Update on the Targeted Temperature Management (TTM) Trial: TTM in Context

Abstract
The publication of the Targeted Temperature Management (TTM) trial in November 2013 has generated many questions and uncertainties regarding post-resuscitation care, and many centers have made changes in their protocols just to control fever or, in some cases, not cooling patients at all. While this trial had a number of significant findings, it also contains several weaknesses and methodological flaws which could have influenced the outcomes. The key message from the TTM trial is that temperature management remains an important component of the post resuscitation care of the unconscious cardiac arrest patient and that similar results were obtained when either 33°C or 36°C were selected as target temperature. As detailed by the study investigators and the authors, this study does not support a treatment strategy where TTM is abandoned. In addition, it stated that the control group of 36°C is considered as active cooling. It is important to note that precise temperature control is critical, and it is more difficult to maintain a core temperature of 36°C than 33°C.

Key Takeaways

1. The TTM Trial studied a unique patient population and thus showed no difference in outcomes among patients cooled to a target temperature of 33°C compared to patients cooled to 36°C.
2. The TTM trial patient population had an unusually high bystander cardiopulmonary resuscitation (CPR) rate of 73%, compared to a bystander CPR rate of 42% in the United States and 16% in Germany. Similarly, the time from collapse to basic life support was one minute, which suggests a lower rate of ischemia in this patient population. This could have had a significant impact on outcomes and should be considered when comparing the TTM results to previous trials.
3. Delays in reaching target temperature was more of a disadvantage for the 33°C group, as this could contribute to lower benefits in neuroprotection.
4. There were no differences in adverse event rates between the 33°C and 36°C groups, demonstrating that both target temperatures are safe.
5. Targeted temperature management at both 33°C and 36°C are considered active cooling.
6. Precision of temperature control is crucial for patient care, especially for a target temperature of 36°C, where the margin of error is narrow due to its location between the shivering and fever zones.

Background
One of the main causes of death in industrial nations is sudden cardiac death. In the US, out-of-hospital cardiac arrest (OHCA) affects approximately 424,000 people[1]. In Germany, Austria and Switzerland together over 100,000 people suffer from cardiac arrest annually. About 25% of these patients survive this event and make it to the hospital, and even fewer patients survive after 24 hours[2]. For many patients who survived cardiac resuscitation, therapeutic hypothermia (TH) has been utilized as a crucial therapy is added to clinical follow-ups to assess for a qualitatively well-functioning and neurological survival.

TH is the only acknowledged and proven therapy for neuroprotection. Although TH was a firm component of Peter Safar's guidelines for the patient care after cardiac arrest in 1961, many individual outcomes of its effects are still unknown today. TH made headlines in 2002 with the publication of two studies on hypothermia after cardiac arrest, namely the HACA[3] and the Bernard[4] studies. These were published in the same edition of the New England Journal of

Medicine and ushered in the age of a new hypothermia therapy. For ILCOR (International Liaison Committee on Resuscitation) the results were so significant that it published an Advisory Board Statement in 2003[5] that was implemented for the first time in the AHA[6] and ERC[7] guideline.

The guidelines from 2005 recommended that unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C – 34°C for 12 to 24 hours when initial rhythm was VF/VT (class IIa) and non- VF/VT or in-hospital arrest (IIb)[6].

The 2010 guidelines issued for the first time of class I recommendation on VF/VT (Ib). Non VF/VT remained to be class IIb recommendation[8]. The guidelines were again updated in 2015, with the use of TH for both shockable, non-shockable and in hospital arrest patients given as a class I recommendation[9]. In addition, the updated guidelines widen the temperature range between 32° to 36°C, which suggests that more patients would benefit from temperature management and TH.

As further support, the Cochrane review was originally published in 2009 based upon a systematic review and meta-analysis and was later updated in 2012[10] and 2016[11]. The latest revision includes findings from six randomized clinical trials (Bernard 2002; HACA 2002; Hachimildrissi 2001; Laurent 2005; Mori 2000; Nielsen 2013) in 1,412 patients. Results showed that 63% of patients who were cooled to a target temperature between 32 to 34°C after resuscitation have better neurological outcomes compared to only 33% patients who did not receive cooling (30% absolute value favors cooling). Cooling had an effect on survival, with or without brain damage: 57% would survive if cooled compared to 42% if not cooled. In addition, when data from all studies were pooled, cooling to 33°C was still superior to no cooling or temperature management at 36°C (RR 1.53, 95% CI 1.02 to 2.29 p=0.04). No serious side effects occurred when patients were cooled to 33°C. The meta-analyses showed that therapeutic hypothermia after cardiac arrest has a greater effect on neurological outcome than on survival. Neurological outcome as a functional measure has been becoming an important parameter to assess the benefit of therapy than survival.

