia. TTM is a newer term resulting from the influence of the TTM trial results on the 2015 AHA and ILCOR guidelines.

The publication of the TTM trial has generated some questions and uncertainties regarding post-resuscitation care. The translation of knowledge and the findings of the TTM trial have influenced routine clinical practice for temperature management, but resulted in worse patient outcomes. The interpretation of the TTM results has led to a decline in the use of therapeutic hypothermia in clinical practice, and in some cases cooling has been abandoned completely.

**TH and TTM utilization**

In late 2018, four physician-initiated studies were published that called into question the position that hypothermia after cardiac arrest is not necessary[11-14].

In a registry of 45,935 OHCA from 649 US hospitals, the odds of therapeutic hypothermia use decreased by 18% (OR 0.82; 95% CL, 0.71-0.94; p = 0.006) right after the publication of TTM trials[11]. There was a statistically significant decrease in patient survival each year following the TTM trial publication: 36.9% in 2013, 37.5% in 2014, 34.8% in 2015 and 34.3% in 2016 ($p < 0.001$). Figure 1 below illustrates the use of therapeutic hypothermia over time.

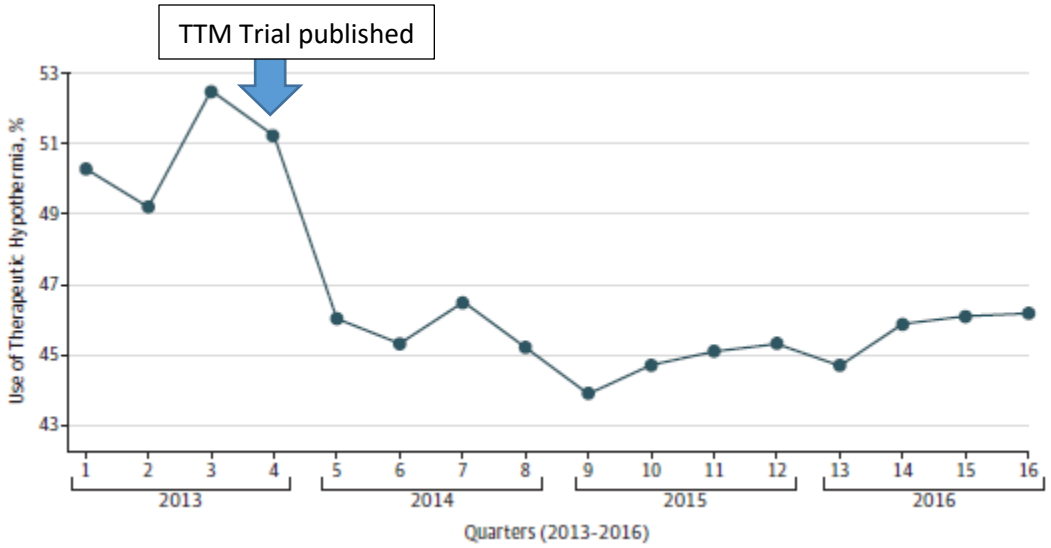


*Figure 1. Therapeutic hypothermia use over time[11].*

Table 1 below listed 3 recent larger studies in North America and Australia at 836 hospitals; all demonstrated a decline in utilization of therapeutic hypothermia in OHCA after the TTM trial publication.

Table 1. Comparison of TH utilization post-TTM

| | **The ROC*[12] registry N=37,898** | | **CARES**[11] registry N=45,935** | | **Australia[15] N=76** | |
|---|---|---|---|---|---|---|
| | Pre-TTM | Post-TTM | Pre-TTM | Post-TTM | Pre-TTM | Post-TTM |
| | | | | | | |
| Shockable | 73% | 46% | 60% | 53% | 100% | 77% |
| Non-shockable | 49% | 14% | 46% | 42% | NA | NA |
| All (% utilize TTM) | 58% | 27% | 53% | 46% | NA | NA |

*ROC: The Resuscitation Outcomes Consortium (ROC) Cardiac Arrest Registry
**CARES: Cardiac Arrest Registry to Enhance Survival (CARES) Surveillance Group

A single-center study investigated integration and compliance of TTM protocols into routine clinical practice. Results showed that the TTM group experienced significantly lower mortality rates when compared with the non-TTM group (75% vs 89%, p=0.05). A logistic regression model also showed that patients who did not receive the TTM protocol were almost 3 times more likely to die than those who received TTM (p=0.05; odds ratio, 2.8). Patients who received TTM therapy were more likely to be discharged home compared with non-TTM (21.1% vs. 5.1%, p< 0.05)[16].

