








# Should targeted temperature management be used in cardiogenic shock patients? Systematic review and meta-analysis

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## Abstract

**Background:** Therapeutic hypothermia, or targeted temperature management (TTM), is a strategy of reducing the core body temperature of survivors of sudden cardiac arrest, cardiogenic shock (CS) or stroke. Therefore, a systematic literature review and meta-analysis were performed to tackle the question about whether the implementation of TTM is actually beneficial for patients with CS.

**Methods:** Study was designed as a systematic review and meta-analysis. PubMed, Cochrane Library, Web of Science and Scopus were searched from these databases inception to July 17, 2022. Eligible studies were those comparing TTM and non-TTM treatment in CS patients. Data were pooled with the Mantel-Haenszel method.

**Results.** Thirty-day mortality was reported in 3 studies. Pooled analysis of 30-day mortality was 44.2% for TTM group and 48.9% for non-TTM group (risk ratio: 0.90; 95% confidence interval: 0.75 to 1.08;  $p = 0.27$ ). Other mortality follow-up periods showed also no statistically significant differences ( $p > 0.05$ ). The occurrence of adverse events in the studied groups also did not show statistically significant differences between TTM and non-TTM groups ( $p > 0.05$  for myocardial infarction, stent thrombosis, sepsis, pneumonia, stroke or bleeding events).

**Conclusions:** The present analysis shows no significant benefit of TTM in patients with CS. Moreover, no statistically significant increase of the incidence of adverse effects was found. However, further randomized studies with higher sample size and greater validity are needed to determine if TTM is worth implementing in CS patients. (Cardiol J)

**Key words:** targeted temperature management, therapeutic hypothermia, cardiogenic shock, outcome, meta-analysis

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## Introduction

Cardiogenic shock (CS) is a life-threatening condition characterized by hypoxia and end-organ hypoperfusion, caused by severe impairment of the myocardium and diminished cardiac output [1]. With its mechanical complications, acute myocardial infarction (AMI) is responsible for most CS cases still burdened by significant mortality [2]. The persistence of high mortality rates, varying from 38% to 65% [3, 4] is very distressing despite the fact that technical treatment of AMI complicated by CS has improved over the last decades [5].

In this regard, targeted temperature management (TTM) through therapeutic hypothermia (32°C – 34°C for 12 to 24 hours by surface cooling or endovascular cooling) has been investigated in several studies [6–9]. This level of hypothermia has a potentially neuroprotective effect [10, 11]. It works by reducing the brain's metabolism and thus the oxygen, adenosine triphosphate, and glucose consumption, which are associated with reducing reperfusion injury [6, 9]. The large randomised controlled trial brought more evidence of the beneficial use of TTM in patients after cardiac arrest (CA) with no shockable rhythm, leading to a higher percentage of patients with a favourable neurologic outcome at day 90 [12].

According to current recommendations, TTM is the standard of care in adult patients with return of spontaneous circulation after out-of-hospital and in-hospital ventricular fibrillation CA [13–16]. A common complication after CA is fever, which has an incidence of 42%, and therefore TTM is effective in these patients [15, 16]. Randomized studies on porcine models showed possible benefits of TTM in CS with reduced acute mortality and hemodynamic parameter improvements [17, 18]. Unfortunately, this finding was not confirmed in humans [19].

Based on these assumptions, a systematic literature review and meta-analysis to tackle whether the implementation of TTM is beneficial for patients with CS was conducted herein.

## Methods

The systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [20]. Due to study character (meta-analysis), ethical approval or patient consent was not suitable for this study.

