Interventional procedure overview of temperature control to improve neurological outcomes after cardiac arrest

Cardiac arrest is when the heart suddenly stops pumping blood around the body. A person whose heart is restarted after cardiac arrest can have poor neurological outcomes. This is because their brain has not had enough oxygen during the cardiac arrest, which can cause brain injury.

In this procedure, after a person's heart is restarted and while they are still in a coma, their body temperature is controlled. Either their body is kept at a normal temperature of between 36.5°C and 37.5°C to prevent fever, or it is cooled to between 32°C and 36°C. Both are done for 1 to 3 days. The aim is to improve survival and neurological outcomes.

Contents

Table 1 Abbreviations

Abbreviation	Definition
CI	confidence interval
CPC	Cerebral Performance Category
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
IHCA	in-hospital cardiac arrest
IV	intravenous
NSR	non-shockable rhythm
NWMA	network meta-analysis
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
RCT	randomised controlled trial
ROSC	return of spontaneous circulation
RR	risk ratio
SR	shockable rhythm
TSA	trial sequential analysis
TTM	targeted temperature management
VAS	visual analogue scale
VF	ventricular fibrillation
VT	ventricular tachycardia/tachyarrhythmias

Indications and current treatment

Cardiac arrest is when normal blood circulation suddenly stops because the heart fails to contract effectively. The underlying abnormal cardiac rhythms most commonly associated with cardiac arrest are ventricular fibrillation (VF), asystole, pulseless electrical activity, and pulseless ventricular tachycardia (VT). Cardiac arrest leads to loss of consciousness, respiratory failure and, ultimately, death.

Treatment for cardiac arrest includes immediate cardiopulmonary resuscitation to restore the circulation and prevent subsequent brain injury. Defibrillation may be

used to treat VF and pulseless VT rhythms. Standard care may also include mechanical ventilation, and drugs such as adrenaline and amiodarone. Resuscitation Council UK's 2021 resuscitation guidelines contain guidance on basic and advanced life support.

Temperature control may also be described as targeted temperature management.

Unmet clinical need

Neurological outcomes from cardiac arrest remain poor despite advances in cardiac arrest management and post resuscitation care.

What the procedure involves

After cardiac arrest, people in a coma who have return of spontaneous circulation (ROSC) can have their core body temperature actively controlled. This is done to prevent fever (by maintaining a normal temperature of between 36.5°C and 37.5°C), or to induce therapeutic hypothermia (by cooling to a core temperature typically between 32.0°C and 36.0°C).

The aim is to reduce brain injury and improve neurological outcomes. The exact mechanism by which cooling may protect against brain injury is unknown. Possible mechanisms include reductions in metabolic demand, release of excitatory neurotransmitters and inflammation after ischaemia.

Temperature control is done using surface techniques (for example, heat exchange cooling pads, cooling blankets and ice packs), or internal techniques (for example, an endovascular cooling device). Core body temperature is monitored using a temperature probe (such as a bladder, rectal or nasopharyngeal temperature probe) and is controlled to a preset point determined by the clinician.

If therapeutic hypothermia is induced, controlled rewarming is usually done over several hours. In addition, people who have had cardiac arrest generally have standard critical care measures and may require intravenous sedation and muscle relaxants, to prevent shivering.

Outcome measures

The main outcomes included survival and neurological outcomes. The measures used are detailed in the following paragraphs.

A range of validated instruments are used to evaluate neurological outcome including:

- Cerebral performance categories (CPC): this is a 5-category measure used to assess neurological outcome. Categories 1 (good cerebral performance: conscious, alert, capable of normal life) and 2 (moderate cerebral disability: conscious, alert, sufficient cerebral function for activities of daily life) are considered to indicate a good neurological outcome. Categories 3 (severe cerebral disability), 4 (coma/vegetative state) and 5 (certified brain death) are considered to be a poor neurological outcome.

- Pittsburgh cerebral performance category: this is a 4-level illness severity score of 1 (good recovery), 2 (moderate disability), 3 (severe disability) or 4 (coma).

- The modified Rankin Scale: this is used to measure the degree of disability of people who have suffered a stroke or other causes or neurologic disability. The scale ranges from 0 to 6, with 0 for no symptoms, 3 for moderate disability (requires some help but able to walk without assistance), and 6 for dead.

Evidence summary

Population and studies description

This interventional procedures overview is based on 27,292 patients from 8 systematic reviews and meta-analyses and 1 RCT. There is an overlap between included primary studies (RCTs) within 7 of the systematic reviews. So, the actual number of patients in RCTs who had TTM with hypothermia was 3,082 patients, and those with normothermia was 1,610 patients. Another systematic review with 6 observational studies included 1,845 patients in the TTM with hypothermia group and 12,762 patients in the control group (TTM without hypothermia).

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 9 studies as the key evidence in table 2 and table 3, and lists 39 other relevant studies in table 5.

Most systematic reviews and meta-analyses were published between 2021 and 2023. Seven of the systematic reviews included the same 8 to 10 RCTs published up to 2021 (Fernando 2021, Granfeldt 2021, Elbadawi 2022, Sanfilippo 2021, Zhu 2022, Arrich 2023, Duhan 2023). Therefore, there is an overlap between included primary studies within the 7 systematic reviews. Only 1 systematic review and meta-analysis included observational studies (Yin 2022). One study did a network meta-analysis of different TTM strategies (Fernando 2021).

The systematic reviews listed first authors from Canada, Austria, Denmark, USA, Italy and China.

Seven systematic reviews included RCTs with adult patients after cardiac arrest with both OHCA and/or IHCA, SR or NSR and TTM was done pre-hospital or after hospital arrival. Two studies limited inclusion to patients with OCHA who remained unresponsive following signs of ROSC (Fernando 2021, Granfeldt 2021). One systematic review included patients with only IHCA (Yin 2022) and another systematic review focused on OHCA caused by NSR (Zhu 2022).

The mean age of patients in 3 systematic reviews was approximately 57 to 77 years (Fernando 2021, Granfeldt 2021, Elbadawi 2022). Most of the included population in 2 of these studies were male, ranging from 50% to 100% (Fernando 2021, Granfeldt 2021,).

Studies reported mainly survival, neurological outcomes and adverse events. The modified Rankin Scale, and CPC scale were the validated measures used to describe level of function and neurological outcomes in the studies.

The quality of evidence was assessed using GRADE methodology. The level of evidence was judged to be of low certainty in 3 systematic reviews (Fernando 2021, Granfeldt 2021, Arrich 2023). The Cochrane review included studies published from 2000 to 2021. Cooling methods varied across studies.

Follow up varied across studies ranging from hospital discharge to 6 months.

The RCT in patients with coma after IHCA was underpowered and was terminated early as interim analysis failed to show any difference in outcomes between the hypothermic temperature control (32 to 34°C) for 24 hours and normothermic groups (Wolfrum 2022).

Table 2 presents study details.

