

## Review Article

# Pro-hospital initiation of therapeutic temperature management after cardiac arrest: a meta-analysis of randomized controlled trials

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**Abstract:** Objectives: To review whether cardiac arrest patients who received therapeutic temperature management (TTM, 32-34 °C) have decreased mortality and improved neurological outcomes compared with those who received regular treatment by conducting a systematic review of randomized controlled trials (RCTs). Methods: The MEDLINE, EMBASE and Cochrane Library were searched for English-language RCTs published before March 2016. Comparing TTM (core body temperature 32-34 °C) with control (core body temperature about 36 °C), after cardiac arrest among adults. The outcomes assessed were all-cause mortality and good neurological outcome (cerebral performance category 1-2). Results: Of 2179 citations, nine RCTs (n = 2149 patients) met inclusion criteria ultimately in the meta-analysis. TTM group was associated with a non-significant reduction in all-cause mortality (random-effects RR 0.92; 95% CI, 0.85-1; P = 0.21, I<sup>2</sup> = 26%) compared with the control group. However, the possibility of neurological outcome recovery was higher than that of the control group (random-effects RR 1.12; 95% CI, 1-1.25; P = 0.02, I<sup>2</sup> = 58%). Conclusions: Randomized trial data demonstrate that there is non-significant reduction in all-cause mortality, but improve neurological outcomes in patients with ROSC after cardiac arrest. More and larger RCTs need to be carried out to confirm these findings in the future.

**Keywords:** Cardiac arrest, therapeutic temperature management, therapeutic hypothermia, cardiopulmonary resuscitation, meta-analysis

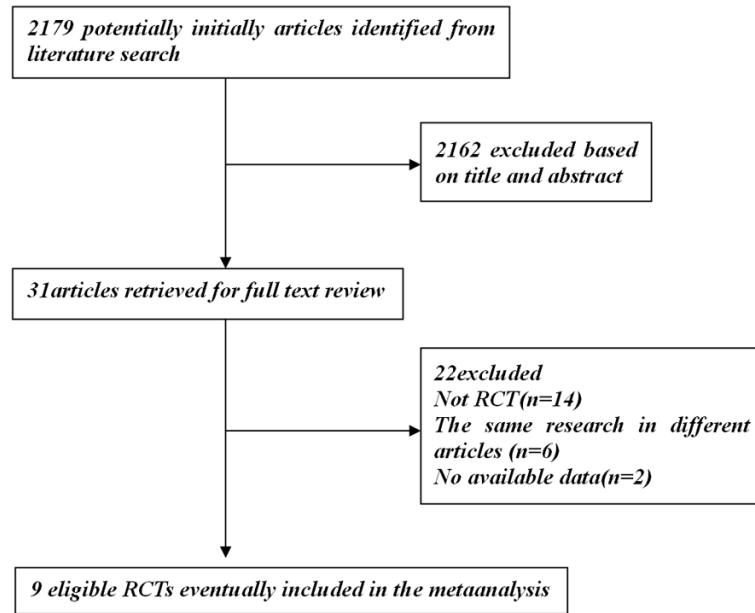
## Introduction

Out-of-hospital cardiac arrest (OHCA) remains a leading cause of human death and profound clinical and public health challenge around the world [1]. Studies shows that the most affected by the OHCA is the Australia (113/100,000 population per year), followed by North America, Europe and Asia (the incidence of each area is 94, 86, 55/100,000 population per year) [2]. Thanks to the improvement of resuscitation therapy for cardiac arrest patients, such as emphasis on high-quality and timely cardiopulmonary resuscitation (CPR), therapeutic temperature management (TTM), hemodynamic support and standardized postresuscitation protocols, the number of mortality by cardiac arrest decreased from 90% historically to about 50% recently [3]. Although the patients have successful return of spontaneous circulation

(ROSC), they may also fall into coma or even death because of neurological injury [4].