The publication of the Targeted Temperature Management (TTM)[12] trial in November 2013 has generated many questions and uncertainties regarding post-resuscitation care, and many centers have made changes in their protocols just to control fever or, in some cases, not cooling patients at all. While this trial had a number of significant findings, it also contains several weaknesses and methodological flaws which could have influenced the outcomes. It is important to understand the details of the TTM trial in order to provide the right therapy and better outcomes in post-cardiac arrest patients.

TTM Trial Summary

Nielsen et al conducted[12] a large multicenter randomized control trial that include 36 hospital/ICUs in 10 counties in Europe and Australia. The study randomized 950 unconscious survivors of out-of-hospital cardiac arrest with presumed cardiac cause to a target temperature of either 33°C or 36°C following return of spontaneous circulation (ROSC), irrespective of the initial rhythm. In both groups, cooling was conducted for 24 hours followed by 6 hours of re-warming up to 37°C. Subsequently, the temperature was kept under 37.5°C according to ROSC for 72 hours to avoid fever.

All patients were sedated to a minimum of 36 hours and used feedback controlled cooling devices including intravascular temperature management, or IVTM (24%), and surface cooling (76%). 473 patients were assigned to 33°C and 466 were assigned to 36°C.

Results showed 50% (235/473) of patients in the 33°C group died as compared to 48% (225/466) of patients in the 36°C group (p=0.51). At 6 months, 54% of patients in the 33°C group had died or had poor neurologic function according to CPC scores, as compared with 52% patients in the 36°C group (risk ratio 1.02; 95% CI, 0.88 to 1.6; p=0.78).

The conclusion of the TTM trial is that hypothermia at targeted temperature of 33°C did not show neurological or survival advantage compared with a target temperature of 36°C.

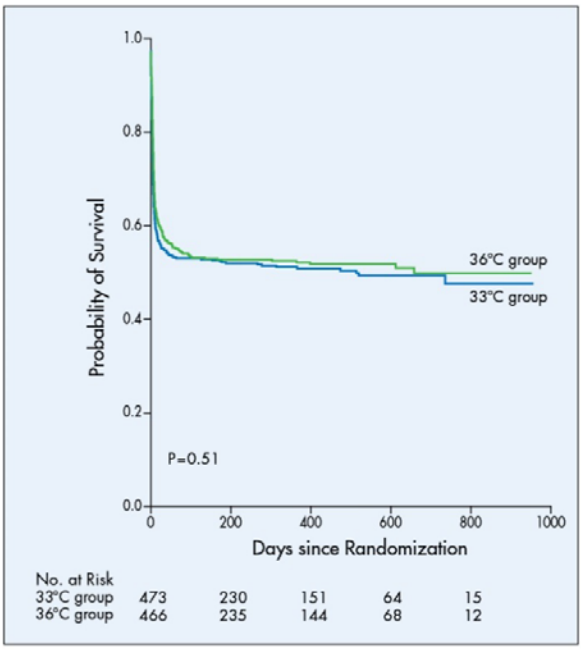

Figure 1. Survival curves for the 33°C and 36°C groups[12].

Strengths of the TTM Trial

The strengths of the TTM trial are outlined as follows:

- It was the largest published RCT study addressing the therapeutic hypothermia and temperature management in post cardiac arrest.
- The study protocol was well-executed and routine quality measures were followed. There were very few protocol deviations and only 6 patients were lost to follow up.
- All participating centers had experience in use of TH.
- This study also confirmed that fever control post TH is important.
- The TTM trial showed no difference in complications, adverse events or any other safety issues with target temperature of 33°C as compared with 36°C[12]. This result confirms the findings in the meta data analysis of the Cochrane review that there were no significant difference in adverse events between hypothermia group and control group[10].

Comparison of TTM Results to Prior Studies

Contrary to other previous studies, there were no differences between the two groups for either survival or neurological outcomes. The TTM trial achieved far better outcomes in controls group than any previous randomized controlled trial (RCT) or any nonrandomized study where no fever control was applied. On the other hand, rate of favorable outcomes in the TH group (46.5%) of TTM trial were lower than in previous RCTs 48.8% in the Bernard trial, 55.2% in the HACA trial, 55.3% in the J-PULSE-HYPO trial[13] and 57.5% in the Kim trial[14]. Table 1 is a comparison of outcomes from several large clinical trials.