Figure 1 Flowchart of study selection

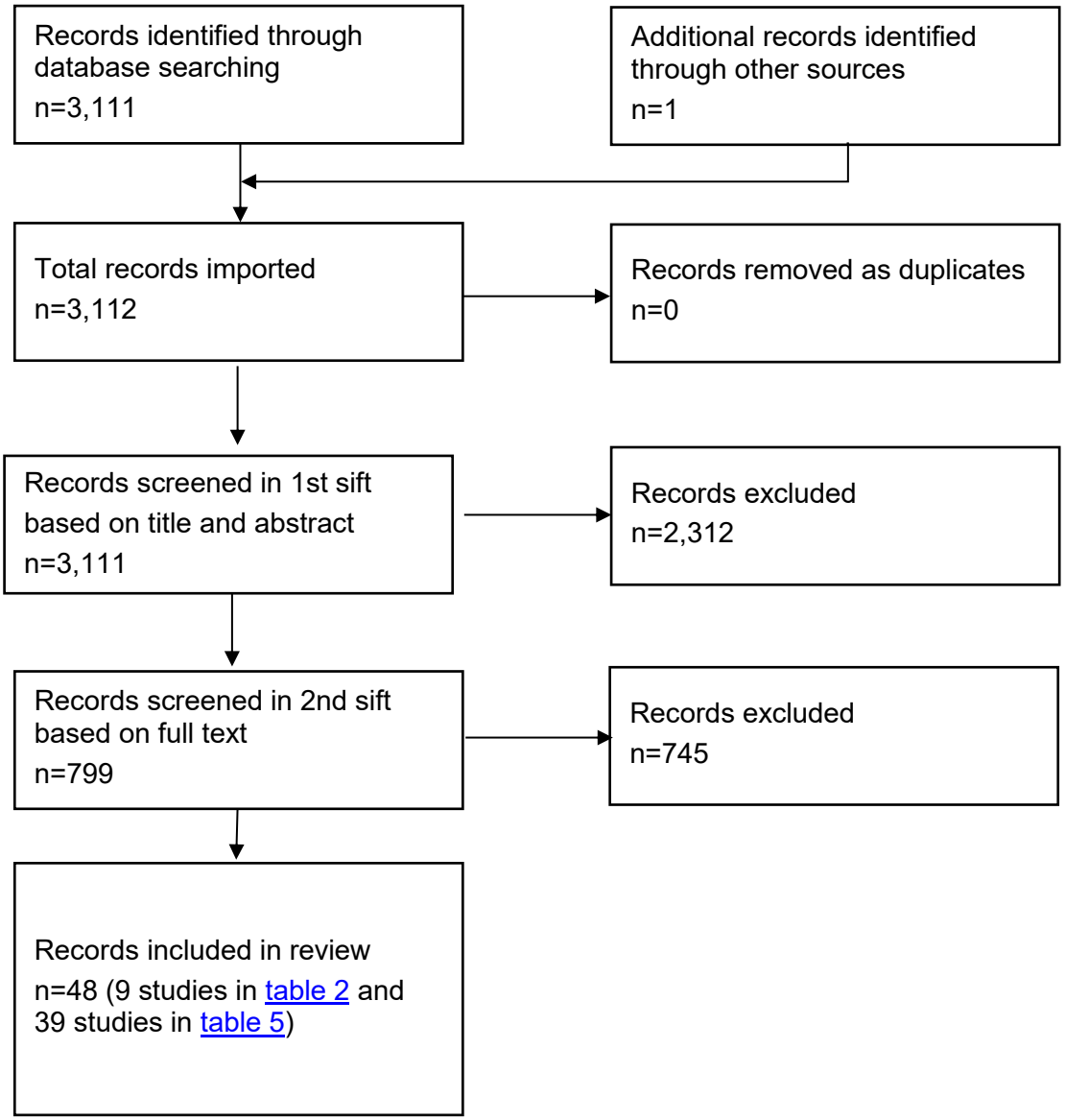

Table 2 Study details

Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
1	Fernando (2021) Canada	10 RCTs (between 2000-2021) (N = 4,218 patients with OHCA; range 30 to 1,861) Range 60 to 89% male patients with initial SR, (3 studies, n=502) patients with initial NSR (2 studies, n=452), mixed populations regardless of initial rhythm (5 studies, n=3,264).	Mean age range 56-75 years	Systematic review with network meta-analysis	Adult patients with OHCA and decreased level of consciousness post-ROSC for 10 minutes; with any initial cardiac rhythm; randomised to receive TTM with treatment arms of at least 2 different target temperatures, and with at least 1 arm having a targeted temperature ≤ 37.0°C; TTM continued for 24 hours; and reporting at least 1 outcome.	4 different target temperatures evaluated. Normothermia (37.0°C to 37.8°C) (n = 1,390) TTM with deep hypothermia (31.0°C to 32.0°C) (n = 276) TTM with moderate hypothermia (33.0°C to 34.0°C) (n = 2,086) TTM with mild hypothermia (35.0°C to 36.0°C) (n = 466)	6 months for primary and secondary outcomes

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Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
2	Granfeldt 2021 Denmark	Total 32 RCTs 9 RCTs (between 2001-2021) on TTM (n=2,968, range 16 to 1,861) % male, range TTM with hypothermia 56 to 100 Normothermia 63 to 80	Mean normothermia 51-80 years Hypothermia 52-77 years	Systematic review with network meta-analysis	Adult patients with cardiac arrest in any setting (in-hospital or out-of-hospital) who underwent TTM	Normothermia (no TTM, no clear description of TTM, or TTM to maintain normothermia generally 36.5°C to 38.0°C) required active cooling. TTM with hypothermia (at 32.0°C to 34.0°C)	90-180 days
3	Elbadawi A 2022 USA	8 RCTs (n=2,927) with OHCA (1 included 27% IHCAs) 72% men (TTM with hypothermia n=1,462 versus normothermia n=1,465)	Mean 62.4 years	Systematic review and meta-analysis	Adults with coma after cardiac arrest with SR or NSR, any targeted degree of hypothermia compared with normothermia, reporting survival and neurological outcomes.	TTM with hypothermia (varied from 31.7°C to 34.0°C) versus normothermia	Weighted mean follow up 4.9 months.

Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
4.	Sanfilippo F 2021 Italy	8 RCTs (n=3,855 patients; TTM at 32-34C, n=1,930; Normothermia n=1,925).	Not reported	Systematic review and meta-analysis	RCTs only, adult patients with both OHCA and/or IHCA, (SR or NSR), with TTM done after hospital arrival, reporting survival and neurological outcomes.	TTM range set at 32.0–34.0°C compared to controls (TTM with "actively controlled normothermia avoiding fever [3 RCTs, n=1,688]" or "uncontrolled" normothermia [5 RCTs, n=237]).	Ranged from 2 weeks or hospital discharge to 6 months.
5	Zhu YB 2022 China	14 RCTs [published between 2007-2021] n=4,009, (range from 10-776); with 2,022 patients in the TTM group and 1,987 patients in without-TTM group.	Not reported	Systematic review and meta-analysis	Adult survivor patients with OHCA caused by NSR asystole, or pulseless electrical activity who underwent TTM, regardless of the methods (evaporative cooling, infusion of cold saline, and surface or systemic cooling), duration of TTM, and targeted temperature (32.0 - 34.0°C).	Patients with NSR with TTM with hypothermia (32.0-34.0^{0}C) or without TTM (36.0-38.0^{0}C) (6 studies) Patients with NSR who had TTM (32.0-34.0°C) before hospital admission compared with in-hospital TTM (32.0°C -38.0°C) (8 studies)	Ranged from hospitalisation to 180 days.

Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
6	Yin L 2022 China	6 retrospective controlled cohort studies with a total of 14,607 patients (TTM group: 1,845, control group: 12,762).	Not reported	Systematic review and meta-analysis	Observational studies with more than 10 adult patients with IHCA; treated with TTM after ROSC and comparing with a control group; reporting discharge survival and neurological outcomes.	TTM with hypothermia compared with control group with no TTM with hypothermia	Hospital discharge
7	Duhan S 2023 USA	12 RCTs with 4,262 inpatients after a cardiac arrest. N=2,146 in therapeutic hypothermia (<36°C) arm versus n=2,116 in normothermia (≥36°C) arm 25% were female.	65 years in the therapeutic hypothermia arm and 64 years in the normothermia arm.	Systematic review and meta-analysis	RCTs with adults (aged ≥18 years) with OHCA or IHCA, comparing therapeutic hypothermia (<36°C) with normothermia (≥36°C), reporting clinical outcomes: mortality or neurological outcomes.	Therapeutic hypothermia (<36°C) with normothermia (≥36°C) Cooling methods: External cooling in 6 studies, internal and external cooling in 5 studies, not mentioned in 1 study. Mean cooling duration was 26 hours, and the warming duration ranged from 6 to 72	Varied from hospital discharge, or 1 to 6 months.

Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
						hours or until functional recovery.	
8	Arrich J 2023 Austria, Denmark.	12 studies (RCTs and quasi RCTs) with 3,956 patients who had had a cardiac arrest (in or out of hospital) and were successfully resuscitated.	Not reported	Systematic review and meta-analysis (Cochrane review)	RCTs and quasi-RCTs in adults comparing therapeutic hypothermia after cardiac arrest with standard treatment (control). Studies with adults cooled by any method, applied within 6 hours of cardiac arrest, to target body temperatures of 32°C to 34°C.	Therapeutic hypothermia (body target temperature 32°C to 34°C), regardless of how body temperature was reduced, applied within 6 hours of arrival at hospital versus control (standard treatment following cardiac arrest, i.e. no cooling or fever prevention).	6 months
9	Wolfrum S 2022 Germany	N=249 patients after IHCA (126 randomised to hypothermic temperature control and 123 to normothermia) 64% (152/236) male	72.6±10.4 years	RCT HACA in-hospital trial	patients 18 years and above who remained unconscious (Glasgow Coma Scale score ≤8) for more than 45 minutes after IHCA, irrespective of the initial rhythm or aetiology of cardiac	hypothermic temperature control (32-34°C) for 24 hours versus normothermia (avoid fever, temperature >37°C). in hypothermia group slow rewarming was done at a rate of 0.25°C/h	180 days

Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
					arrest, induction of hypothermic temperature control within 4 hours of return of spontaneous circulation.	to achieve a targeted temperature of 37.5°C. Target temperature (<34°C) was reached within 4.2 hours in the hypothermic group in 72% of patients and temperature was controlled for 48 hours at 37.0°C in the normothermia group.	

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Fernando (2021) Canada	**Survival with good functional neurological outcome** (at hospital discharge, or the latest time point reported up until 6 months post-discharge) NWMA estimates (10 RCTs included) TTM with deep hypothermia (31.0°C to 32.0°C) versus normothermia (37.0° to 37.8°C) (OR 1.30, 95% CI 0.73–2.30)	**Adverse events** NWMA estimates (10 RCTs included, compared TTM with hypothermia with normothermia) Arrhythmia: TTM with deep hypothermia (31.0°C to 32.0°C): OR 3.58 (95% CI 1.77 to 7.26)

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First author, date	Efficacy outcomes	Safety outcomes
	TTM with moderate hypothermia (33.0°C to 34.0°C) versus normothermia (OR 1.34, 95% CI 0.92–1.94) TTM with mild hypothermia (35.0°C to 36.0°C) versus normothermia (OR 1.44, 95% CI 0.74– 2.80) (GRADE all low certainty of evidence). TTM with deep hypothermia versus TTM with moderate hypothermia (OR 0.97, 95% CI 0.61–1.54, GRADE low certainty of evidence). TTM with deep hypothermia versus TTM with mild moderate hypothermia (OR 0.90, 95% CI 0.44–1.86; GRADE low certainty of evidence) TTM with mild hypothermia versus moderate hypothermia (OR 1.07, 95% CI 0.62–1.87; GRADE low certainty of evidence). **Overall survival** (survival at hospital discharge, or the latest time point reported up until 6 months post-discharge) NWMA estimates (10 RCTs included) TTM with deep hypothermia (31.0°C to 32.0°C) versus normothermia: OR 1.27 (95% CI 0.70 to 2.32) TTM with moderate hypothermia (33.0°C to 34.0°C) versus normothermia: OR 1.23 (95% CI 0.86 to 1.77) TTM with mild hypothermia (35.0°C to 36.0°C) versus normothermia: OR 1.26 (95% CI 0.64 to 2.49). TTM with deep hypothermia versus moderate hypothermia (OR 1.03, [95% CI 0.64 to 1.68])	TTM with moderate hypothermia (33.0°C to 34.0°C): OR 1.45 (95% CI 1.08 to 1.94) TTM with mild hypothermia (35.0°C to 36.0°C): OR 1.16 (95% CI 0.76 to 1.78) Bleeding: TTM with deep hypothermia (31.0°C to 32.0°C): OR 1.21 (95% CI 0.68 to 2.15) TTM with moderate hypothermia (33.0°C to 34.0°C): OR 1.10 (95% CI 0.78 to 1.55) TTM with mild hypothermia (35.0°C to 36.0°C): OR 1.21 (95% CI 0.66 to 2.21) Pneumonia: TTM with deep hypothermia (31.0°C to 32.0°C): OR 0.91 (95% CI 0.42 to 2.09) TTM with moderate hypothermia (33.0°C to 34.0°C): OR 1.24 (95% CI 0.79 to 1.95) TTM with mild hypothermia (35.0°C to 36.0°C): OR 1.21 (95% CI 0.41 to 2.33) Pair-wise meta-analysis estimates Sepsis: TTM with deep hypothermia (31.0°C to 32.0°C): Not available TTM with moderate hypothermia (33.0°C to 34.0°C): OR 1.36 (95% CI 0.88 to 2.10) TTM with mild hypothermia (35.0°C to 36.0°C): Not available • Seizure:

IP overview: temperature control to improve neurological outcomes after cardiac arrest.