TTM (also known as therapeutic hypothermia, TH) is an effective treatment for the post-cardiac arrest syndrome, which has been created by Negovsky in 1988, and recommended in guidelines by International Liaison Committee on Resuscitation (ILCOR) during 2003, for the reason that two human randomized trials show a significant benefit for both survival and favorable neurologic outcome in patients suffering from OHCA [5]. The primary content of the recommendation is that unconscious adult patients with spontaneous circulation after OHCA should be cooled to 32-34°C for 12-24 hours when the rhythm is ventricular fibrillation and other rhythms (may also beneficial), as well as in-hospital cardiac arrest [6]. It has also been recommended in the 2010 International Con-

## A meta-analysis of TTM after cardiac arrest



**Figure 1.** Flow diagram of the study selection process in the meta-analysis. RCTs = randomized controlled trial.

sensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations [7].

The potential mechanism of TTM are multifaceted, chief among them is reductions in the cerebral metabolism of glucose and oxygen consumption. As a result, such process could inhibit excitotoxic neurotransmitters, intracellular acidosis, apoptosis, inflammation, free radical production, and seizure activity. So far, a large number of short or long trials have been reported that this therapeutic method can improve mortality and neurological outcome more or less. However, not all scholars support this conclusion. Several studies show that the TTM does not improve survival and neurological status for OHCA [8, 9]. Here we conducted a meta-analysis of randomized controlled trials (RCTs) of the survival and neurological function improvement of the TTM on the treatment of OHCA.

### Methods

#### Search methods

A meta-analysis of the available published researches about studies of TTM on the treatment of OHCA was performed. In Jan 2016, a literature search was conducted at Department

of Cardiology, the First College of Clinical Medical Sciences, Institute of Cardiovascular Diseases, China Three Gorges University. A systematic search of the English literature was conducted using the Medline, EMBASE, Cochrane Library Database for the years 1990 to 2016. The literature searches (based on English only) by using medical subject headings and free-text words: (“hypothermia” or “therapeutic temperature management” or “targeted temperature management” or “therapeutic hypothermia”) plus (“cardiac arrest” or “heart arrest” or “cardiopulmonary resuscitation” or “out-of-hospital arrest (OHCA)”).

Ethical approval was obtained

from the Scientific Research Committee of the Three Gorges University.

#### Data selection and extraction

The inclusion criteria are revealed as follows: (1) study design: all randomized, cluster-randomized or quasi-randomized trials comparing pre-hospital TTM to standard treatment (without TTM) in humans were included in this systematic review and meta-analysis, (2) type of participants: patients without-of-hospital cardiac arrest, (3) intervention: TTM, (4) comparator: standard treatment (without TTM), (5) outcomes: survival to hospital discharge and neurological status. Studies were excluded from the analysis if (1) it unable to extract the concrete data from the published results such as comments, letters, case reports, abstracts, reviews, as well as experimental studies (for example, cell culture and isolated organs) and animal studies, (2) studies with small-sized groups (<10 patients), (3) the outcomes were not clearly reported between the two different routes, (4) studies of traumatic cardiac arrest, pediatric arrest, and in-hospital arrest. The identifying of titles, abstracts and the abstracting of data were actualized by two investigators independently. All disagreements were discussed by the two viewers and ultimately

## A meta-analysis of TTM after cardiac arrest

**Table 1.** Characteristics of the clinical trials included in the meta-analysis

First Author	Year	Participating site	Number (n)			Gender (M/F)	Age, Y (TTM/N)	Shockable rhythm		Cooling methods in field		Temperature (TTM/C)
			Total	TTM	C			TTM (n)	C (n)	TTM	C	
Hachimi-Idrissi [10]	2001	Belgium	30	16	14	18/12	76.5/74	Unclear	Unclear	A helmet device containing an aqueous glycerol solution	No cooling	34°C/36°C
HACA [11]	2002	European	275	137	138	210/65	59/59	133/137 (97%)	132/138 (96%)	Cooling blanket that covered the body	No cooling	33°C/36°C
Bernard [12]	2002	Australia	77	43	34	52/25	66.8/65	43/43 (100%)	34/34 (100%)	Applying cold packs to the patient's body	No cooling	33°C/36°C
Laurent [13]	2005	France	42	20	22	32/8	56/52	Unclear	Unclear	Direct external cooling of blood	No cooling	33°C/36°C
Kamarainen [14]	2009	Finland	37	19	18	35/2	59/63	Unclear	Unclear	Internal cooling using a specific device	No cooling	33°C/36°C
Nielsen [9]	2013	Europe, Australia	939	473	466	761/178	64/64	375/473 (79%)	377/466 (81%)	Internal cooling using a specific device	No cooling	34°C/35°C
Frydland [15]	2015	Europe, Australia	178	96	82	135/43	68/68	0/96 (0%)	0/82 (0%)	Surface temperature management devices and cold packs	No cooling	33°C/36°C
Perman [16]	2015	American	402	201	201	221/181	60/62	0/201 (0%)	0/201 (0%)	Internal or external cooling	No cooling	33°C/36°C
Bro-Jepesen [17]	2015	Denmark	169	86	83	148/21	Unclear	Unclear	Unclear	The use of a surface cooling device	No cooling	33°C/36°C