Table 1. Comparison of Outcomes from Major Therapeutic Hypothermia Trials[15]

	HACA[3]	Bernard[4]	Nielsen[12]	Kim[14]	J-PULSE-HYPO[13]
Cooling methods	Cooling Tent	Cold saline + cooling blanket	76% Cooling blanket 24% IVTM	Cold saline + Cooling blanket	51% Cooling blanket + 48% Extracorporeal circulation + 1% IVTM
Participating ICUs	11	4	36	N/A (prehospital)	14
Duration	4 yr 9 mo	2 yr 9 mo	2 yr 2 mo	5 yr	5 yr
Number of patients enrolled	275	77	939	1364	452
Number of patients w VT/VF†	265	77	752	583	314
Patients enrolled/screened	7.8% (275/3551)	Unknown, but <20%‡	65.6% (939/1431)	22.9% (1364/5969)§	NA
Temperature targets	32-34°C vs normal	33.0°C vs 37.0°C	33.0°C vs 36.0°C	32.0–34.0°C	32-34°C
Temperatures achieved	33.0°C vs 37.8°C	33.0°C vs.37.4°C	33.0°C vs 36.0°C	32.0–34.0°C	32-34°C
Good outcome TH group	55.2%	48.8%	46.5%	57.5%	55.3%
Good outcome controls	39.4%	26.5%	47.8%	N/A	NA
Bystander CPR	46%	59%	73%	66%	51%
Time to initiation of cooling	105 min	<5 min	130 min	<5 / 30 min	57.5 min
Time to target temperature	480 min	120 min	600 min	252 min	180 min
Difference absolute (RRR)#	+15.8% (+35.1%)	+22.3% (+43.7%)	-1.3% (-2.6%)	N/A	NA
Control group	Normothermia	Normothermia	TH at 36C	None	None

†Or any other, undefined shockable rhythm.[15]
‡No accurate records were kept of the number of patients screened but not enrolled in the Bernard trial, but at least 400 patients were screened (personal communication from study PI).[15]
§Most patients ineligible because CPR was ultimately not successful.[15]
#Percent of patients with good neurological outcome. Positive, favors hypothermia; negative, favors normothermia.[15]

Figure 2 shows a comparison of temperature graphs from TTM (Figure 2a) and HACA (Figure 2b) trials. The main difference is in the control group. In the TTM control, it is an active cooling or warming to 36°C instead of no temperature control in the HACA control group.

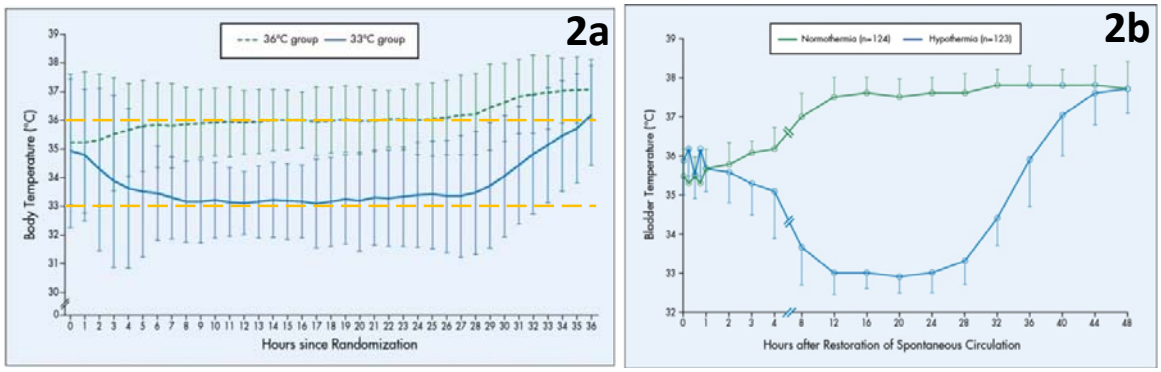

Figure 2. Comparison of the a) TTM[12] and b) HACA[3] trial results. In 2a, the orange dotted lines represent the target temperature at 33°C and 36°C, respectively.