First author, date	Efficacy outcomes	Safety outcomes
	TTM with deep hypothermia versus mild hypothermia (OR 1.01, [95% CI 0.47 to 2.14]) TTM with mild hypothermia versus moderate hypothermia (OR 1.02, [95% CI 0.79 to 1.32	TTM with deep hypothermia (31.0°C to 32.0°C): Not available TTM with moderate hypothermia (33.0°C to 34.0°C): OR 0.95 (95% CI 0.67 to 1.35) TTM with mild hypothermia (35.0°C to 36.0°C): Not available
Granfeldt 2021 Denmark	**Specific target temperature** Meta-analyses of TTM with hypothermia at 32-34°C compared to normothermia (9 RCTs) Favourable neurological outcome at hospital discharge or 30 days (3 RCTs): RR 1.30 (95% CI 0.83 to 2.03), p=0.26, I^2=84%. at 90 or 180 days (5 RCTs): RR 1.21 (95% CI 0.91 to 1.61), p=0.18, I^2=64%. Survival at hospital discharge or 30 days: RR 1.12 (95% CI 0.92 to 1.35), p=0.25, I^2=57%. at 90 or 180 days after CA: RR 1.08 (95% 0.89 to 1.30), p=0.43, I^2=49%. **Different temperature targets** (3 RCTs) 3 trials compared different temperature targets and found no difference in outcomes (TTM trial [Neilsen 2013] between 33.0°C and 36.0°C and 2 other trials [Lopez -de-Sa 2012, 2018] found no difference between 32.0°C, 33.0°C, and 34.0°C); (GRADE low certainty of evidence).	

IP overview: temperature control to improve neurological outcomes after cardiac arrest.

First author, date	Efficacy outcomes	Safety outcomes
	Timing of initiating TTM Meta-analyses of pre-hospital cooling versus no pre-hospital cooling (10 trials) Favourable neurological outcome at hospital discharge RR 1.00 (95% CI 0.90 to 1.11), p=0.76, I^2=0%. (moderate certainty of evidence) Survival at hospital discharge RR 1.01 (95% CI 0.92 to 1.11), p=0.93, I^2=0% (moderate certainty of evidence) Subgroup analysis Post-arrest cold IV fluid Survival to hospital discharge (6 studies): pre-hospital cooling (447/1,249) versus no pre-hospital cooling (442/1,251) RR 1.00 (95% CI 0.90 to 1.11), p=0.83, I^2=0%. Favourable neurological outcome at hospital discharge (5 studies): pre-hospital cooling (381/1,181) versus no pre-hospital cooling (383/1177), RR 0.98 (95% CI 0.87 to 1.10), p=0.65, I^2=0%. Intra-arrest cold IV fluid (2 studies) Survival to hospital discharge: pre-hospital cooling (70/741) versus no pre-hospital cooling (71/702), RR 0.93 (95% CI 0.68 to 1.27), p=0.46, I^2=0%. Favourable neurological outcome at hospital discharge: pre-hospital cooling (70/741) versus no pre-hospital cooling (67/702), RR 0.98 (95% CI 0.71 to 1.35), p=0.90, I^2=0%. Intra-arrest nasal cooling (2 studies)	

First author, date	Efficacy outcomes	Safety outcomes
	Survival to hospital discharge: pre-hospital cooling (77/428) versus no pre-hospital cooling (6/435) RR 1.15, (95% CI 0.85 to 1.54), p=0.37, I^2=0%. Favourable neurological outcome at hospital discharge: pre-hospital cooling (64/428) versus no pre-hospital cooling (53/435) RR 1.00 (95% CI 0.90 to 1.11), p=0.25, I^2=0%. **Methods used for TTM** Endovascular cooling versus surface cooling methods (3 RCTs) Survival to hospital discharge or 28 days: Endovascular (120/265) versus surface cooling (103/258); RR 1.14 (95% CI 0.93 to 1.38), p=0.21, I^2=0%. Favourable neurological outcome at hospital discharge or 28 days: Endovascular (94/265) versus surface cooling (75/258); RR 1.22 (95% CI 0.95 to 1.56), p=0.12, I^2=0%. **Duration of TTM** (1 RCT) Kirkegaard 2017 (n=355 OHCA) comparing 48 hours versus 24 hours found no difference in outcomes between durations.	
Elbadawi 2022 USA	Long-term mortality: TTM with hypothermia versus normothermia: 56.2% (785/1398) versus 56.9% (804/1,411), RR 0.96 (95% CI 0.87 to 1.06); p=0.45; I^2=41%.	TTM with hypothermia versus normothermia In-hospital mortality (5 studies): 64.7% (325/502) versus 72.2% (363/503); RR 0.88 (95% CI 0.77 to 1.01); p=0.07; I^2=35%.

First author, date	Efficacy outcomes	Safety outcomes
	OHCA with shockable rhythm: RR 0.87 (95% CI 0.68 to 1.11); p=0.09; I^2=59%. OHCA with non-shockable rhythm: RR 1.00 (95% CI 0.94 to 1.05); p=0.40; I^2=0%. Favourable neurological outcome (CPC 1 and 2, modified Rankin score 0 to 3): TTM with hypothermia versus normothermia 37.9% (535/1,412) versus 34.2% (479/1,399), RR 1.31 (95% CI 0.99 to 1.73); p=0.06, I^2=56%. Excluding the TTM2 trial: RR 1.45 (95% CI 1.17 to 1.79); p<0.001, I^2=1%.	Ventricular arrhythmias (4 studies): 22.8% (312/1,368) versus 16.6% (229/1,376); RR 1.36 (95% CI 1.17 to 1.58); p<0.001; I^2 =0%. Bleeding complications: 7.1% (95/1,346) versus 6.6% (89/1,357); RR 1.10 (95% CI 0.83 to1.44); p=0.51; I^2=0% Sepsis: 9.5% (128/1,345) versus 7.6% (103/1,357); RR 1.24 (95% CI 0.97to 1.59); p=0.08; I^2=0% Pneumonia: 22.8% versus 16.6%; RR 1.36 (95% CI 1.17 to1.58); p=0.42; I^2=0%.
Sanfilippo 2021 Italy	Survival (8 studies) with varied follow up. TTM with hypothermia at 32.0°C –34.0°C compared to normothermia (875/1,930) versus (861/1,925); RR 1.06 (95% CI 0.94 to 1.20), p=0.36; I^2=40%). Subgroup analysis TTM with hypothermia at 32.0°C -34.0°C compared to actively controlled normothermia (3 studies) (751/1,682) versus (770/1688); RR 0.97 (95% CI 0.90 to 1.04), p=0.41, I^2=0%. TTM with hypothermia at 32.0°C -34.0°C compared to passively controlled normothermia (5 studies) (124/248) versus (91/237), RR 1.31 (95% CI 1.07 to 1.59), p=0.008, I^2=0%. Neurological outcome (8 studies with varied follow up)	Bleeding (3 RCTs) TTM with hypothermia at 32.0°C -34.0°C versus normothermia RR 1.10; (95% CI 0.83 to 1.44). Pneumonia (3 RCTs) TTM with hypothermia at 32.0°C -34.0°C versus normothermia RR 1.11, (95% CI 0.96 to 1.29). Arrhythmias (3 RCTs): TTM with hypothermia at 32.0°C –34.0°C (306/1,346) versus normothermia (227/1,356); RR 1.35 (95% CI 1.16 to 1.57), p=0.0001, I^2=0%.

First author, date	Efficacy outcomes	Safety outcomes
	TTM with hypothermia at 32.0°C –34.0°C compared to normothermia (753/1,881) versus (701/1,863); RR 1.17 (95% CI 0.97 to 1.41), p=0.10; I^2=60%. Subgroup analysis TTM with hypothermia at 32.0°C -34.0°C compared to actively controlled normothermia (3 studies) (640/1,634) versus (626/1,627); RR 1.02 (95% CI 0.88 to 1.18), p=0.79, I^2=51%. TTM with hypothermia at 32.0°C -34.0°C compared to passively controlled normothermia (5 studies) (113/247) versus (75/236), RR 1.42 (95% CI 0.99 to 2.04), p=0.05, I^2=27%. Excluding 1 study (Laurent 2005) in which patients received hemofiltration, RR 1.20, (95% CI 0.99 to 1.46), p=0.06. TTM with hypothermia at 32.0°C -34.0°C compared to uncontrolled normothermia RR 1.50, (95% CI 1.19 to 189); p=0.0007.	
Zhu YB 2022 China	Pooled rate TTM with hypothermia (32.0°C -34.0^{0}C) versus without TTM (36.0-38.0°C) Mortality (short-term [within 28-90 days] or long-term mortality [more than 180 days]) 6 studies TTM with hypothermia (542/677) versus without TTM (520/646); RR 1.00 (95% CI 0.94 to 1.05), p=0.89, I^2=0%.	