TTM, therapeutic temperature management; C, control group; M, male; F, female; Y, year; HACA: The hypothermia after cardiac arrest study group.

## A meta-analysis of TTM after cardiac arrest

**Table 2.** Summary of the quality evaluation by Jadad scale of clinical trials of TTM after CA

Trials	Random sequence generation	Allocation concealment	Double blinding	Description of withdrawals and drop-out	Score
Hachimi-Idrissi 2001 [10]	2	1	1	1	5
HACA 2002 [11]	2	2	1	1	6
Bernard 2002 [12]	2	1	1	1	5
Laurent 2005 [13]	2	1	1	0	4
Kamarainen 2009 [14]	2	1	1	1	5
Nielsen 2013 [9]	2	2	2	1	7
Frydland 2015 [15]	2	2	1	1	6
Perman 2015 [16]	2	2	2	1	7
Bro-Jeppesen 2015 [17]	2	1	1	1	6

TTM, therapeutic temperature management; CA, cardiac arrest.

resolved for the potential of disagreement and discordance by corresponding author.

### Study quality assessment

The quality assessments were evaluated by the Jadad composite scale, a numerical score from zero (the weakest) to seven (the strongest), which contains the following points: (1) random sequence generation (0-2), (2) double blinding (0-2), (3) allocation concealment (0-2), (4) description of withdrawals and drop-outs (0-1). When the total score of 0-3 indicates a low quality and 4-7 shows a high quality.

### Data synthesis methods

All statistical analyses were performed by using Review Manager 5.3 to provide the mean difference (MD) and relative risk ratio (RR) with 95% confidence intervals (95% CI), and the statistical method of Mantel-Haenszel were used for dichotomous data, well as heterogeneity index  $I^2$  statistics were used for assess heterogeneity. Entire statistical significance was set at 0.05.

## Result

### Included clinical trials

**Figure 1** shows the selection process of the literature search. Out of 2179 reports initially found, of which 2148 were eliminated for various reasons through screening of the title and abstract. The full texts of the remaining 9 articles [9-17], finally matched inclusion criteria for

analyses, which were published between 2002 and 2016.