Weaknesses of the TTM Trial

The weaknesses of the TTM study have the potential to mislead readers to the wrong conclusions; for the purposes of this analysis, these are divided into two main categories: patient population and temperature management performance. A summary of these weaknesses is as follows:

- Patient demographics indicate potential selection bias
  - The bystander CPR rate was unusually high in the TTM trial.
  - The "no flow time" was short in the TTM trial population.
  - Factors such as higher rate of pupillary response and lower levels of serum lactate suggest that the TTM trial population had milder brain injury than in comparative trials.
  - Within the TTM population, the 33°C group may have had a greater severity of initial injury than the 36°C group.
  - TTM had a higher percentage of patients with shockable rhythms in an "all-comer" population and lower enrollment rate for the centers that had target temperature of 33C as the standard-of-care.
- Poor temperature management performance
  - Delays in reaching target temperature can contribute to a lower neuroprotection benefit, which could have contributed to the results shown in the 33°C group.
  - Wide fluctuations in temperature could have affected the TTM trial outcomes.
  - The rewarming rate in the TTM trial was reported to be 0.67°C/hour, which is well above the AHA recommended rate of 0.25°C/hour.

1. Patient Demographics Comparison between TTM and Other Therapeutic Hypothermia Trials

Bystander CPR rate is very high in TTM Trial

Table 2 provides a comparison of patient demographics between TTM and published data from TH studies conducted in various countries. Of note, the TTM trial had an unusually high bystander cardiopulmonary resuscitation (CPR) rate of 73%. The exact reason for this statistic is unknown, but it is well known that higher rates of bystander CPR are linked to better survival[16].

Table 2. Comparison of Patient Bystander CPR Rate in Therapeutic Hypothermia Trials

	Nielsen[12]	HACA[3]	Calaway[17]	German registry[18]	ICEREA[19]	Bernard[4]	J-PULSE[13]
Country	Multi/OUS	Multi/OUS	US	Germany	France	Australia	Japan
Number of patients	939	275	3981	28,080	400	77	452
Bystander CPR rate	73%	46%	42%	16%	49%	59%	51%

No Flow Time is short

In addition, the "no flow time", or time from arrest to start of CPR, was a median of 1 min (0 – 2 min) in the TTM trial. As a comparison, the average time to receive basic life support (BLS) care in North America is about 8.9 min (6.7 – 11.1 min)[17] and 5 min (2-7) in HACA trial[3] and thus the majority of patients would not have matched the TTM criteria (Table 3). The impact of this finding is that patients in the TTM study population had a lesser hypoxic injury and would probably have done well regardless of the type of temperature management. This also explains the relatively good outcomes in both groups.

Table 3: Comparison of patients no flow time and low flow time

	TTM[12]	HACA[3]	Calaway[17]	THAPCA-OH[20]	Kim[21]
Country	Multi/OUS	Multi/OUS	US	Multi/US	Single/US
Number of patients	939	275	3981	295	174
No flow time (min)	1 (0-2)	5 (2-7)	8.9 (6.7-11.1)	3 (0-7)	3.5 (2-4)
Low flow time (Min)	25 (18-40)	22 (17-33)	NA	23 (15-35)	15.0 (8.0-28.8)

Additional data supporting this finding comes from a retrospective registry by SPARC network in Canada[22], where 20,165 patients were studied after cardiac arrest. Of the 871 patients who had been cooled, 71% left the clinic alive, 56% with a good neurological outcome. Good functional survival was also linked to younger age as well as shorter time from collapse to defibrillation and therapeutic hypothermia to ROSC. Furthermore, this study explained that the big impact of TH post cardiac arrest is in patients who had a longer no flow time (i.e. the time from collapse to defibrillation is > 4 min) (Table 4).

Table 4. Effect of Time to Defibrillation and Therapeutic Hypothermia on Functional Survival[22]

Time from collapse to defibrillation	Good functional outcome, n (%)			P value
	Overall	TH*	No TH	
<4 min	68 (65.3%)	10 (33.3%)	58 (62.4%)	<0.001
4-10 min	214 (61.7%)	178 (66.1%)	36 (46.2%)	
>10 min	132 (50.2%)	118 (57.6%)	18 (27.3%)	

*TH=Therapeutic Hypothermia

Another comparison of no flow time was reported in a retrospective cohort study by Testori et al., in which 1,200 out-of-hospital cardiac arrest (OHCA) patients showed the beneficial effect of TH starting from 2 minutes of no-flow, with the larger benefit for patients who experienced more than 8 minutes without CPR (OR: 6.15; 95% CI: 2.23-16.99)[23]. The three-phase model of cardiac arrest, established by Weisfeldt and Becker in 2002[24], offers the explanation to this finding. The first phase indicates immediate electrical therapy (defibrillation and cardiac pacing) is the most effective intervention in the first 4 min of cardiac arrest (electrical phase). In the second phase a period of chest compression and ventilation prior to electric counter-

shock may improve outcome after cardiac arrest (circulatory phase). The third phase called metabolic phase is characterized by tissue injury from global ischemic events and from reperfusion. The findings from the HACA and Bernard trials also support the existence of a metabolic phase.