First author, date	Efficacy outcomes	Safety outcomes
	Good neurological function (defined as a CPC score of 1 or 2; 6 studies) TTM with hypothermia (48/618) versus without TTM (33/614); RR 1.39, (95% CI 0.92 to 2.11), p=0.11, I^2=0%. Subgroup analysis: pre-hospital versus in-hospital pooled rate (8 studies, n=2,686, 1,345 in pre-hospital and 1,341 in-hospital cooling) Mortality: RR 0.99 (95% CI 0.97 to 1.01); p=0.32, I^2=0%. Good neurological function: (6 studies) RR 1.13, (95% CI 0.93 to 1.18), p=0.22, I^2=0%.	
Yin L 2022 China	Survival to hospital discharge; pooled analysis rate 6 studies (n=14,607; TTM with hypothermia [512/1,845] versus control TTM without hypothermia [3,870/12,762]): OR 1.02, (95% CI 0.77 to 1.35), p=0.89, I^2=47%. Favourable neurological outcome 6 studies (n=14,215, TTM with hypothermia [284/1,641] versus control TTM without hypothermia [2,447/12,547]): OR =1.06 (95% CI 0.56 to 2.02), p=0.85, I^2=79%. Subgroup analysis: pooled rate Survival to hospital discharge:	

First author, date	Efficacy outcomes	Safety outcomes
	Shockable initial rhythm (2 studies, n=1,327, TTM with hypothermia 428 versus control 899): OR 0.89, (95% CI 0.71 to 1.13), p=0.35, I^2=0%. Small sample size (n≤50 patients; 4 studies, n=1,327 patients, TTM with hypothermia 116 versus control 1,019): OR 0.82, (95% CI 0.17 to 3.99), p=0.81, I^2=90%. Large sample size (n≥50 patients; 2 studies, 13,599, TTM with hypothermia 1,783 versus control 11,816): OR 0.90, (95% CI 0.80 to 1.02), p=0.11, I^2=0%. Neurological outcome Small sample size: (4 studies, n=1,053 patients, TTM with hypothermia 107 versus control 946): OR=0.97, 95% CI 0.19 to 5.03, I^2=86%, p=0.97. Large sample size: (2 studies, n=13,165, TTM with hypothermia 1,534 versus control 11,631): OR=0.81, 95% CI 0.69 to 0.94, I^2=0%, p=0.006.	
Duhan S 2023 USA	**Neurological outcomes pooled risk ratio** (n=12 studies). Compared with normothermia, therapeutic hypothermia was associated with significant decrease in poor neurologic outcomes (therapeutic hypothermia 58% [1,249/2,135] versus normothermia 61% [1,287/2,106]; RR 0.90, 95% CI 0.83 to 0.98, p = 0.02, I^2=61%).	**Mortality pooled risk ratio** (n=10 studies, 4 trials contributed to 80% of the events) The risk of death was similar in both groups (TH arm 55% [1,088/1,978] versus normothermia arm 55% [1,079/1,969]; RR 0.97, 95% CI 0.90 to 1.06, p = 0.55, I^2=38%). **Mortality in patients with an initial shockable rhythm** pooled risk ratio

First author, date	Efficacy outcomes	Safety outcomes
		TH 71% [903/1276] versus normothermia 74% [964/1297]; RR 0.82 (95% CI 0.57 to 1.18, p=0.29, I^2=94%).
Arrich J 2023 Austria, Denmark	**Good neurological outcome** Conventional cooling versus control (no cooling, fever control or TTM at 36°C; 11 studies, n=3,914) (41.5% [817/1,969] versus 37.7% [733/1,945]; RR 1.41, 95% CI 1.12 to 1.76; I^2=67%, p=0.003). Conventional cooling methods [32°C to 34°C] versus standard care (no cooling or fever control; 8 studies, n=2,870) (cooling to 33°C=39.9% [572/1435] versus control 35.2% [505/1,435]; RR 1.60, 95% CI 1.15 to 2.23; I^2 = 68%, p=0.005). Conventional cooling (32°C to 34°C) versus TTM at 36°C (3 studies, n=1,044) (45.9% [245/534] versus 44.7% [228/510]; RR: 1.78, 95% CI: 0.70 to 4.53; I^2 = 73%, p=0.230. Therapeutic hypothermia + high flow haemofiltration versus high flow haemofiltration normothermia (1 study, n=42) (31.8% [7/22] versus 45.0% [9/20] patients]; RR: 0.71, 95% CI: 0.32 to 1.54, p=0.38).	7 studies (3,788 patients) reported on 26 different adverse events. For most adverse events, there was no evidence of differences between groups. **Pneumonia** (4 studies, 3,634 patients) RR 1.09, (95% CI 1.00 to 1.18). **severe, haemodynamically compromising or long-lasting arrhythmia** (3 studies, n=2,163 patients) RR 1.40, (95% CI 1.19 to 1.64). **Any arrhythmia** (1 study, n=933) RR 0.98 (95% CI 0.93 to 1.04). **Hypokalaemia** (2 studies, n=975 patients) RR 1.38, (95% CI 1.03 to 1.84). **Bleeding of any severity** (4 studies, n= 3,636) RR 1.09 (95% CI 0.94 to 1.27). **Need for platelet transfusion** (1 study, n= 273) RR 5.11 (95% CI 0.25 to 105.47). **Pancreatitis** (1 study, n=273) RR 0.51 (95% CI 0.05 to 5.57). **Sepsis** (3 studies, n=3,054) RR 1.17 (95% CI 0.94 to 1.45). **Septic shock** (1 Study, n= 933) RR 0.87 (95% CI 0.50 to 1.52). **Renal failure or oliguria** (2 studies, n=303) RR 0.88 (95% CI 0.48 to 1.61). **Haemodialysis** (4 studies, n=1,869) RR 1.12 (95% CI 0.85 to 1.48).

First author, date	Efficacy outcomes	Safety outcomes
	Survival to hospital discharge, 3 months or within 6 months Conventional cooling versus all types of control treatment (no cooling, fever control or TTM at 36°C) (9 studies, n=3,871) (46% [886/1,936] versus 45% [866/1,935]; RR 1.07, 95% CI 0.95 to 1.20; I^2=34%, p=0.26). Conventional cooling methods (32°C to 34°C) versus standard care (no cooling or fever control; 7 studies, n=2,875) (45% [638/1,434] versus control 43% [616/1,441]; RR 1.17, 95% CI 0.96 to 1.42; I^2 = 48%, p=0.11). Conventional cooling (32°C to 34°C) versus TTM at 36°C (2 studies, n=996) (49% [248/502] versus 51% [250/494]; RR: 0.98, 95% CI: 0.86 to 1.10, I^2 =0%, p=0.70). Hypothermia + haemofiltration versus haemofiltration only (1 study, n=42) (32% [7/22] versus 45% [9/20]; RR: 0.71, 95% CI: 0.32 to 1.54; p=0.38). There is no data on long-term survival. **Quality of life (6 months)**	**Seizures** (3 studies, n=1,783) RR 1.11 (95% CI 0.95 to 1.30). **Pulmonary oedema** (2 studies, n= 850) RR 0.93 (95% CI 0.57 to 1.52). **Hypophosphatemia** (2 studies, n= 975) RR 1.10 (95% CI 0.92 to 1.33). **Hypoglycaemia** (1 study, n= 933) RR 1.12 (95% CI 0.64 to 1.97). **Hypomagnesaemia** (1 study, n= 933) RR 1.20 (95% CI 0.88 to 1.65). **Skin complications related to device** (1study, n=1,849) RR 1.99 (95% CI 0.68 to 5.80). **Bacteraemia** (1 study, n= 581) RR 1.14 (95% CI 0.51 to 2.54). **Central venous catheter infection** (1 study, n=581) RR 2.09 (95% CI 0.39 to 11.33). **Urinary tract infections** (1 study, n= 581) RR 0.78 (95% CI 0.34 to 1.83). **Nosocomial infections, other than central venous catheter infection and urinary tract infections** (1 study, n=581) RR 1.05 (95% CI 0.31 to 3.57). **Ventilator-associated pneumonia** (1 study, n=581) RR 1.31 (95% CI 0.87 to 1.99). **Vasopressors between day 0 and 7** (1 study, n=581) RR 1.01 (95% CI 0.94 to 1.09).

First author, date	Efficacy outcomes	Safety outcomes
	One study (Dankiewicz 2021) reported that there was no difference between the groups when assessing quality of life using 2 scoring systems (EQ-5DL and VAS). Another study (Cornberg 2015b, a substudy to Nielsen 2013), comparing TTM at 33°C versus TTM at 36°C reported Mental and Physical Component Summary of SF-36. The mean Mental Component Summary score was 49.1±12.5 for survivors in the 33°C group compared with 49.0±12.2 in the 36°C group (p=0.77). The mean Physical Component Summary scores were 46.8±13.8 for survivors in the 33°C group and 47.5±13.8 in the 36°C group (p=0.44).	
Wolfrum S 2022	**Favourable functional outcome using the Cerebral Performance Category scale (defined as 1 or 2) after 180 days** Favourable functional outcome (Cerebral Performance Category 1 or 2) after 180 days was 22.5% (27/120) in the hypothermic temperature control group compared with 23.7% (28/118) in the normothermia group (RR, 1.04, [95% CI, 0.78 to 1.44]; p=0.822). **Survival function (estimated using Kaplan -Meier method)** A favourable functional outcome after 180 days was observed in 81.8% (27/33) survivors of the hypothermic temperature control group and in 82.4% (28/34) survivors treated with normothermia.	**All-cause mortality after 180 days (primary outcome)** Mortality by day 180 was 72.5% (87/120) in hypothermic temperature control group, compared with 71.2% (84/118) in the normothermia group (RR, 1.03 [95% CI, 0.79 to 1.40]; p=0.822). **In-hospital mortality** In-hospital mortality was 62.5% (75/120) in the hypothermic temperature control as compared with 57.6% (68/118) in the normothermia group (RR, 1.11 [95% CI, 0.86 to 1.46]; p=0.443). **Factors associated with mortality.** Hypothermic temperature control did not show a reduced hazard of death (HR, 1.13 [95% CI, 0.83 to 1.55]; p=0.446). Hypothermic temperature control was not associated with good functional outcome (OR 0.90; [95% CI, 0.45 to 1.77]; p=0.751).

First author, date	Efficacy outcomes	Safety outcomes
		Shockable rhythm, and lower age, significantly reduced the risk of death and increased the probability for good functional outcome. In a sub-group analysis, the initial rhythm—shockable or non-shockable did not affect the effect of temperature control on the primary end point (p=0.853). **Adverse events** **Pneumonia** Pneumonia was observed in 31% cases in the hypothermic temperature control group compared to 45% in the normothermia group; RR 0.74 [95% CI, 0.54 to 0.97]; p=0.026). Other adverse events were similar in both groups and did not show statistically significant differences.