These studies confirm that the utilization of TH and TTM has declined since the publication of the TTM trial. Moreover, the effect of the decline in TH and TTM utilization is evident in the decrease in survival for OHCA patients in these trials.

**TTM compliance**

After the TTM trial, not only did the use of TH decline, but also the TTM compliance and quality declined. TTM compliance includes time-to-target temperature, maintaining target temperature, and the administration of TTM for a minimum of 24 hours. A wide variation in TTM practices across hospitals highlights a dual challenge of initiating TTM and effectively implementing the TTM protocol[12,17,18]. Barriers include lack of a standardized approach, knowledge of the TTM protocol, and the proper cooling equipment[17,19].

In a study by Khera et al. in 186 hospitals across 10 North American Resuscitation Outcome Consortium sites, there was wide variation in adherence to recommended practices for TTM[12]. This registry is also known as the ROC registry, and it showed that a majority of patients (60%) at hospitals received TTM therapy with at least one deviation from recommended practices. Among those treated with TTM, 13% of patients had a delay in TTM initiation of greater than 4 hours. Additionally, 20% of patients were treated with TTM for less than 24 hours, and 18% of patients experienced overcooling, defined as patient temperatures below 32°C being reached[12]. Hospitals with higher volumes of cardiac arrest cases used TTM more frequently and were less likely to be non-adherent to recommended practices.

A single center study by Akin et al., also known as the Hannover Cooling Registry (HACORE), enrolled 233 patients and demonstrated a better outcome compared to the TTM trial patient cohorts by using a standardized protocol, advanced cooling technology via intravascular temperature management (IVTM) and mandatory coronary angiography[14]. The analysis focused on a subgroup of patients that were “TTM-like” in order to compare the efficacy of the trial with TTM. Figure 2 showed 30 day in-hospital survival of the “TTM-like” populations, separated into two groups:

1) HACORE TTM: patients who met all of the TTM trial inclusion criteria without any exclusion criteria (HACORE TTM) (n=145)
2) HACORE TTM*: HACORE TTM plus patients who meet all of the TTM trial inclusion with the TTM trial exclusion criterion of active circulatory support for cardiogenic shock (n=186)

Both groups showed a better survival than the original TTM trial population (TTM-TH) at 30 days. The TTM-like cohort showed a markedly higher 30-day survival rate of 73% compared with 56% in-hospital survival in the original TTM trial[14].