### Characteristics of the included clinical trials

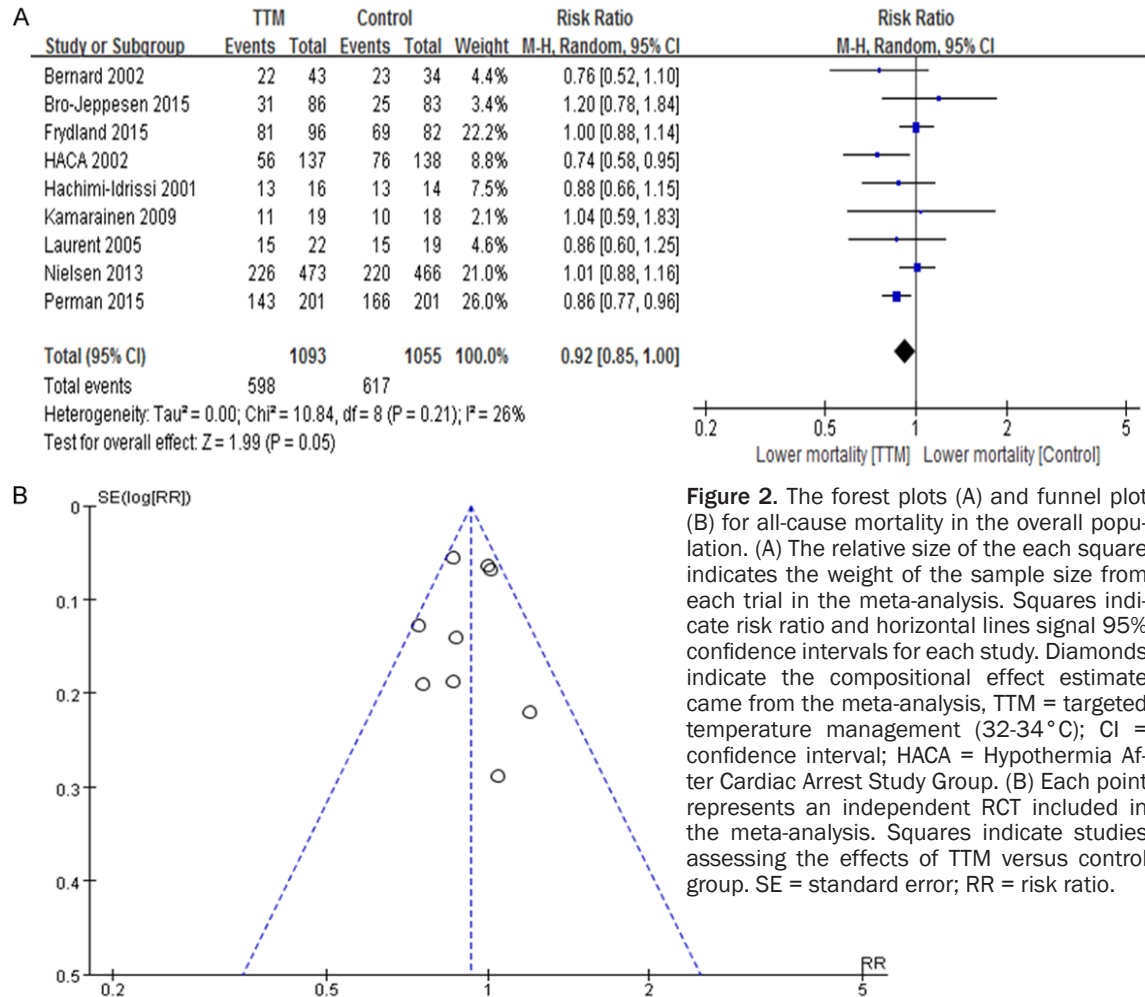
The baseline characteristics of the study populations are shown in **Table 1**. In total, 9 randomized controlled trials (RCTs) enrolling 2149 participants (TTM group:  $n = 1091$ , control group:  $n = 1058$ ) were included in the studies and ana-

lyzed ultimately (most of them are male). Sample sizes of the individual researches ranged between 37 and 939. They were conducted in the European, American and Australia. Types of cardiac arrest include shockable rhythm and non-shockable rhythm. The cooling methods varied among the studies and some used a mixture of methods such as ice packs, cooling blankets, direct external cooling of blood, internal or external cooling using a specific device. All RCTs included are of high quality (4 to 7 points) according to the Jadad quality scale, which is shown in **Table 2**.

### The results of data analysis

Dichotomous data on all-cause mortality were reported in all the 9 RCTs [9-17] included in the meta-analysis. They have a good homogeneity. **Figure 2A** shows the effect of TTM on all-cause mortality. The frequency of mortality was 54.7% in the TTM group versus 58.4% in the control group (random-effects RR 0.92; 95% CI, 0.85-1;  $P = 0.21$ ,  $I^2 = 26\%$ ). Although the all-cause mortality in the TTM group was lower than that in the control group, but the difference was not statistically significant. Dichotomous data on good neurological outcome (cerebral performance category 1-2) were reported in 8 included RCTs [9-16]. **Figure 3A** shows the effect of TTM on neurological outcome. The frequency of good neurological outcome (cerebral performance category 1-2) was 39.1% in the TTM group versus 35.3% in the control group (random-effects RR 1.12; 95% CI, 1-1.25;  $P = 0.02$ ,  $I^2 = 58\%$ ). The difference was statistically significant.