Procedure technique

All studies detailed the interventions and comparators used. They compared different target temperature ranges of hypothermia with normothermia.

One systematic review with network meta-analysis compared 3 temperature ranges of hypothermia: 31.0°C to 32.0°C (deep hypothermia), 33.0°C to 34.0°C (moderate hypothermia), and 35.0°C to 36.0°C (mild hypothermia) with normothermia (37.0°C to 37.8°C; Fernando 2021)

One systematic review with meta-analysis compared TTM with hypothermia (at 32.0°C to 34.0°C) with normothermia which involved active cooling as part of TTM (Granfeldt 2021). In another meta-analysis, TTM in the hypothermia arm in the included trials varied from 31.7°C to 34.0°C (Eldbadawi 2022).

One systematic review with meta-analysis compared TTM with hypothermia at 32.0°C to 34.0°C with “actively controlled” (avoiding fever) or “uncontrolled” normothermia (Sanfilippo 2021).

Three studies also compared the methods of temperature management (evaporative cooling, infusion of cold saline, and surface or systemic cooling), timing (in-hospital or pre-hospital cooling), and duration of TTM (Granfeldt 2021, Zhu 2022, Yin 2022).

Efficacy

Survival with good functional/neurological outcomes

Optimal target temperature

A systematic review and network meta-analysis of 10 RCTs (n=4,218 patients) on TTM in comatose survivors of OHCA showed no difference in 6-month functional outcome between any target temperature in the hypothermic range of 31.0°C and 36.0°C and normothermia (37.0°C to 37.8°C) during TTM. Compared with normothermia, there was no effect on survival with good functional outcome using deep hypothermia (OR 1.30 [95% CI 0.73 to 2.30]), moderate hypothermia (OR 1.34 [95% CI 0.92 to 1.94]), or mild hypothermia (OR 1.44 [95% CI 0.74 to 2.80]). Also, there was no effect using deep hypothermia when compared with moderate hypothermia (OR 0.97 [95% CI 0.61 to 1.54]) or mild hypothermia (OR 0.90 [95% CI 0.44 to 1.86]); or comparing mild hypothermia with moderate hypothermia (OR 1.07 [95% CI 0.62 to 1.87](; GRADE, all low uncertainty; Fernando 2021).

In a systematic review and meta-analysis on TTM in adult patients with cardiac arrest, pooled analysis showed that TTM with hypothermia of a target 32.0°C to

34.0°C compared with normothermia (no TTM, no clear description of TTM, or TTM to maintain normothermia) did not result in favourable neurological outcomes at hospital discharge or 30 days (3 studies, RR 1.30, [95% CI 0.83 to 2.03]) and at 90 to 180 days (5 studies, RR 1.21, [95% CI 0.91 to 1.61]; GRADE low certainty of evidence; Granfeldt 2021). In the same study, 3 RCTs compared different temperature targets (TTM trial, [Neilsen 2013], between 33.0°C and 36.0°C and 2 other trials [Lopez-de-Sa 2012, 2018] between 32.0°C, 33.0°C, and 34.0°C) and found no difference in neurological outcomes (GRADE low certainty of evidence).

A meta-analysis of 8 RCTs showed that there was no statistically significant difference between TTM with hypothermia (varied from 31.7°C to 34.0°C) and normothermia in rates of favourable neurological outcome (38% versus 34%, RR 1.31; [95% CI, 0.99 to 1.73], p=0.06, I^2=56%), Sensitivity analysis, excluding the large TTM2 trial showed higher rates of favourable neurological outcome with TTM with hypothermia compared with normothermia (RR 1.45, [95% CI, 1.17 to 1.79], p<0.001, I^2=1%; Elbadawi 2022).

A meta-analysis of 8 RCTs showed that TTM with hypothermia at 32.0°C to 34.0°C does not improve neurological outcome compared with normothermia (RR: 1.17, [95% CI 0.97 to 1.41], p=0.10; I^2=60%). A subgroup analysis showed improved neurological outcomes with TTM at 32.0°C to 34.0°C when compared with 'uncontrolled normothermia' (RR 1.50, 95% CI 1.19 to 1.89; p=0.0007) but had no improved neurological outcome when compared with 'actively controlled' normothermia (RR 1.02, [95% CI 0.88 to 1.17], p=0.79; Sanfilippo 2021).

In a systematic review and meta-analysis of 12 studies, a pooled analysis of all 11 studies comparing conventional cooling methods with different types of control treatment (no cooling, fever control or temperature management at 36°C) showed better neurological outcomes with cooling to 36°C, (42% [817/1,969] versus 38% [733/1,945]; RR 1.41, 95% CI 1.12 to 1.76; I^2=67%, p=0.003). Significant heterogeneity was mainly driven by including 2 studies (TTM1 trial [Nielsen 2013], and TTM2 trial [Dankiewicz 2021]). The pooled analysis of 8 studies (n=2,870) comparing conventional cooling with control (no cooling or fever control) showed a better neurological outcome for the conventional cooling group (cooling to 33°C (40% [572/1,435] versus control 35% [505/1,435]; RR 1.60, 95% CI 1.15 to 2.23; I^2 = 68%, p=0.005). Heterogeneity was caused by including TTM2 trial (Dankiewicz 2021). A pooled analysis of 3 studies comparing the effects of conventional cooling with TTM at 36°C, found no evidence of a difference in neurological outcome (46% [245/534] versus 45% [228/510]; RR 1.78, 95% CI 0.70 to 4.53; I^2 = 73%, p=0.23). The certainty of the evidence was low for all. One study comparing haemofiltration cooling with haemofiltration normothermia showed that there was no difference in neurological outcome

between the 2 groups (32% [7/22] versus 45% [9/20]; RR 0.71, 95% CI 0.32 to 1.54; p=0.38; Arrich 2023).

In a meta-analysis of 14 RCTs on TTM for adults with OHCA caused by NSR, a pooled analysis of 5 studies comparing TTM with hypothermia to TTM without hypothermia showed that it was not associated with favourable neurological outcomes (RR 1.39, [95% CI 0.92 to 2.11]; p=0.11, I^2=0%; Zhu Y-B 2022).

In a systematic review and meta-analysis of 6 retrospective controlled studies (with 14,607 patients with IHCA) comparing TTM with hypothermia (n=1,845) to control (TTM without hypothermia, n= 12,762), there were no statistically significant differences between the 2 groups in favourable neurological outcomes (OR =1.06, [95% CI: 0.56 to 2.02], p=0.85, I^2 =79%). A subgroup analysis according to small or large study sample size also showed no significant improvement between the 2 groups in neurological outcomes (Yin 2022).

In a meta-analysis of 12 RCTs comparing therapeutic hypothermia (<36°C) with normothermia (≥36°C) in patients after a cardiac arrest, therapeutic hypothermia was associated with a significant decrease in poor neurologic outcomes compared with normothermia (therapeutic hypothermia 58% [1,249/2,135] versus normothermia 61% [1,287/2,106]; RR 0.90, 95% CI 0.83 to 0.98, p=0.02, I^2=61%; Duhan 2023).

An RCT of 249 patients comparing hypothermic temperature control (32°C to 34°C) for 24 hours (in 126 patients) with normothermia (in 123 patients) after IHCA reported no statistically significant difference in favourable functional outcome (Cerebral Performance Category 1 or 2) by day 180 (22.5% (27/120) versus 23.7% (28/118), RR, 1.04 [95% CI, 0.78 to 1.44]; p=0.822; Wolfrum 2022).

Methods of TTM: Endovascular versus surface cooling methods

In the systematic review and meta-analysis on TTM in adult patients with cardiac arrest, a pooled analysis of 3 RCTs targeting hypothermia at 33.0°C or 34.0°C comparing endovascular cooling with surface cooling (that is, using fans, or applying cooling pads or ice packs) did not result in a statistically significant improvement in survival with a favourable neurologic outcome (RR 1.22, [95% CI: 0.95 to 1.56]; GRADE low uncertainty of evidence; Granfeldt 2021).

TTM duration

In the systematic review and meta-analysis on TTM in adult patients with cardiac arrest, 1 RCT (Kirkegaard 2017) with 355 patients who had TTM with hypothermia of 32.0°C to 34.0°C comparing 24 hours to 48 hours of TTM found no difference in neurological outcomes (GRADE low certainty; Granfeldt 2021).

Timing of initiation of TTM

In the systematic review and meta-analysis on TTM in adult patients with OHCA, a pooled analysis of 10 trials reported that pre-hospital cooling did not result in favourable neurological outcomes at hospital discharge when compared with no pre-hospital cooling (RR 1.00, [95% CI 0.90 to 1.11], p=0.76, I^2=0%). Subgroup analyses of different cooling methods (5 studies assessing post-cardiac arrest rapid intravenous cold fluid infusion, 2 studies assessing intra-cardiac arrest intravenous cold fluid infusion, and 2 studies assessing intra-cardiac arrest intra-nasal cooling) also found no difference in favourable neurological outcome at hospital discharge between groups (Granfeldt 2021).

In the meta-analysis of 14 RCTs on TTM for adults patients with OHCA caused by NSR, a pooled analysis of 5 studies comparing pre-hospital TTM with in-hospital TTM showed that pre-hospital TTM did not result in favourable neurological outcomes (RR 1.13, [95% CI 0.93 to 1.18]; p=0.22, I^2 = 0%; Zhu Y-B 2022).

Overall survival

Optimal target temperature

The systematic review and network meta-analysis of 10 RCTs (n=4,218 patients) on TTM in comatose survivors of OHCA showed no difference in 6-month overall survival between any target temperature in the hypothermic range of 31.0°C and 36.0°C and normothermia. Compared with normothermia, there is no effect on overall survival using deep hypothermia (OR 1.27, [95% CI 0.70 to 2.32]), moderate hypothermia (OR 1.23, [95% CI 0.86 to 1.77]), or mild hypothermia (OR 1.26, [95% CI 0.64 to 2.49]). Also, there was no effect on overall survival using deep hypothermia when compared with moderate hypothermia (OR 1.03, [95% CI 0.64 to 1.68]) or mild hypothermia (OR 1.01, [95% CI 0.47 to 2.14]) or when comparing mild hypothermia with moderate hypothermia (OR 1.02, [95% CI 0.79 to 1.32; Fernando 2021).