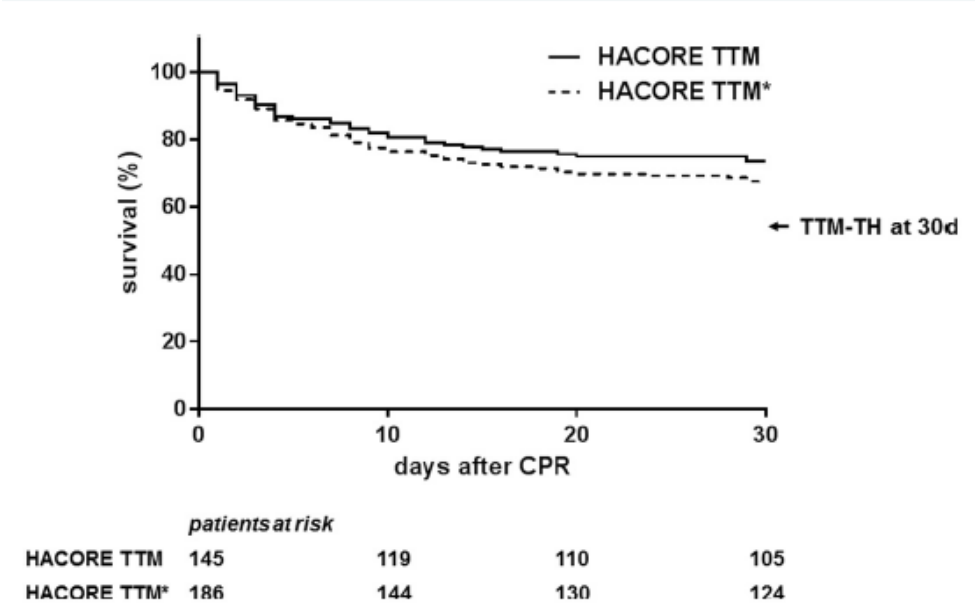


*Figure 2. Thirty-day in-hospital survival of total HACORE population meeting the inclusion/exclusion criteria of the TTM trial (HACORE TTM) and in patients with active hemodynamic support being the only exclusion criterion for the original TTM trial (HACORE TTM*). For comparison, the arrow represents the 30-day survival in the hypothermia group of the original TTM trial (TTH-TH)[19].*

These trials demonstrate that the compliance with TTM guidelines has been highly variable since the publication of the TTM trial. The lack of compliance directly affects the survival of OHCA patients, as the HACORE registry demonstrated the increase in patient survival if a standardized TTM protocol is followed and proper cooling is administered and maintained.

**Impact from expanding the TTM range**

A common misconception is that maintaining a core temperature of 36°C is easier than a core temperature of 32°C or 33°C. However, 36°C is actually a more difficult core temperature to maintain as the shivering response is likely more pronounced around 36°C than around 33°C, especially with surface cooling methods[20]. Thus, the likelihood of entering into shivering zone will be much greater. There is also the likelihood that the patient could become febrile with the fluctuation in temperature in surface cooling methods.

A multicenter study by the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS-CORE) showed the impact on clinical practice and patient outcome after switching the target temperature from 33°C to 36°C[13]. Most hospitals in this observational study had quickly adopted a new target temperature of 36°C from 33°C, due to the local providers' interpretation of the TTM trial results. The study reviewed 16,250 out-of-hospital cardiac arrest patients from 140 hospitals. In the pre-TTM trial period, the in-hospital mortality rate decreased by 1.3% points per year. Despite a younger patient population with less severe conditions and receiving better resuscitation and prehospital care, the outcome in the post-TTM trial period was associated with a statistically significant increased mortality risk (OR: 1.27; CL, 1.13-1.143, $p < 0.001$). The change in target temperature to 36°C was also associated with an increased frequency of fever, which is a known mortality risk in OHCA patients[21]. Even

though the TTM trial did not observe an increased frequency of fever in 36°C group, the increased mortality in the ANZICS-CORE study may have resulted from lack of TTM protocol compliance and less aggressive temperature management after the publication of TTM trial. The following figures demonstrate the statistically significant stepwise changes in lower body temperature in the first 24 hours in the ICU (Figure 3) as well as the increase in in-hospital mortality (Figure 4) after the TTM trial results were published.