## A meta-analysis of TTM after cardiac arrest



**Figure 2.** The forest plots (A) and funnel plot (B) for all-cause mortality in the overall population. (A) The relative size of each square indicates the weight of the sample size from each trial in the meta-analysis. Squares indicate risk ratio and horizontal lines signal 95% confidence intervals for each study. Diamonds indicate the compositional effect estimate came from the meta-analysis, TTM = targeted temperature management (32-34 °C); CI = confidence interval; HACA = Hypothermia After Cardiac Arrest Study Group. (B) Each point represents an independent RCT included in the meta-analysis. Squares indicate studies assessing the effects of TTM versus control group. SE = standard error; RR = risk ratio.

### Evaluation for publication bias

Considering all the 9 RCTs, the funnel plot of all causes of mortality (**Figure 2B**) and neurological outcome (**Figure 3B**) were symmetrical. The results indicate that publication bias is low for the 9 RCTs included in the meta-analysis.

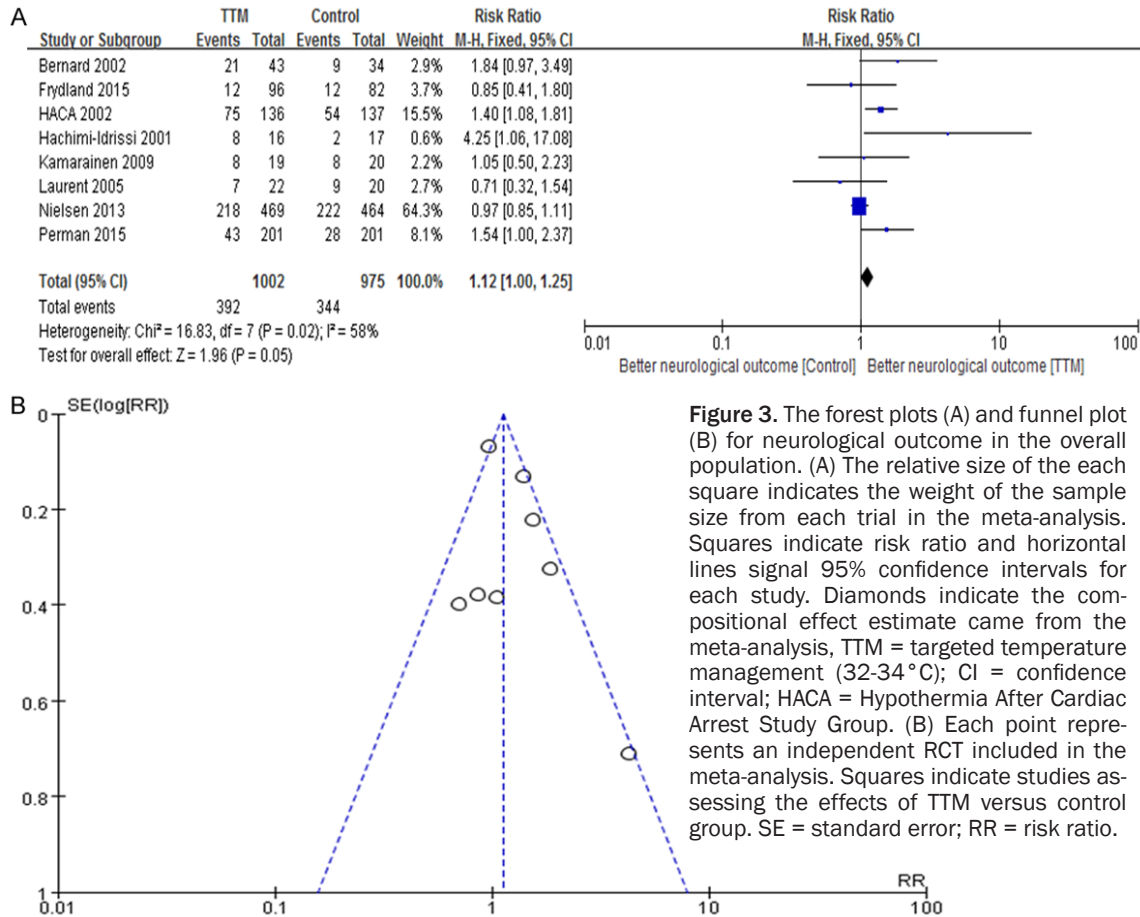
### Discussion

TTM currently has a place in post-resuscitation care. However, whether it can make patients benefit from the treatment is still controversial. In order to compare the efficacy of TTM group (core body temperature 32-34 °C) with the control group (core body temperature about 36 °C) in the treatment of adult cardiac arrest. We identified nine randomized trials (total patients n = 2149), assessing the impact of pre-hospital TTM on improve mortality and neurological outcome in patients suffering from cardiac arrest.