In the systematic review and meta-analysis on TTM in adult patients with cardiac arrest, a pooled analysis showed that TTM with hypothermia at a target 32.0°C to 34.0°C compared with normothermia (no TTM, no clear description of TTM, or TTM to maintain normothermia) did not result in an improvement in survival at hospital discharge or 30 days (5 studies, RR 1.12, [95% CI 0.92 to 1.35]) or at 90 to 180 days (5 studies, RR 1.08, [95% CI 0.89 to 1.30]; GRADE low certainty of evidence; Granfeldt 2021).

The meta-analysis of 8 RCTs showed that there was no significant difference in long-term mortality between the TTM with hypothermia and normothermia groups (56% versus 57%, RR 0.96; [95% CI 0.87 to 1.06], p=0.45, I^2=41%; Elbadawi

2022). Similarly, a subgroup analysis of patients with cardiac arrest caused by SR (RR 0.87; [95% CI, 0.68 to 1.11]; p=0.09; I^2=59%) and patients with cardiac arrest caused by NSR (RR 1.00; [95% CI, 0.94 to 1.05]; p= 0.40; I^2=0%) showed no significant difference between the groups (Elbadawi 2022).

The meta-analysis of 8 RCTs showed that TTM with hypothermia at 32.0°C to 34.0°C did not improve survival when compared with normothermia (RR 1.06 [95% CI 0.94 to 1.20], p=0.36; I^2=40%). Subgroup analyses showed that TTM with hypothermia at 32.0°C to 34.0°C is associated with improved survival when compared with passively controlled normothermia (RR 1.31 [95% CI 1.07 to 1.59], p=0.008) but showed no improved survival when compared with 'actively controlled' normothermia (RR 0.97, [95% CI 0.90 to 1.04], p=0.41; Sanfilippo 2021).

In a systematic review of 12 studies, a pooled analysis of all 9 studies comparing conventional cooling methods with different types of control treatment (no cooling, fever control or temperature management at 36°C) found that there was no survival benefit for cooling at 36°C, (46% [886/1,936] versus 45% [866/1,935]; RR 1.07, 95% CI 0.95 to 1.20; I^2=34%, p=0.26). The pooled analysis of 7 studies (n=2,875) comparing conventional cooling with control (no cooling or fever control) showed no survival benefit for the conventional cooling group (cooling to 33°C (45% [638/1,434] versus control 43% [616/1,441]; RR 1.17, 95% CI 0.96 to 1.42; I^2 = 48%, p=0.11), Heterogeneity was caused by including TTM2 trial (Dankiewicz 2021). A pooled analysis of 2 studies comparing the effects of conventional cooling with TTM at 36°C, found no survival benefit for the conventional cooling group (49% [248/502] versus 51% [250/494]; RR 0.98, 95% CI 0.86 to 1.10; I^2 = 0%, p=0.70). The certainty of the evidence was low for all. One study comparing haemofiltration cooling with haemofiltration normothermia showed that there was no difference in survival between the 2 groups (RR 0.71, 95% CI 0.32 to 1.54; p=0.38; Arrich 2023).

In the meta-analysis of 14 RCTs on TTM for adults with OHCA caused by NSR, a pooled analysis of 6 studies (n=1,323) comparing TTM with hypothermia to TTM without hypothermia showed that TTM with hypothermia did not statistically significantly improve survival (RR 1.00; [95% CI 0.94 to 1.05]; p=0.89, I^2=0%; Zhu Y-B 2022).

In the systematic review and meta-analysis of 6 retrospective controlled studies (with 14,607 patients with IHCA), comparing TTM plus hypothermia (n= 1,845) to control (TTM without hypothermia, n=12,762), there were no statistically significant differences between the 2 groups in survival to hospital discharge (OR 1.02, [95% CI 0.77 to 1.35], p=0.89, I^2 =47%; Yin 2022). A subgroup analysis of 2 studies with 1,327 patients with cardiac arrest caused by SR (TTM group 428 versus control group 899) showed that TTM did not show any significant

improvement in survival to hospital discharge (OR 0.89, [95% CI 0.71 to 1.13], p=0.35, I^2 =0%). A subgroup analysis according to small or large sample size also showed no significant improvement between the 2 groups in terms of survival to hospital discharge (Yin 2022).

Methods of TTM: endovascular versus surface cooling methods

In the systematic review and meta-analysis on TTM in adult patients with cardiac arrest, a pooled analysis of 3 RCTs targeting 33.0°C or 34.0°C comparing endovascular cooling with surface cooling (that is, using fans, or applying cooling pads or ice packs) did not result in a statistically significant improvement in survival to hospital discharge or 28 days (RR 1.14, [95% CI 0.93 to 1.38]; Granfeldt 2021).

Timing of TTM initiation

In the systematic review and meta-analysis on TTM in adult patients with OHCA, a pooled analysis of 10 trials reported that pre-hospital cooling did not result in improved survival to hospital discharge when compared with no pre-hospital cooling (RR 1.01 [95% CI 0.92 to 1.11], p=0.93, I^2=0%). Subgroup analyses of different cooling methods (6 studies assessing post-cardiac arrest rapid intravenous cold fluid infusion, 2 studies assessing intra-cardiac arrest intravenous cold fluid infusion, and 2 studies assessing intra-cardiac arrest intra-nasal cooling) also found no difference in survival to hospital discharge between groups (Granfeldt 2021).

In the meta-analysis of 14 RCTs on TTM for adults with OHCA caused by NSR, a pooled analysis of 8 studies (n=2,686) comparing use of pre-hospital TTM with in-hospital TTM showed that pre-hospital TTM did not statistically significantly improve survival (RR 0.99, [95% CI 0.97 to 1.01], p=0.32, I^2 =0%; Zhu Y-B 2022).

Quality of life

In the systematic review and meta-analysis of 12 studies, 2 studies reported quality-of-life outcomes. One study (Dankiewicz 2021) reported that there was no difference in quality of life between the hypothermia and normothermia groups when assessed using EQ-5DL and VAS. Another study (Cornberg 2015b, a sub-study to Nielsen 2013), comparing TTM at 33°C versus TTM at 36°C reported that the mean Mental Component Summary score of SF-36 was 49.1±12.5 for survivors in the 33°C group compared with 49.0±12.2 in the 36°C group (p=0.77). The mean Physical Component Summary scores were 46.8±13.8 for survivors in the 33°C group and 47.5±13.8 in the 36°C group (p=0.44; Arrich 2023).

Safety

Mortality

In the meta-analysis of RCTs comparing therapeutic hypothermia (<36°C) with normothermia (≥36°C) in patients after a cardiac arrest, no significant difference in mortality was observed between the groups (RR 0.97, 95% CI 0.90 to 1.06, p=0.55, I^2=38%; Duhan 2023).

The RCT of 249 patients comparing hypothermic temperature control (32°C to 34°C) for 24 hours (in 126 patients) with normothermia (in 123 patients) after IHCA reported no statistically significant difference in mortality by day 180 (72.5% [87/120] versus 71% [84/118], RR 1.03 [95% CI, 0.79 to 1.40, p=0.822; Wolfrum 2022).

In-hospital mortality

In the systematic review and meta-analysis of 8 RCTS, a pooled analysis of 5 studies showed that there was no statistically significant difference in in-hospital mortality between the TTM plus hypothermia and the normothermia groups (65% versus 72%; RR 0.88; [95% CI 0.77 to 1.01]; p=0.07; I^2=35%; Elbadawi 2022).

The RCT of 249 patients comparing hypothermic temperature control (32°C to 34°C) for 24 hours (in 126 patients) with normothermia (in 123 patients) after IHCA reported no statistically significant difference in in-hospital mortality (62.5% [75/120] versus 57.6% [68/118], RR 1.11 [95% CI, 0.86 to 1.46, p=0.443; Wolfrum 2022).

Arrhythmia

In the network meta-analysis of 10 RCTs (n=4,218 patients) on TTM for OCHA, compared with normothermia, arrhythmia was more common among patients receiving TTM with deep hypothermia (OR 3.58, [95% CI 1.77 to 7.26], GRADE high certainty) and moderate hypothermia (OR 1.45, [95% CI 1.08 to 1.94], GRADE high certainty); Fernando 2021).

In the systematic review and meta-analysis of 8 RCTs, a pooled analysis of 4 studies showed higher risk for ventricular arrhythmias among TTM with hypothermia groups compared to normothermia groups (23% [312/1,368] versus 17% [229/1,376]; RR 1.36; [95% CI 1.17 to 1.58]; p<0.001; I^2=0%; Elbadawi 2022).

The meta-analysis of 8 RCTs showed that TTM with hypothermia at 32.0°C to 34.0°C increases the risk of arrhythmias compared to normothermia (TTM at 32.0°C to 34.0°C [306/1,346] versus normothermia [227/1,356]; RR 1.35, [95% CI 1.16 to 1.57], p=0.0001, I^2=0%; Sanfilippo 2021).

In the systematic review and meta-analysis of 12 RCTs, a pooled analysis of 3 studies (n=2,163 patients) showed higher incidence of severe haemodynamically compromising or long lasting arrhythmias among patients who had therapeutic cooling compared to control groups (RR 1.40; [95% CI 1.19 to 1.64]). The certainty of evidence was low (Arrich 2023).

Bleeding

In the network meta-analysis of 10 RCTs (n=4,218 patients) on TTM with hypothermia for OCHA, compared with normothermia, there were no statistically significant differences in the incidence of bleeding across the various hypothermia range of temperature comparisons (deep hypothermia [OR 1.21, 95% CI 0.68 to 2.15], moderate hypothermia [OR 1.10, 95% CI 0.78 to 1.55], or mild hypothermia [OR 1.21, 95% CI 0.66 to 2.21], GRADE all low or very low certainty; Fernando 2021).

