Mini Review

Open Access Journal of Biomedical Science
ISSN: 2690-487X

# A Brief History of Targeted Temperature Management in Post Cardiac Arrest Patients: A Mini-Review

**Ananta Subedi[1]*, Rakshya Sharma[2], Anup Shrestha[3] and Raiko Munankarmi[4]**

[1]*Clinical Assistant Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, South Dakota, USA*

[2]*Clinical Assistant Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, South Dakota, USA*

[3]*Clinical Assistant Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, South Dakota, USA*

[4]*Hospital Medicine, Avera McKennan Hospital and University Health Center, South Dakota, USA*

## ABSTRACT

Therapeutic hypothermia (TH), also known as targeted temperature management (TTM), is a treatment method that has been used for centuries and has been employed for the management of post-cardiac arrest patients in the 21st century. However, the efficacy of TH in improving outcomes after cardiac arrest has been debated due to conflicting results from earlier studies with various limitations. Recent studies have provided higher quality evidence suggesting that therapeutic hypothermia may not be superior to targeted normothermia in out-of-hospital cardiac arrest patients, regardless of the initial cardiac rhythm. The adverse effects of hypothermia also need to be considered, including electrolyte abnormalities, arrhythmias, bleeding, and infection. Therefore, routine use of targeted hypothermia in out-of-hospital cardiac arrest patients may not be necessary, however active temperature management to prevent hyperthermia should be continued.

## INTRODUCTION

Therapeutic hypothermia (TH) has been employed by mankind since ancient times. Hippocrates recommended treating wounded soldiers with ice. In the 1950s, hypothermia was used in cerebral aneurysm surgery [1]. In modern medicine, Targeted Temperature Management (TTM), previously known as therapeutic hypothermia, has been incorporated in the guidelines of the management of post cardiac arrest patients. TTM is a treatment method in which a specific body temperature is targeted for a specific duration. The objective is to improve outcomes after poor cerebral circulation, mostly due to cardiac arrest [2]. Typically, the targeted temperature is lower than the normal body temperature, ranging from 32-37.5°C. An estimated 292,000 cases of adult in-hospital cardiac arrests occur annually [3]. Additionally, around 350,000 patients experience out-of-hospital cardiac arrest in the United States every year [4]. Despite improvements in resuscitation and aggressive treatment in the Intensive Care Unit over the years, the survival rate for cardiac arrests remains very low [5,6]. In 2003, the American Heart Association recommended Targeted Temperature Management (TTM) after studies showed improved neurological outcomes following TTM [7]. In this article, we will provide a brief history of TTM and explore the potential paradigm shift in the future regarding the implementation of TTM.

## CHRONOLOGY

In 2002, two RCTs published in the NEJM concluded that therapeutic hypothermia increased neurological outcomes and reduced mortality in out-of-hospital cardiac arrest patients due to an initial shockable rhythm who were comatose post-arrest [8,9]. Following these trials, TH was rapidly adopted in the management

**Quick Response Code:**

**Address for correspondence:** Ananta Subedi, Clinical Assistant Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, South Dakota, USA

**Received:** March 29, 2023 **Published:** April 10, 2023

**How to cite this article:** Subedi A, Sharma R, Shrestha A, Munankarmi R. A Brief History of Targeted Temperature Management in Post Cardiac Arrest Patients: A Mini-Review. 2023- 5(2) OAJBS. ID.000555. **DOI:** 10.38125/OAJBS.000555