This includes 2 RCTs not previously cited in meta-analysis, including the latest trial published by Perman et al [16] in *Circulation* and by Bro-Jeppesen et al [17] in *Critical care medicine*.

The first recordation of the use of TTM was published around 1960 [18, 19]. 30 years later, TTM is thought to be to reduce the cerebral metabolism of glucose and oxygen consumption in patients suffering from cardiac arrest [20]. In 2001, Hachimi-Idrissi reported that, TTM induced by a helmet device was feasible, and effective improve survival and neurological outcomes, with no increase in complications [10]. A relative large sample sizes randomized controlled trials accomplished by the Hypothermia after Cardiac Arrest Study Group in 2002 [11], they found that among patients with ROSC after cardiac arrest, systemic cooling core body temperature to 32-34 °C improved

## A meta-analysis of TTM after cardiac arrest



**Figure 3.** The forest plots (A) and funnel plot (B) for neurological outcome in the overall population. (A) The relative size of the each square indicates the weight of the sample size from each trial in the meta-analysis. Squares indicate risk ratio and horizontal lines signal 95% confidence intervals for each study. Diamonds indicate the compositional effect estimate came from the meta-analysis, TTM = targeted temperature management (32-34 °C); CI = confidence interval; HACA = Hypothermia After Cardiac Arrest Study Group. (B) Each point represents an independent RCT included in the meta-analysis. Squares indicate studies assessing the effects of TTM versus control group. SE = standard error; RR = risk ratio.

the possible of survival and neurological outcomes compared with standard care. In the same year accomplished by Bernard et al [12], in 2005 accomplished by Laurent [13]. They got similar results with the Hypothermia after Cardiac Arrest Study Group. However, Kamarainen et al [14] and Nielsen et al [9] reported that there were no significant differences between the TTM group and control standard care group in mortality and neurological outcomes among adult cardiac arrest patients. In 2015, Perman et al [16] superinduce new evidence for the benefit of TTM in the treatment of cardiac arrest. In spite of the fact that the number of the sample sizes was not much. According to the patient's age, gender, location of arrest, witnessed arrest, and duration of arrest. 402 patients (201 pairs) were selected from 519 patients. Allow each pair to be matched to its closest neighbor. Thus the patient and arrest characteristics between TTM group and control group are similar. The RCT is more convincing because it excludes other differences.

For the recovery of neurological outcomes, Bro-Jeppesen's article does not have a concrete numerical value. And they concluded that the mortality rate was higher in the TTM group than control group. If they calculate the recovery of neurological function, the comprehensive result of the recovery of neurological outcomes may be altered.

A number of limitations existed in the process of the meta-analysis. Firstly, the patients and investigators could not be double-blinded to the treatment, but it seems to be completely avoided. Secondly, there are significant differences between the TTM group and the control group in the basic features of the cardiac arrest patients. For example, Bernard's work showed that the proportion of male patients in TTM group was 58%, while that of the control group was 79%, *P* value = 0.05, the difference was statistically significant. Although they confirmed that TTM could improve mortality and neurological outcomes. But they did not rule out the possibility that the results were affect-

ed by gender differences. Thirdly, the cooling methods varied among the studies and some used a mixture of methods such as ice packs, cooling blankets, internal or external cooling using a specific device. In addition, the sample size of some RCTs is too small, such as complete by Hachimi-Idrissi et al (n = 30), Kamarainen et al (n = 37), Laurent et al (n = 42).

### Conclusion

Despite the limitation of this meta-analysis for randomized controlled trials. The present meta-analysis demonstrated that TTM was associated with a non-significant reduction in all-cause mortality, but with a significant improvement in neurological outcome recovery. Long-term randomized controlled trials with larger sample sizes should be carried out to confirm the exact mechanisms of TTM in the treatment of adult cardiac arrest

### Acknowledgements

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### Disclosure of conflict of interest

None.

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