In the systematic review and meta-analysis of 8 RCTS, there was no statistically significant difference between the TTM plus hypothermia and the normothermia groups in rates of bleeding complications (7% [95/1,346] versus 7% [89/1,357]; RR 1.10; [95% CI, 0.83 to 1.44]; p=0.51; I^2=0%; Elbadawi 2022).

In the systematic review and meta-analysis of 12 RCTs, a pooled analysis of 4 studies (n=3,636 patients) comparing therapeutic cooling to control groups showed no difference in rates of bleeding of any severity between the groups (RR 1.09; [95% CI 0.94 to 1.27]). The certainty of evidence was low (Arrich 2023).

Pneumonia

In the network meta-analysis of 10 RCTs (n=4,218 patients) on TTM with hypothermia for OCHA, compared with normothermia, there were no statistically significant differences in the incidence of pneumonia across the various temperature comparisons (deep hypothermia [OR 0.91, 95% CI 0.42 to 2.09]), moderate hypothermia [OR 1.24, 95% CI 0.79 to 1.95], or mild hypothermia [OR 0.98, 95% CI 0.41 to 2.33], GRADE all low or very low certainty; Fernando 2021).

In the systematic review and meta-analysis of 8 RCTS, there was no statistically significant difference between the TTM plus hypothermia and the normothermia groups in rates of pneumonia (23% versus 17%; RR 1.36; [95% CI 1.17 to 1.58]; p=0.42; I^2 =0%; Elbadawi 2022).

In the systematic review and meta-analysis of 12 RCTs, a pooled analysis of 4 studies (n=3,634 patients) showed a higher incidence of pneumonia among patients who had therapeutic cooling compared to control groups (RR 1.09; [95% CI 1.00 to 1.18]). The certainty of evidence was low (Arrich 2023).

Sepsis

In a pair-wise meta-analysis of 10 RCTs (n=4,218 patients) on TTM with hypothermia for OCHA, compared with normothermia, the incidence of sepsis was more common among patients receiving moderate hypothermia (33.0°C to 34.0°C; OR 1.36, [95% CI 0.88 to 2.10]; Fernando 2021).

In the systematic review and meta-analysis of 8 RCTS, there was no statistically significant difference between the TTM plus hypothermia and the normothermia groups in rates of sepsis (10% versus 8%; RR 1.24; [95% CI, 0.97 to 1.59]; p=0.08; I^2=0%; Elbadawi 2022).

In the systematic review and meta-analysis of 12 RCTs, a pooled analysis of 3 studies (n=3,054 patients) comparing therapeutic cooling to control groups showed no difference in rates of sepsis between the groups (RR 1.17; [95% CI 0.94 to 1.45]; Arrich 2023).

Seizures

In a pair-wise meta-analysis of 10 RCTs (n=4,218 patients) on TTM with hypothermia for OCHA, compared with normothermia, there was no statistically significant difference in the incidence of seizures for moderate hypothermia (33.0°C to 34.0°C; OR 0.95, 95% CI 0.67 to 1.35; Fernando 2021).

In the systematic review and meta-analysis of 12 RCTs, a pooled analysis of 3 studies (n=1,783 patients) comparing therapeutic cooling to control groups showed no difference in incidence of seizures between the groups (RR 1.11; [95% CI 0.95 to 1.30]; Arrich 2023).

Hypokalaemia

In the systematic review and meta-analysis of 12 RCTs, a pooled analysis of 2 studies (n=975 patients) showed higher incidence of hypokalaemia among patients who had therapeutic cooling compared to control groups (RR 1.38; [95% CI 1.03 to 1.84]). The certainty of evidence was very low (Arrich 2023).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal adverse events:

- peripheral vasoconstriction with increased afterload
- the use of neuromuscular blockers may mask seizures.

They listed the following theoretical adverse events:

- injury to skin from some external cooling systems.

Five professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- Most of the key papers included are systematic reviews with meta-analyses. There was a significant amount of overlap identified across the systematic reviews included in the overview; much of the available evidence identified in this review is based on the same RCTs. Evidence was mainly for adult patients resuscitated from OHCA with SR and NSR.
- Targeted temperature in the hypothermia arm in the trials included in the systematic reviews varied from 31.0°C to 36.0°C. Control group management also varied, and a variety of patient populations was included.

- There is a lack of standardised TTM protocols in TTM trials included in the meta-analyses. Substantial heterogeneity in terms of patient characteristics, devices used to achieve cooling, TTM strategies, initiation time, duration of the procedure, and timing of outcome measurements was noted.
- The recent TTM2 trial included in these systematic reviews included patients from 14 countries and is generalisable.
- One RCT evaluated TTM in adult IHCA. The RCT was terminated early because of ineffectiveness.
- There is no long-term data greater than 6 months.
- Recent systematic reviews have conflicting conclusions on therapeutic hypothermia.
- Ongoing trials:

  NCT04217551: Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECAP; shockable and non-shockable rhythm). A multicentre, randomised, adaptive allocation clinical trial to determine if increasing durations of induced hypothermia of 33.0°C (6, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours) are associated with an increasing rate of good neurological outcomes, and to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of cardiac arrest. Estimated enrolment: 1,800 participants, primary outcome modified Rankin Scale states to capture changes in functional status; location USA; estimated study completion date: July 2025.

- NCT05564754: Sedation, Temperature and Pressure After Cardiac Arrest and Resuscitation (STEPCARE). A RCT of 3500 patients who are comatose after cardiac arrest, all patients will be randomised to a control or an intervention arm for sedation, temperature and blood pressure targets. These are

  1. Continuous deep sedation for 36 hours or minimal sedation (SEDCARE)

2. Fever management with or without a feedback-controlled device (TEMPCARE)

3. A mean arterial pressure target of > 85 mmHg or > 65 mmHg (MAPCARE).

Participants will be followed up at 30 days and 6 months. The primary outcome will be survival at 6 months. Location: Finland, Sweden, study completion date June 2026.

Existing assessments of this procedure

International guidance

International Liaison Committee on Resuscitation (ILCOR): International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations – for adult advanced life support (2022) includes updated recommendations on targeted temperature management after cardiac arrest. This is based on the systematic review on temperature management after cardiac arrest (Granfeldt 2021). These include the following:

Suggest actively preventing fever by targeting a temperature ≤37.5°C for patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low-certainty evidence).

Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32°C to 34°C remains uncertain.

Comatose patients with mild hypothermia after ROSC should not be actively warmed to achieve normothermia (good practice statement).

Recommend against the routine use of prehospital cooling with rapid infusion of large volumes of cold intravenous fluid immediately after ROSC (strong recommendation, moderate-certainty evidence). Recommendation unchanged from 2015 because they found no evidence that any method of prehospital cooling improved outcomes.

Suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low-certainty evidence).

When a cooling device is used, they suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).

Suggests active prevention of fever for at least 72 hours in post–cardiac arrest patients who remain comatose (good practice statement).

The Task Force proposes that the following terms be used for clarity in future studies and recommendations:

• Temperature control with hypothermia: Active temperature control with the target temperature below the normal range

• Temperature control with normothermia: Active temperature control with the target temperature in the normal range

• Temperature control with fever prevention: Monitoring temperature and actively preventing and treating temperature above the normal range

• No temperature control: No protocolized active temperature control strategy.

American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (2020) includes the following recommendations for targeted temperature management:

- 'Prompt initiation of targeted temperature management is necessary for all patients who do not follow commands after return of spontaneous circulation to ensure optimal functional and neurological outcomes.
- Use TTM for adults who do not follow commands after ROSC from OHCA with any initial rhythm.
- Use TTM for adults who do not follow commands after ROSC from IHCA with initial non-shockable rhythm.
- Use TTM for adults who do not follow commands after ROSC from IHCA with initial shockable rhythm.
- TTM between 32°C and 36°C for at least 24 hours is currently recommended for all cardiac rhythms in both OHCA and IHCA.'

European Resuscitation Council (ERC): Guidelines for resuscitation (2021) on temperature control post-resuscitation recommends as follows:

- 'We recommend targeted temperature management (TTM) for adults after either OHCA or in-hospital cardiac arrest (IHCA) (with any initial rhythm) who remain unresponsive after ROSC.
- Maintain a target temperature at a constant value between 32°C and 36°C for at least 24 h.
- Avoid fever (> 37.7°C) for at least 72 h after ROSC in patients who remain in coma.
- Do not use pre-hospital intravenous cold fluids to initiate hypothermia.'

ERC-ESICM Recommendations for temperature control after cardiac arrest in adults (2022): 'these updated temperature control guidelines are the result of a collaboration between the European Resuscitation Council and the European

Society of Intensive Care Medicine and emphasize the importance of active prevention of fever after cardiac arrest.

- We recommend continuous monitoring of core temperature in patients who remain comatose after ROSC from cardiac arrest (good practice statement).

- We recommend actively preventing fever (defined as a temperature >37.7° C) in post-cardiac arrest patients who remain comatose (weak recommendation, low-certainty evidence).

- We recommend actively preventing fever for at least 72 hours in post-cardiac arrest patients who remain comatose (good practice statement).

- Temperature control can be achieved by exposing the patient, using anti-pyretic drugs, or if this is insufficient, by using a cooling device with a target temperature of 37.5°C (good practice statement).

- There is currently insufficient evidence to recommend for or against temperature control at 32–36°C in sub-populations of cardiac arrest patients or using early cooling, and future research may help elucidate this.

- We recommend not actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia (good practice statement).

- We recommend not using prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation; moderate certainty evidence).'

UK post resuscitation care guidelines (2021) on temperature control recommends that:

- ‘Targeted temperature management (TTM) is recommended for adults after either out-of-hospital or in-hospital cardiac arrest (OHCA or IHCA) with any initial rhythm who remain unresponsive after ROSC.
- Maintain a target temperature at a constant value between 32°C and 36°C for at least 24 h.
- Avoid fever (> 37.7°C) for at least 72 h after ROSC in patients who remain in coma.
- Do not use pre-hospital intravenous cold fluids to initiate hypothermia.’