of post-arrest patients. However, these studies had a few limitations. Firstly, the treatment was not blinded, and protocols were not standardized between the different groups. Additionally, the trial was small, with only 352 patients. A significant number of patients in the control arm became febrile, which could have confounded the findings since fever has detrimental effects on neurological recovery [10]. The RICH Trial, published in 2010, compared Ice Cold IV Fluids en-route to the hospital to standard care in patients with out-of-hospital cardiac arrest due to Ventricular Fibrillation, but showed no significant difference in survival to discharge [11]. The Targeted Temperature Management Trial published in 2013 compared mortality between TTM at 36°C vs 33°C and did not find any significant differences. There was also no significant difference in the composite of poor neurological outcome or death at 180 days [12]. The FROST-I trial published in 2018 did not find statistically significant differences in favourable neurological outcome among the study groups with TTM at 32°C, 33°C, and 34°C after out-of-hospital cardiac arrest with a shockable rhythm [13]. These trials suggested that cooling to lower temperatures would not provide further benefits compared to mild cooling. Major limitations of these trials include not including normothermic temperature and underrepresentation of non-shockable rhythms in the trials. Hence, there is some argument that the true benefit is from the prevention of hyperthermia rather than therapeutic cooling. The HYPERION Trial published in 2019 compared survival with favourable neurological outcomes as well as mortality in cardiac arrests due to non-shockable rhythm between patients receiving TTM at 33°C and normothermia at 37.5°C. It showed a significant improvement in survival with favourable neurological outcome in the hypothermia group at 90 days [14]. While this is the only trial in subjects with non-shockable rhythm, it did not show statistically significant benefits in mortality. Although the primary result is statistically significant, the fragility of the result is obvious. The method employed to assess cerebral performance was via a telephone interview performed by a single psychologist. Also, the p-value of 0.04 was almost equal to 0.05, and changing a single patient's result could result in making the result statistically insignificant. The TTM2 Trial, published in 2021, compared survival and performance outcomes between targeted hypothermia and normothermia in patients with out-of-hospital cardiac arrest with coma. The results showed no difference in survival at 6 months or performance status but showed that the hypothermia group had a higher incidence of arrhythmias [15]. The results of this study provide evidence that targeted hypothermia does not improve outcomes in out of hospital cardiac arrest, which is similar to the results of the TTM trial but contradict the results of the 2002 studies and the HYPERION trial. Compared to previous studies, the TTM2 trial provided higher quality evidence. The trial was large, including 1,861 patients, the subjects were randomized, outcome assessors of the study were blinded, the follow-up was almost 100%, prognostication was performed by a standardized protocol, and both groups received similar treatment. It is noteworthy that active cooling needed to be used in 46% of the normotensive patients, which accentuates the prevalence of fever in post-arrest patients.

## CONCLUSION

Based on the results of the TTM2 trial, it appears that targeted hypothermia may not provide improved outcomes compared to targeted normothermia in out-of-hospital cardiac arrest patients. Therefore, routine use of therapeutic hypothermia in these patients may not be necessary. However, active temperature management to maintain normothermia should still be continued. It's important to note that the recommendation for therapeutic hypothermia for neuroprotection in patients with cardiac arrest is based on weak evidence from earlier trials that had numerous limitations. Furthermore, it's worth mentioning that the studies show a higher degree of evidence supporting the efficacy of TTM in cardiac arrest with shockable rhythm but show conflicting data in patients with non-shockable rhythm. Finally, the adverse effects of hypothermia, which include "cold diuresis" and electrolyte abnormalities, arrhythmias, bleeding, and infection, among others, should also be considered [16].

## REFERENCES


1. Polderman KH (2004) Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. Intensive Care Med 30(4): 556-575.
2. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, et al. (2010) Part 9: post-cardiac arrest care: 2010 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 122(18 Suppl 3): S768-S786.
3. Holmberg MJRC, Fitzmaurice GM, Chan PS, Duval-Arnould J, Grossestreuer AV, et al. (2019) Annual incidence of adult and paediatric in-hospital cardiac arrest in the United States. Circ Cardiovasc Qual Outcomes 12(7): e005580.
4. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, et al. (2020) Heart disease and stroke statistics-2020 update: a report from the American heart association. circulation 141(9): e139-e596.
5. Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, et al. (2012) Trends in survival after in-hospital cardiac arrest. N Engl J Med 367(20): 1912-1920.
6. Chan PS, McNally B, Tang F, Kellermann A, Group CS (2014) Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 130(21): 1876-1882.
7. Arrich J, Holzer M, Havel C, Mullner M, Herkner H (2016) Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2(2): CD004128.
8. Hypothermia after Cardiac Arrest Study G (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346(8): 549-556.
9. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, et al. (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346(8): 557-563.
10. Zeiner A, Holzer M, Sterz F, Schorkhuber W, Eisenburger P, et al. (2001) Hyperthermia after cardiac arrest is associated with an unfavourable neurologic outcome. Arch Intern Med 161(16): 2007-2012.
11. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, et al. (2010) Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation 122(7): 737-742.
12. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, et al. (2013) Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 369(23): 2197-2206.
13. Lopez-de-Sa E, Juarez M, Armada E, Sanchez-Salado JC, Sanchez PL, et al. (2018) A multicentre randomized pilot trial on the effectiveness of different levels of cooling in comatose survivors of out-of-hospital cardiac arrest: the FROST-I trial. Intensive Care Med 44(11): 1807-1815.
14. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, et al. (2019) Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med 381(24):2327-2337.
15. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, et al. (2021) Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 384(24): 2283-2294.
16. Polderman KH, Peerdeman SM, Girbes AR (2001) Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurg 94(5): 697-705.