## Literature search

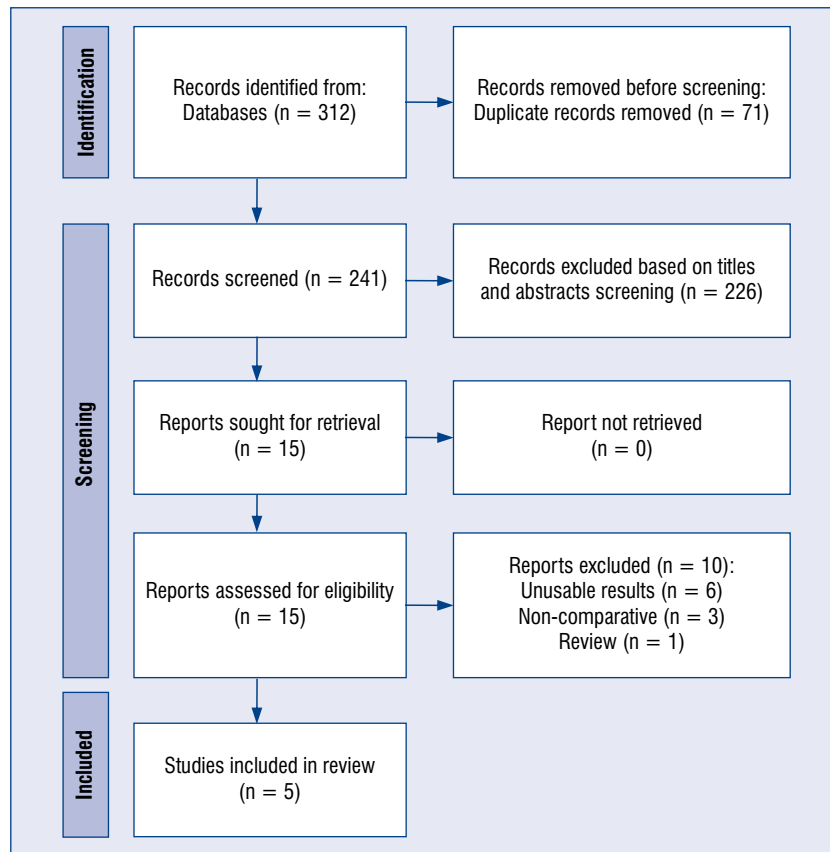
In this systematic review and meta-analysis, PubMed, Cochrane Library, Web of Science and Scopus was searched from these databases inception to July 17, 2022, for peer-reviewed original primary research articles, including observational or interventional studies, describing the outcomes of targeted temperature management in cardiogenic shock. For the search, the search term: “targeted temperature management” OR “TTM” OR “hypothermia” OR “therapeutic hypothermia” OR “mild hypothermia” AND “cardiogenic shock” OR “cardiogenic” OR “shock” was used. Additionally, manually checking the reference lists was done in each involved publication to identify eligible studies. Language and publication year restrictions were not applied. De-duplication and screening were carried out on EndNote software (X9; Claritive; Philadelphia, PA, USA).

## Inclusion and exclusion criteria

Two reviewers (M.P. and L.S.) independently screened the titles and abstracts against the agreed inclusion criteria and then extracted and relevant full-text records were selected. Discrepancies were resolved through discussion at each stage by consensus. Two additional reviewers (M.J.J. and A.G.) verified the eligibility of inclusion of the studies when necessary. Studies that were included in this meta-analysis had to fulfil the following PICOS criteria: (1) Participants, patients with 18 years old or older with cardiogenic shock; (2) Intervention, TTM; (3) Comparison, non-TTM; (4) Outcomes, detailed information for survival or mortality; (5) Study design, randomized controlled trials (RCT) and observational trials (non-RCT) comparing TTM and non-TTM care for their effects in patients with CS. Studies were excluded if they were reviews, observational studies, animal studies, case reports, letters, conference or poster abstracts, or articles not containing original data.

## Data extraction

Two reviewers (L.S. and M.P.) independently extracted data which were then checked for accuracy by a third reviewer (J.S.). Extracted data included: year of study, country, study design, patient demographics, and study outcomes. Mortality (within 30-days) was evaluated as the primary outcome. The secondary endpoint was major adverse cardiovascular and cerebrovascular events, i.e. a composite of death, myocardial infarction, stent thrombosis or stroke during a long-term observation period.



**Figure 1.** Flow diagram showing stages of the database search and study selection as per Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

### Quality assessment

Two reviewers (A.G. and M.P.) independently evaluated studies for risk of bias and quality assessment. Any disagreements were discussed and resolved in a consensus meeting with the third reviewer (L.S.). The RoB 2 tool (revised tool for risk of bias in randomized trials) was used to assess the quality of randomized studies [21], and the ROBINS-I tool (tool to determine the risk of bias in non-randomized studies of interventions) was used to assess the quality of non-randomized trials [22]. The risk of bias assessments was visualized using the Robvis application [23].