Other Demographic Factors indicating lower injury severity in TTM patients
A comparison of the HACA and TTM trials can be made with regard to two other demographic factors: pupillary response and serum lactate (Table 5). Pupillary response after resuscitation is infrequent but correlates with clinical outcome after OHCA. A previous study showed that if pupillary response occurred at admission, 75% patients awake at 3 months compared to only 26% without pupillary response[25]. In the TTM trial, 75% of the 33°C group and 79% of the 36°C group already had pupillary reflexes when admitted to the ER, which reinforces the fact that TTM patients had milder injuries.

The serum lactate is also a marker of injury severity. In the TTM trial, the serum lactate was only 6.7 mmol/L at admission, compared to HACA trial which was 8.1 mmol/L in the hypothermia group and 9.1 mmol/L in the normothermia group. A single study of 174 patients in US showed a strong trend of initial lactate value with downtime, the longer the downtime, the higher the lactate value[21] and a better outcome associated with lactate value less than 7 mmol/L.

Table 5. Comparison of HACA and TTM Demographics: Pupillary Response and Serum Lactate

	HACA		TTM	
	HT	NT	33C	36C
Pupils reactive (%)	53	47	75	79
Serum lactate	8.1 $\pm$ 4.2	9.1 $\pm$ 4.1	6.7 $\pm$ 4.5	6.7 $\pm$ 4.5

2. Patient Demographic Differences between the 33°C and 36°C Groups
There are subtle differences between the two groups that may indicate a greater severity of initial injury in the 33°C group. The factors in the following table are known to be associated with unfavorable prognosis. None of these individual differences are statistically significant, but cumulatively they could have had an impact on the overall TTM results. There were 18 items favor 36°C group versus only 4 favor 33°C group or 39% vs 7% (Appendix 1)[26]. The other observation from TTM showed a lower initial temperature in 33°C group, which is considered a spontaneous hypothermia; this result potentially indicates greater severity of brain injury with diminished shivering response[15]. A higher incidence of myoclonic seizure in the 33°C group, again suggesting a greater severity in the 33°C group[15,27].

3. Potential for Selection Bias
A total of 1,431 OHCA patients were screened in the TTM trial, 1,242 of which met the inclusion criteria and 950 were randomized. Many of the participating centers reported much better outcomes with a target temperature of 32-34°C than those achieved in either 33 or 36°C group in TTM[12,28-30]. In addition, the enrollment was very low for those high volume centers compared to previous published data.

It is important to note that many of the participating centers at TTM were experienced with TH, and as a result, hypothermia was already standard of care at those hospitals. Thus, the default option for all patients not enrolled in the TTM trial was TH with a target of 32 to 34°C. Some have argued that this fact indicates a selection bias[27]. Some patients with a greater potential to

benefit from TH might have been excluded from study in order for the standard TH to be applied, leaving a higher proportion of non-salvageable patients (severely damaged, unlikely benefit from any TH) or a higher proportion of those with less severe injuries who would have done well regardless of the type of target temp. Based on the unusually higher percentage of patients with median of 1 min bystander CPR, the latter hypothesis is more likely.

Another potential contributor to selection bias was the inclusion of shockable rhythms vs. other initial rhythms. The TTM study was designed to evaluate all patients who survived OHCA regardless of the initial rhythm, while HACA and Bernard trials enrolled only patients with shockable rhythms. Nearly 80% of patients in the TTM trial had shockable rhythms, a much higher rate than other trials that include "all comers" (Table 6), which contradicts recent epidemiological data showing that shockable rhythms account for less than 30% of OHCA[31]. This also raises question of patient selection bias[32].