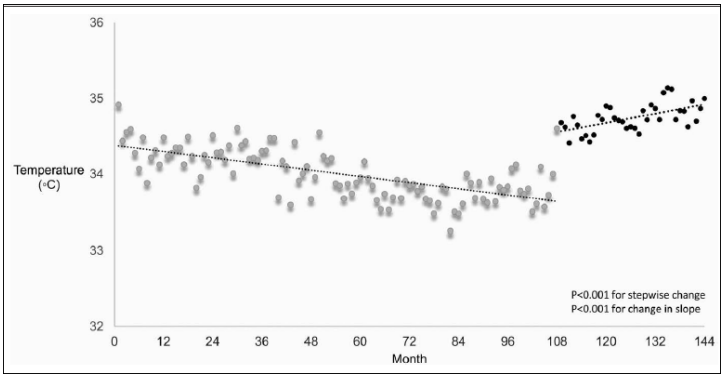


*Figure 3. Lowest body temperature in the first 24 hr in the ICU by month[13].*

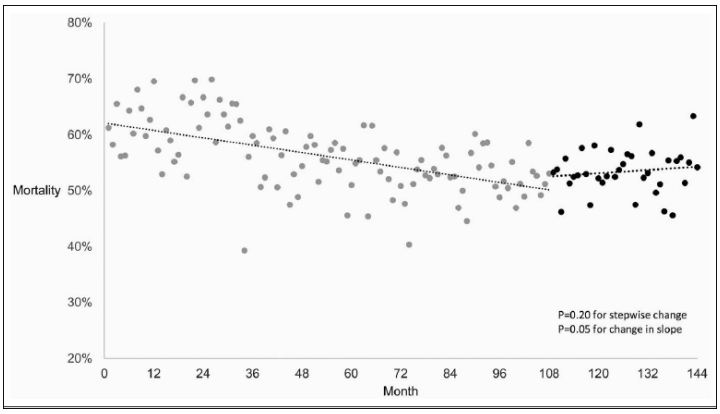


*Figure 4. In-hospital mortality by month[13].*

A single center study from Melbourne, Australia described outcomes before (N=24) versus after (N=52) changing the target temperature from 33°C to 36°C[15]. Patients in the after group (36°C) received less active cooling, reached target temperature less often, had more fever, and worse patient outcomes (Table 2).

Table 2: Relationship between TTM compliance and outcomes in VF-OHCA.

| | Target temperature | | P value |
|---|---|---|---|
| | **33°C N=24** | **36°C N=52** | |
| Patients receiving active cooling | 100% | 70% | <0.001 |
| Patients reaching target temperature | 87% | 50% | <0.001 |
| Developed fever | 0% | 19% | =0.03 |
| Survival to discharge | 71% | 58% | =0.31 |
| Mortality within 24 hours | 0% | 14% | =0.08 |
| Discharged to home | 58% | 40% | =0.08 |
| Good neurological outcome | 71% | 56% | =0.22 |

Thus, the expansion of the targeted temperature range to include 36°C has shown an increase both in mortality and in fever burden since the publication of the TTM trial. Many studies have shown that fever post TH treatment linked to worse outcomes[22]. Similar to the other studies that documented a lack of adherence to standard TTM protocols, the adoption of 36°C as a target temperature is associated with less aggressive temperature management and worsening of patient outcomes over time.

**Patient outcomes before and after TTM trial**

Since the TTM trial results were published, there has been a trend towards reversal in overall survival for post-resuscitation patients despite concurrent improvements in pre-hospital care and resuscitation. Many recent studies have highlighted the misinterpretations of TTM trial and the overall trend toward less aggressive temperature management and increasingly poor compliance. Table 3 compares studies conducted prior to the TTM trial, along with the TTM trial and studies after the TTM trial. The Post-TTM study (HACORE) with the best outcomes surpasses pre-TTM and TTM studies and reports an aggressive protocol, cooling by intravascular device to 33°C for 24 hours and mandatory coronary angiography.

Table 3: Comparison of TTM to studies before and after TTM

| | Pre TTM | | TTM | Post TTM | | |
|---|---|---|---|---|---|---|
| | HACA[1] | Bernard[2] | TTM[7] | CARES[11] | ANZICS-Core[13] | HACORE[14] |
| Cooling Methods | Cooling tent | Cold saline + surface | 76% surface 24% IVTM | Mostly surface cooling | Surface cooling | IVTM only |
| # of hospitals | 11 | 4 | 36 | 649 | 140 | 1 |
| # of patients | 275 | 77 | 939 | 45,935 | 17,788 | 233 |
| Continent/Country | Europe | Australia | Europe & Australia | North America (US) | Australia & New Zealand | Europe (Germany) |
| % of patients w VF/VT | 96% | 100% | 80% | 36.2% | NA | 73% |
| Temperature targets | 32˚C-34˚C vs normal | 33˚C vs 37˚C | 33˚C vs 36˚C | 33˚C - 36˚C | 36˚C | 33˚C |
| Bystander CPR | 46% | 59% | 73% | 37% | 90% | 62% |
| Survival | 59% (33°C) 45% (37°C) | 49% (33°C) 32% (37°C) | 50% (33°C) 52% (36°C) | 34% | 46% | 73% |

The American Academy of Neurology (AAN), partnering with the cardiology, emergency and critical care communities, has issued a guideline for the post-resuscitation population[23]. Their mission is to focus on neurologic outcomes even beyond survival. The recommendation includes:

- Therapeutic hypothermia (TH) to 33°C is still recommended as a first approach for out-of-hospital cardiac arrest shockable rhythms (Level A evidence): TTM to 36°C as an "acceptable alternative" (Level B)
- Further, TH to 33°C "may be offered" in case of non-shockable rhythms
- TH to 32°C is possibly better than 34°C

The guideline also suggest that expanding criteria for hypothermia to all cardiac arrest settings (OHCA and IHCA, witnessed or unwitnessed), and all rhythms, even with known sepsis and shock, is likely safe and judicious. Neurologists should wholly embrace cooling as a default mode for nearly all cardiac arrest survivors, making it harder to exclude patients. Clinical experience has shown that it is easier to maintain a patient at 33°C than at 36°C[8,13].