### Statistical analyses

All statistical analyses were performed using Review Manager 5.4 Software (RevMan; The Cochrane Collaboration, Oxford, UK). An alpha criterion of a p-value less than 0.05 was considered statistically significant. Depending on the reported effect size measures, pooled risk ratios (RR), odds ratios (OR) or mean difference (MD), and 95% confidence intervals (CI) were calculated. When the continuous outcomes were reported in a study as

median, range, and interquartile range, means and standard deviations were estimated using the formula described by Hozo et al. [24]. A random-effects approach (inverse variance or Mantel-Haenszel) was chosen to allow expected heterogeneity across the studies. The degree of heterogeneity among studies was based on the Cochrane Q statistics and  $I^2$  statistics [25].  $I^2$  values of 50% or less corresponded to low to moderate, and 75% or higher indicated large amounts of heterogeneity.

### Results

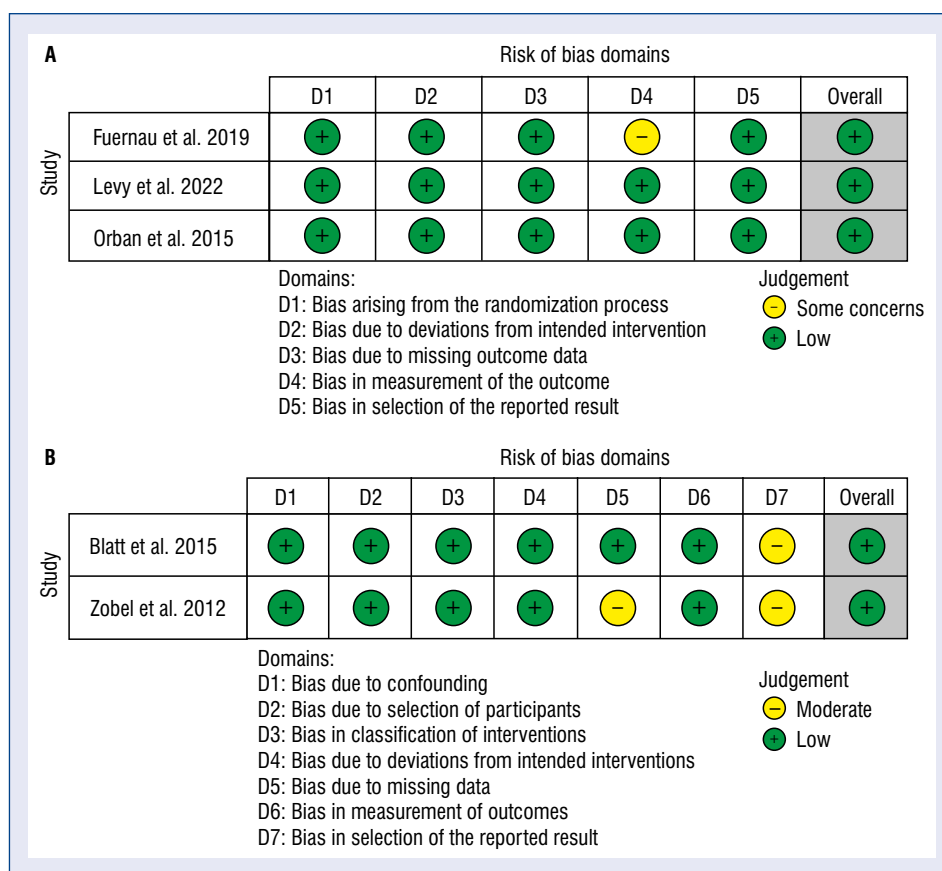
The flow diagram describing study selection is shown in Figure 1. A total of 5 studies [19, 26–29] comprising of 580 patients met the inclusion criteria. They included patients with cardiogenic shock between 2012 and 2022. Table 1 displays the baseline characteristics between patients with CS with or without TTM.