Table 6. Percent of Patients with Shockable Rhythms in Therapeutic Hypothermia Trials

First Author	Number of Patients	% of shockable
Nielsen[12]	950	80%
Callaway[17]	4,468	56%
Deye[19]	400	35%
Kim[14]	1,364	43%
Yokoyama[13]	452	69%

4. Temperature Management Performance Factors

Time to reach target temperature

In the TTM trial, the average delay to initiate cooling was 130 minutes, with the longest delay being up to 4 hours. Time to target temperature in the TTM trial was 8 hours, meaning that patients reached the target of 33C on average 10 hours after ROSC. The majority of patients were cooled with surface cooling, which implies that the benefit of neuroprotection from hypothermia may not be evident due to the delay to target temperature. Getting temperature to target of 33C faster is crucial as the neuroprotection begins only after a temp below 34C is reached. Studies have shown that an hour of delay to reach a target temperature of 33C can worsen the likelihood of a favorable outcome by approximately 31%[33]. In addition, for every 1 hour in delay to reach target temperature, the risk of death increased by 20%[34]. Nagao et al. also demonstrated shorter time to 34°C statistically predicted increased survival to hospital discharge and favorable neurological outcome up to 1 year[35]. In an observation cohort study from 1,036 post cardiac arrest patients, nearly one-third of patients (32%) who had surface cooling failed to achieve target temperature (the definition of the failure is to reach a temperature below 34°C during the first 12 hours after cardiac arrest onset). The failure to reach target temperature is one of the strongest predictors of bad outcomes[36].

Temperature Control Variations During Maintenance of Therapeutic Hypothermia

The outcome in the TTM trial could also have been affected by temperature fluctuations in the maintenance phase. The temperature in both 33 and 36°C group showed wide error bars ranging between 2°C and 6°C (Figure 2a), with the temperature curves separating only about 8 hours after cooling had commenced. If one also considers the fact that inclusion in the study was only possible up to 4 hours after ROSC, the patients in both groups would not have been subjected to any difference in temperature in the first 10-12 hours, which is the most important time period for neuroprotection. Because of this lack of temperature separation, no great differences in outcome are to be expected[15].

A small RCT published in 2012 comparing two temperature regimens of significantly better outcomes with 32.0°C compared to 34.0°C[37]. This study used IVTM and clearly showed tight control and speed reaching target between two target temperatures. In addition, an observation study by Shinozaki (1,026 patients) in Japan[38] showed that post arrest patients who maintained at target of 33°C over 18 hours independently correlated with favorable neurological outcome. These results emphasize that not only is the speed to target temperature important, but the maintenance of that target temperature also needs to be maintained for a specified period in order to improve neurological outcome in OHCA patients.

Rapid rewarming phase and fever control

Rapid rewarming can have severe detrimental effects in post hypoxia brain injury and can completely negate the protective effect of TH[39-41]. TTM trial had a rewarming phase from 33°C to 37°C in 6 hours, which corresponds to a rewarming rate of 0.67°C per hour. As a comparison, the HACA trial took 12 hours for the 33 group to rewarm from 33°C to 36°C (0.3C/hr). Thus, the rewarming rate in the TTM trial was much faster than in previous studies and is much higher than the AHA recommended rewarming rate[8].

Another important factor in therapeutic hypothermia is the final phase of fever control. In the TTM trial, the temperature graphs in the TTM publication are cut off at 36 hours, which does not give a good indication of the fever control status. At the cutoff point, the 33°C group was still rapidly warming and the temperature between the two groups had not yet equalized, with a difference of 0.7°C. One criticism of the TTM trial is that, if the 33°C had fever control post rewarming, the outcomes could have been greatly affected. Many studies have shown that fever post TH treatment linked to worse outcomes; in other words, fever is more harmful after TH treatment[42].

Outcomes from the Change to 36C and Future Considerations

Therapeutic hypothermia with targeted temperature management is the only neuroprotective strategy shown to have positive outcomes in post cardiac arrest patients. AHA upgraded 2015 guideline[9] to class I regarding the use of TH for both shockable, non-shockable and in hospital arrest patients. In addition, the guidelines widen the temperature range between 32 to 36°C, which suggests that more patients would benefit from temperature management and TH, similar to the recommendation from ERC[43]. Canada's guidelines continue to state a target temperature between 32 to 34°C. The Canadian resuscitation committee did not find a reduction in cost or resources by targeting 36°C or a reduction in adverse events by targeting 36°C[44].

It is a common 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 33°C especially with surface cooling method and thus the likelihood of accidentally slipping into shivering zone and 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 =NS)[45]. Canadian resuscitation committee also acknowledge that the greater risk of potential hyperthermia due to the drift when selecting a higher target temperature, this is one of the reason for maintaining the original guideline of target temperature of 32 to 34°C[44]. Direct communications with physicians have also suggested that hospitals who switched target temperature to 36°C

have experienced more shivering, using more sedation and have more temperature out of range, especially with surface cooling.