Based on the evidence, Neurocritical Care Society (NCS) also provides practice guidance in how to implement TTM[24]. This guidance includes cooling device recommendations, shivering management and optimal temperature measurement to laboratory parameters and medication management. Examples of the NCS guidance include:

1. To maintain constant patient temperature, the society recommends using intravascular catheters, or gel pads if such catheters are not available (Strong recommendation, high-quality evidence).

This recommendation is based on all studies where TH was used in OHCA populations, and that intravascular catheters demonstrated less variability than gel pad surface devices or conventional methods.

2. The society suggests increased vigilance for skin breakdown when using surface cooling devices, especially patients with shock or left ventricular failure.

   The article stated that patients undergoing TTM may be at heightened risk due to immobility and contact of cooling devices with the skin.

**Limitations**

All studies reported in this paper after the TTM trial were either prospective or retrospective observational studies, which may be viewed as having a lower level of evidence compared to randomized controlled trials. However, these registries include nearly 100,000 patients from 837 hospitals and are thus more representative of the routine clinical practice and how hospitals have adopted TTM guidelines.

The argument that correlation reported in these trials is not indicative of a cause-and-effect relationship may exist. However, factors such as increased public access to defibrillators and bystander CPR have been noted as improvements in many parts of the world, and therefore mortality would be expected to decline with time as demonstrated in Figure 4. The temporal trends towards reducing mortality (prior to TTM trial) would be expected to bias against an increase in mortality at a later time point (after TTM trial). Thus, the results from the studies reported here suggest that observed trends in patient increased mortality are unlikely to be a function of the changing severity of patient illness, but instead more likely to be related to clinical practice.

Another limitation is the consideration of repeatability of these results in other institutions. It should be noted that there were minimal differences in patient population or cardiac arrest characteristics over time. All patients studied in these trials consistently showed better results when better TTM compliance and more aggressive temperature management was implemented, and this was evident in various geographies (US, Germany, Australia and New Zealand). The combination of these studies also provides a more diverse patient population compared to that of a single randomized controlled trial. The 30-day survival rate reported by the HACORE registry should be the level of achievement that all institutions should strive for in their respective TTM programs.

Adverse event rates should also be considered in this discussion. Only one study[15] reported a difference in adverse events between the pre-TTM trial group (33°C) and the post-TTM trial group (36°C). According to this study, it seemed that fewer patients in the 36°C group experienced shivering, bleeding requiring transfusion, pneumonia, and less time on ventilator support. However, patients in the 36°C group received more propofol, spent significantly less time at target temperature, developed more fever, and most importantly, had a decrease in survival rate and in good neurological outcomes.

Estimates show as few as 2.49% of patients with cardiac arrest received TH, and only 22% of hospitals used TH[25]. Recent studies in nearly 100,000 patients showed a reduction of TH and TTM utilization, and consequently a downtrend in patient survival rates; this is despite improvements made in pre and post-hospital resuscitation care. This suggests poor translation of guidelines into clinical practice. Studies showed that patients receiving TTM more frequently survived to hospital discharge 37.6% vs. 15.3%, ($p<0.001$)[12] versus patients not receiving TTM. Advanced cooling technology, quicker time-to-target temperature, and standardization of TTM are also factors associated with better outcomes[14].

## Conclusion

Although the TTM trial supports a more lenient temperature threshold, the temperatures evaluated in the trial continued to require the use of cooling techniques. However, the trial may have been inaccurately interpreted and applied in clinical practice as demonstrating that therapeutic hypothermia lacks benefit in the management of cardiac arrest.

While 80% of patients with OHCA are comatose at hospital presentation and international professional societies give the strongest recommendation for TTM in these patients, there has been a substantial decline in the utilization of TH and TTM as well as significant variation in its real-world implementation subsequent to the publication of the TTM trial. Further standardization of contemporary practice is critical to realize the potential survival benefits of TTM.

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