No significant differences between two patient cohorts were observed in the age ( $68.7 \pm 12.8$  vs.  $69.1 \pm 12.7$  years, respectively; MD: 0.18; 95% CI:  $-135$  to  $1.72$ ;  $p = 0.81$ ) or male gender (79.5%

**Table 1.** Patient characteristics among included trials.

Study	Country	Study design	TTM group			Non-TTM group		
			No.	Age	Sex, male	No.	Age	Sex, male
Blatt et al. 2015	Israel	Prospective, open label	8	69.6 ± 7.0	6 (75.0%)	13	65.1 ± 10	9 (69.2%)
Fuernau et al. 2019	Germany	RCT	20	76.5 ± 2.3	12 (60.0%)	20	76.3 ± 3.2	14 (70.0%)
Levy et al. 2022	France	RCT	168	57 ± 12	128 (76.2%)	166	59 ± 12	125 (75.3%)
Orban et al. 2015	Germany	RCT	64	69.1 ± 13	55 (85.9%)	81	70.4 ± 12.1	53 (65.4%)
Zobel et al. 2012	Germany	Mached trial	20	59.5 ± 15	16 (80.0%)	20	59.3 ± 16.5	17 (85.0%)

RCT — randomized controlled trial; TTM — targeted temperature management



**Figure 2.** A summary table of review author judgements for each risk of bias item for randomized trials (A) and non-randomized trials (B).

vs. 69.4%, respectively; OR: 1.36; 95% CI: 0.54 to 3.41; p = 0.52). Polled analysis of patient characteristics between TTM and non-TTM groups is shown in **Suppl. Table S1**). The results of the

assessment of risk of bias among the four included studies is provided in Figure 2.

Thirty-day mortality was reported in three studies. Polled analysis of 30-day mortality was

**Table 2.** Pooled analysis of outcomes in targeted temperature management (TTM) and control groups.

Parameter	No. of studies	The frequency of occurrence		Events		Heterogeneity between trials		P-value for differences across groups
		TTM	Control	RR	95% CI	P-value	I <sup>2</sup> statistic	
Mortality:								
30-days	4	44.2%	48.9%	0.90	0.75 to 1.08	0.59	0%	0.27
6-months	1	52.4%	57.8%	0.91	0.75 to 1.10	NA	NA	0.32
1-year	1	75.0%	75.0%	1.00	0.70 to 1.43	NA	NA	1.00
2-years	1	65.0%	60.0%	1.08	0.67 to 1.75	NA	NA	0.74
Myocardial injury	1	6.3%	6.2%	1.01	0.26 to 3.94	NA	NA	0.98
Stent thrombosis	1	4.7%	0.0%	9.28	0.47 to 182.93	NA	NA	0.14
Sepsis	1	5.0%	0.0%	3.15	0.12 to 82.16	NA	NA	0.49
Pneumonia	1	45.0%	30.0%	1.91	0.52 to 7.01	NA	NA	0.33
Stroke	2	3.6%	4.0%	0.85	0.19 to 3.91	0.54	0%	0.84
Bleeding events or blood transfusion	3	42.5%	38.2%	1.18	0.83 to 1.67	0.28	22%	0.36

CI — confidence interval; NA — not applicable; RR — risk ratio

47.8% for TTM group and 46.5% for non-TTM group (RR: 1.04; 95% CI: 0.78 to 1.39;  $p = 0.86$ ). Other mortality follow-up periods showed also no statistically significant differences ( $p > 0.05$ ). The occurrence of adverse events in the studied groups also did not show statistically significant differences between TTM and non-TTM groups ( $p > 0.05$  for myocardial infarction, stent thrombosis, sepsis, pneumonia, stroke or bleeding events). The detailed characteristics of the outcomes are presented in Table 2.

## Discussion

Despite early revascularization strategy and advanced treatment, AMI complicated by CS is still burdened by the high mortality rate. Therapeutic hypothermia has shown its efficacy in the treatment of CA, but recent evidence has not provided significant effectiveness of TTM in case of proceeding AMI complicated by CS. This meta-analysis aims to summarize knowledge of the subject matter.