Bernard et al. presented their new data at ERC and AHA in 2015. This is the first published information showed the impact of changing target temperature from 33 to 36°C. Data showed that 50% of patients temperature above 37.1°C with a target temp at 36°C; average time stay at or below target temperature was significantly shorter after the changes (22 hours vs. 8 hours, $p<0.001$). All resulted in a reduction in survival rate at hospital discharge (from 74% to 63%) and good neurological outcome (from 82% dropped to 63%)[46].

Implementation strategies are vital to success of any new treatment. Understanding the details from clinical studies is very important for improving protocols in daily clinical practice. Hospitals have adapted decision trees to guide the clinician's selection on target temperature in post cardiac arrest patients (Appendix 2)[47].

Conclusion

Unconscious patients admitted to hospital after cardiac arrest are at high risk for death, and neurologic deficits are common among those who survive. Global brain ischemia and the reperfusion injury following resuscitation may lead to brain tissue degeneration and loss of neurological function. Therapeutic hypothermia and avoidance of fever seem to mitigate this damage in both experimental and clinical setting and demonstrate benefit in outcome[48].

The key message from the TTM trial is that temperature management remains an important component of the post resuscitation care of the unconscious cardiac arrest patient and that similar results were obtained when either 33°C or 36°C were selected as target temperature. As detailed by the study investigators and the authors, this study does not support a treatment strategy where TTM is abandoned. In addition, it stated that the control group of 36°C should also be considered as active cooling, not fever control.

The results of the study triggered discussions regarding the value of the hypothermia therapy with resuscitated patients. However, one should note that the studied population in the individual studies differs quite significantly. The part of patients in the TTM trial with occurred bystander CPR was over 70%, the part of patients with ventricular fibrillation was at about 80% and basic life support was started after approximately 1 minute. Those general conditions do occur however not agree with the reality in most places worldwide.

In addition to faster rewarming rate, fluctuation of target temperature should be avoided as well as fever control at any therapeutic targeted temperature. Active temperature management remains an essential component of the post-resuscitation treatment. Since these results have not yet been presented to other population (i.e. longer down time), these patients should still be continued to be cooled to 32°C to 34°C to achieve the currently best possible outcome. 36°C requires greater precision in temperature control with less "margin" before the patient enters febrile territory or shivering zone.

Targeted temperature management is vital regardless of whether the target is 33 or 36°C, and it is important to note that precise temperature control is critical. A recent study showed that when TTM of 33°C achieved, it demonstrated the benefits to hemodynamic effects including lower heart rate, higher systemic vascular resistance index, higher cardiac power index,

reduction or normalization of initial elevated lactate levels and higher mixed venous oxygen saturation. In this study, cooling with IVTM achieved target temperature of 33 at 100%, surface cooling did not achieve target temperature, and the lowest temperature achieved with surface cooling was 35°C despite of receiving double amounts of cold fluid during induction phase. IVTM group not only showed a lower vasopressors and inotropes use, but resulted in a better outcomes[49].

Another recent published RCT compared IVTM to surface cooling, and the cumulative survival rate with favorable neurological outcome at 90 days showed favorable in IVTM group vs. surface cooling (p=0.052). The risk of overcooling was greater in surface cooling vs. IVTM (17.8% vs. 7.8%, p= 0.01). Commentary on this trial stated precision of temperature control may become even more important if centers decide to switch target temperature following CA from 32-34°C to 36°C. The reason for this is that at a core temperature of 36°C, an increase in temperature of 1.5°C due to a shivering episode would immediately put the patient in febrile territory. Maintaining stable temperature is likely more important, and more difficult at a core temperature of 36°C than 32-33°C[50]. IVTM is the only methodology can offer clinicians the most efficient and reliable way for targeted temperature management.

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Appendix 1. Frequency of Demographic Differences in the TTM Trial[12,26]

Characteristic	33°C Group (N=473)	36°C Group (N=466)	Difference (%)	Group Favored
Demographic characteristics				
Male sex – no. (%)	393 (83)	368 (79)	4	36°C
Medical history – no. (%)				
Chronic heart failure	32 (7)	29 (6)	1	36°C
Previous AMI	107 (23)	86 (18)	5	36°C
Ischemic heart disease	145 (31)	115 (25)	6	36°C
Previous cardiac arrhythmia	87 (18)	79 (17)	1	36°C
Arterial hypertension	193 (41)	181 (39)	2	36°C
Previous TIA or stroke	35 (7)	38 (8)	1	33°C
Diabetes mellitus	61 (13)	80 (17)	4	33°C
Asthma or COPD	48 (10)	49 (11)	1	33°C
Previous percutaneous coronary intervention	58 (12)	50 (11)	1	36°C
Previous coronary artery bypass grafting	47 (10)	42 (9)	1	36°C
Characteristics of the cardiac arrest				
Bystander witnessed cardiac arrest – no. (%)	420 (89)	418 (90)	1	36°C
First monitored rhythm – no. (%)				
Shockable rhythm	375 (79)	377 (81)	2	36°C
Ventricular fibrillation	349 (74)	356 (77)	3	36°C
Perfusing rhythm after bystander-initiated defibrillation	9 (2)	4 (1)	1	33°C
Pulseless electrical activity	37 (8)	28 (6)	2	36°C
Unknown first rhythm, not responsive to shock or not shocked	2 (<0.5)	6 (1)	1	36°C
Time from cardiac arrest to event – min				
Start of advanced life support – median	10	9	1 min	36°C
Clinical characteristics on admission				
First measured body temperature – °C	35.2±1.3	35.3±1.1	0.1°C	36°C
Corneal reflex present – no./total no. (%)	264/407 (65)	258/392 (66)	1	36°C
Pupillary reflex present – no./total no. (%)	344/460 (75)	363/458 (79)	4	36°C
Circulatory shock – no. (%)	70 (15)	67 (14)	3	36°C
TOTALS			**36°C: 39% 33°C: 7%**	**36°C: 18 times 33°C: 4 times**

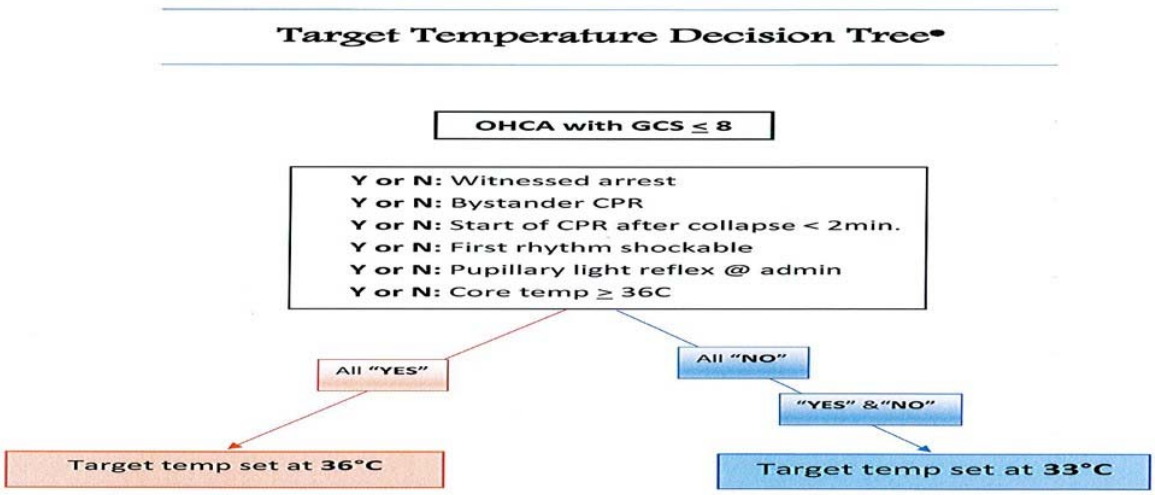
Appendix 2. Sample Protocol Decision Tree for Targeted Temperature Management[47]

Penn Highlands Healthcare	**POLICY/PROCEDURE** **Department: Critical Care**
TITLE: Hypothermia – Targeted Temperature Management	

PURPOSE: To provide nursing guidelines for inducing hypothermia or Targeted Temperature Management (TTM) in adult patients.

POLICY: All patients presenting to Penn Highlands DuBois suffering from out of hospital cardiac arrest are assessed for treatment with therapeutic hypothermia based on the following patient selection and exclusion criteria.

If criteria are met, the patient is cooled using the induced hypothermia physician order set for 24 hours to a goal temperature of 33 or 36 degrees.
(Patients receiving induced hypothermia or TTM must be in the care of a nurse who has been deemed competent in TTM induction within the CVU, ICU, Cath lab or ED.)
The Target Temperature Decision Tree is utilized as a guide to determine the temperature therapy goal.
Begin infusion of 4 degrees C NS emergently and consider external cooling early. External cooling is initiated emergently using cooling blanket and / or ice packs until the ICEY Catheter is inserted.



*The decision tree is based on the TTM trial results