Out of the four studies included in this meta-analysis [19, 26–29], three showed no significant clinical advantages of TTM therapy, with no benefit in terms of 30-day survival (47.8% vs. 46.5; RR: 1.04 [0.78–1.39]). The usefulness of TTM was investigated in several trials, but most of these studies were performed on a small number of patients. Oddo et al. [30] showed that TTM might improve patient outcomes, particularly in the short

duration of CA. On the contrary, Noc et al. [31] demonstrated that the intravascular cooling system favored a longer ischemic delay with increased adverse events rate and no benefit in myocardial tissue protection.

During AMI, TTM may reduce infarct size when performed before reperfusion [32, 33]. However, when CS complicates AMI, outcomes did not show a significant difference compared to a control group (6.3% vs. 6.2%; RR: 1.01; 95% CI: 0.26 to 3.94;  $p = 0.96$ ). In the TTM group, the only mild (but statistically insignificant) trend toward reduction of biochemical markers (creatinine kinase, troponin T) was observed [26]. This may be due to a delayed cooling start time or measuring infarct size with biomarkers only.

Bleeding events and blood transfusions were also included in the analysis. One study showed a higher risk of TIMI significant bleedings ( $p = 0.07$ ). However, most of them were related to the arterial catheterization access for percutaneous coronary intervention [27]. It is known that hypothermia causes coagulopathy with increased clotting time; this event is called hypothermic coagulopathy [34]. One Meta-Analysis of Randomized Controlled Trials [35], which consisted of 43 trials and included 7,528 patients, did not find an increased risk of hemorrhage in patients treated with TTM in general, despite a higher risk of thrombocytopenia and transfusion requirement for patients treated with TTM, particularly in those cooled longer than 48 hours. Thus, TTM should be performed

for a maximum period of 24 hours. One study [27], included in the pooled analysis, suggested a potential higher incidence of stent thrombosis. However, several studies have shown that TTM in AMI patients undergoing percutaneous coronary intervention is safe and is not related to increased incidence of stent thrombosis [36, 37]. However, those studies did not include patients who had CS. An extensive retrospective analysis [38], including 49,109 CA patients with AMI undergoing PCI, considered 1,193 patients treated with TTM. This analysis showed that patients undergoing therapeutic hypothermia, who developed CS, presented a greater incidence of stent thrombosis compared with no TTM group (OR: 1.3; 95% CI: 1.0 to 1.6;  $p = 0.04$ ). No other significant differences in the TTM group regarding stent thrombosis, bleeding events [39], arrhythmias, infection, coagulopathy, or hypotension [40] were observed.

Furthermore, an increased risk of sepsis and pneumonia was not found in the present study. Still, considering the studies that showed an increased risk of these adverse effects in other disease units, such as CA, caution should be exercised [41, 42].

To sum up, the pooled analysis of all four studies showed that using TTM in CS patients is safe. No evidence of excessive adverse events was found in the TTM group. The safety and feasibility of TTM are described in the literature associated with CA's treatment [12, 43] and CS [44].

### Limitations of the study

The findings of this analysis have to be seen in light of some limitations. Firstly, it must be stressed that it included only one randomized control trial. Some studies comprise a retrospective control group, and that increases the risk of bias.

Meaningful drawbacks include a small number of patients in each study who were additionally enrolled by different inclusion and exclusion criteria. It has caused that a part of studies excluded patients who underwent CA, whereas one study included them. Furthermore, one study based its inclusion criteria on the availability of a platelet function assessment. The SHOCK-COOL Trial by Fuernau et al. [19] does not describe any criteria because the trial was started before introducing the data-sharing policy. Zobel et al. [28] presents an analysis of patients who suffered from AMI and had only moderately reduced ejection fraction. Therefore, results could be different in patients with more severe compromised left ventricular function.

Cooling methods were also not consistent. The desired temperature was not reached in all

patients in the TTM group. The duration of cooling in the majority of the studies was 24 hours — however, the odd one comprised 12 hours of the cooling procedure. The meaningful fact is that the standardization of cooling procedures is relevant, which cannot be seen in this review.

### Conclusions

In summary, the present analysis shows no significant benefit of TTM in patients with CS. Moreover, no statistically significant increase was found in the incidence of adverse effects. However, further randomized studies with higher sample sizes and greater validity are needed to determine if TTM is worth implementing in CS patients.

### Acknowledgments

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**Conflict of interest:** Adam Nieborek — work for BARD Poland; all other authors report no conflicts of interest.

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