Guidelines from a French expert panel on targeted temperature management in the ICU (2017) makes the following recommendations

TTM after cardiac arrest

- 1.1 ‘We recommend using TTM in order to improve survival with good neurological outcome in patients resuscitated from out-of-hospital cardiac arrest (OHCA) with shockable cardiac rhythm (ventricular fbrillation and pulseless ventricular tachycardia) and who remain comatose after return of spontaneous circulation (ROSC).
- 1.2 We suggest considering TTM in order to improve survival with good neurological outcome in patients resuscitated from OHCA with non-shockable cardiac rhythm (asystole or pulseless electrical activity) and who remain comatose after ROSC.

- 1.3 We suggest considering TTM in order to increase survival with good neurological outcome in patients resuscitated from in-hospital cardiac arrest (IHCA) who remain comatose after ROSC.
- 1.4 We suggest considering TTM between 32 and 36 °C in order to improve survival with good neurological outcome after cardiac arrest.
- 1.5 We do not suggest initiating TTM with infusion of large volumes of cold saline solution during transportation to the hospital after cardiac arrest'.

The Australian and New Zealand Committee on Resuscitation (ANZCOR) guideline (2016) makes the following recommendations:

1. 'ANZCOR recommends TTM as opposed to no TTM for adults with out-of-hospital cardiac arrest (OHCA) with an initial shockable rhythm who remain unresponsive after ROSC.

2. ANZCOR suggests TTM as opposed to no TTM for adults with OHCA with an initial non-shockable rhythm who remain unresponsive after ROSC.

3. ANZCOR suggests TTM as opposed to no TTM for adults with in-hospital cardiac arrest (IHCA) with any initial rhythm who remain unresponsive after ROSC.

4. ANZCOR recommends selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom TTM is used.

5. No studies specifically address cardiac arrests due to non-cardiac causes, but it is reasonable to assume that these patients might also benefit from targeted temperature management.

6. Rapid infusion of ice-cold intravenous fluid, up to 30 ml kg-1 or ice packs are feasible, safe and simple methods for initially lowering core temperature up to

1.5 degrees. When intravenous fluids are used to induce hypothermia additional cooling strategies will be required to maintain hypothermia.

7. ANZCOR recommends against routine use of pre-hospital cooling with rapid infusion of large volumes of cold intravenous fluid immediately after ROSC.

8. ANZCOR suggests that if TTM is used, duration should be at least 24 hours.

9. ANZCOR suggests that percutaneous coronary intervention during TTM is feasible and safe and may be associated with improved outcome.

10. ANZCOR suggests institutions or communities planning to implement complex guidelines, such as targeted temperature management should consider using a comprehensive, multifaceted approach, including: clinical champions; a consensus-building process; multidisciplinary involvement; written protocols; detailed process description; practical logistic support; multi-modality, multi-level education; and rapid cycle improvement methods.

11. ANZCOR suggests prevention and treatment of fever in persistently comatose adults after completion of TTM between 32°C and 36°C.'

Canada's Drug and Health Technology Agency (CADTH) health technology rapid review on temperature management in patients after cardiac arrest (2022) included 2 systematic reviews (1 with a network meta-analysis and 1 with a meta-analysis), 1 RCT, and 7 non-randomised studies, comparing the clinical effectiveness of normothermia against hypothermia in adult patients after cardiac arrest.

The key messages from the review were:

- 'Normothermia was found to be similar to hypothermia for several clinical- and patient-related outcomes, such as survival, hospital mortality, and quality of life. There was limited evidence to suggest that either type of

targeted temperature management was more efficacious, with findings suggesting that normothermia may be associated with greater protocol adherence and decreased prescription medication use coming from low-quality non-randomized studies.

- Four evidence-based guidelines were identified regarding targeted temperature management (normothermia or hypothermia) in adult patients after cardiac arrest. All guidelines strongly recommend targeted temperature management for eligible patients, particularly for patients resuscitated following out-of-hospital cardiac arrest. Identified guidelines from the Canadian Cardiovascular Society and American Academy of Neurology present strong recommendations for hypothermic targeted temperature management.'

Related NICE guidance

Interventional procedures

- NICE's interventional procedures guidance on therapeutic hypothermia following cardiac arrest (Recommendation: normal arrangements). 'This guidance is currently under review and is expected to be updated in 2023'.

Medical technologies

- NICE's medical technologies guidance on arctic Sun 5000 for therapeutic hypothermia after cardiac arrest
- NICE's medical technologies guidance on Thermogard XP for therapeutic hypothermia after cardiac arrest
- NICE's medical technologies guidance on RhinoChill intranasal cooling system for reducing temperature after cardiac arrest

NICE guidelines

- NICE guideline on acutely ill adults in hospital: recognising and responding to deterioration.
- NICE guideline on acute coronary syndromes.

Professional societies

- Intensive Care Society
- Royal College of Emergency Medicine
- Faculty of Intensive Care Medicine
- Resuscitation Council UK.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

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Methods

NICE identified studies and reviews relevant to temperature control to improve neurological outcomes after cardiac arrest from the medical literature. The following databases were searched between the date they started to 30-04-2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: only systematic reviews, meta-analysis and RCTs on TTM were included. Secondary analyses or sub-studies of larger RCTs, non-randomised studies, observational studies, case reports, reviews, abstracts, editorials, letters to the editor, commentary and laboratory or animal studies, were excluded and so were conference abstracts, unless they reported specific adverse events that not available in the published literature.
- Adult patients with cardiac arrest.
- Intervention or test: temperature control/targeted temperature management.

- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy (mainly focusing on neurological outcomes), or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	12/04/2023	1946 to April 11, 2023
MEDLINE In-Process (Ovid)	12/04/2023	1946 to April 11, 2023
MEDLINE Epubs ahead of print (Ovid)	12/04/2023	April 11, 2023
EMBASE (Ovid)	12/04/2023	1974 to 2023 April 11
EMBASE Conference (Ovid)	12/04/2023	1974 to 2023 April 11
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/04/2023	Issue 4 of 12, April 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/04/2023	Issue 4 of 12, April 2023
International HTA database (INAHTA)	12/04/2023	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The MEDLINE search strategy was translated for use in the other sources.

MEDLINE search strategy

1 Hypothermia, Induced/
2 Cold Temperature/
3 TTM.tw.
4 (Target adj4 temperat* adj4 manage*).tw.
5 ((Therapeut* or Protect* or Induc*) adj4 hypother*).tw.
6 (temperature adj4 (manage* or target*) adj4 (cool* or chill* or reduce* or low* or cold*)).tw.
7 (control* adj4 normoth*).tw.
8 (Intravascular adj4 cool*).tw.
9 ((Cool* or chill*) adj4 (device or blank*)).tw.
10 or/1-9
11 Heart Arrest/
12 Cardiopulmonary Resuscitation/
13 ((cardiac* or heart* or postcard*) adj4 arrest).tw.
14 (cardiopulmon* adj4 resuscitat*).tw.
15 Out-of-Hospital Cardiac Arrest/
16 (out of hospital adj4 (cardiac* or heart*) adj4 arrest*).tw.
17 or/11-16
18 10 and 17
19 Thermogard.tw.
20 RhinoChill.tw.
21 Medicool.tw.
22 Arctic Sun.tw.
23 coolgard.tw.
24 or/19-23
25 18 or 24
26 Animals/ not Humans/
27 25 not 26
28 limit 27 to english language
29 limit 27 to ed=20120101-20220930
30 limit 29 to ed=20220801-20230430

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5. As a result of large body of evidence, studies other than systematic reviews and RCTs were excluded from this overview.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Systematic reviews			
Abdalla M, Mohamed A, Mohamed W et al. (2019) Targeted temperature management after cardiac arrest: updated meta-analysis of all-cause mortality and neurological outcomes. Int J Cardiol Heart Vasc; 24:100400	N=9 RCTs (n=1592 patients) with data for IHCA and OHCA were included in the meta-analysis.	Mortality was lower in TTM group (OR 0.637, 95% CI 0.436–0.93, p=0.019, n=1592). Also demonstrated reduction in poor neurological outcomes (OR 0.582, 95% CI 0.363–931, p= 0.024, n = 1567). Subgroup analysis was done, after excluding IHCA patients, and demonstrated reduction in poor neurological outcome (OR 0.562, 95% CI 0.331–0.955, p= 0.033, n = 1480) and mortality in OHCA patients (OR 0.674, 95% CI 0.454–999, p= 0.049, n = 1505).	More recent and comprehensive systematic reviews and meta-analysis included captured all relevant studies.

Aneman A, Frost S, Parr M et al. (2022) Target temperature management following cardiac arrest: a systematic review and Bayesian meta-analysis. Critical Care; 26:58, 1-13.	Systematic review and Bayesian meta-analysis. 7 RCTs with 3792 adult survivors from cardiac arrest undergoing TTM for at least 12 h comparing TTM versus no TTM or with a separation>2°C between intervention and control groups.	The posterior probability distributions did not support the use of TTM at 32–34°C compared to 36°C also including active control of fever to reduce the risk of death and unfavourable neurological outcome at 90–180 days. Any likely benefit of hypothermic TTM is smaller than targeted in RCTs to date	More recent and comprehensive systematic reviews and meta-analysis included captured all relevant studies.
Annoni F, Peluso L, Fiore M et al. (2020) Impact of Therapeutic Hypothermia During Cardiopulmonary Resuscitation on Neurologic Outcome: A Systematic Review and Meta-analysis. Resuscitation, 162, 365-371.	Systematic review and meta-analysis 8 studies (n = 3493 patients, including 4 randomised trials, RCTs) were included.	Compared to controls (standard in-hospital TTM), the use of intra-arrest therapeutic hypothermia was not associated with improved favourable neurological outcomes (OR 0.96 [95% CIs 0.68–1.37]; p = 0.84), increased ROSC rate (OR 1.11 [95% CIs 0.83–1.49]; p = 0.46) or survival (OR 0.91 [95% CIs 0.73–1.14]; p = 0.43). Trans-nasal evaporative cooling and cold fluids were explored in 2 RCTs each and no differences were observed on FO, event when only patients with an initial shockable	More recent updated systematic reviews and meta-analysis included.

		rhythm were analysed (OR 1.62 [95% CI 1.00–2.64]; p = 0.05]).	
Arrich J, Holzer M, Havel C et al. (2016) Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev; 2:CD004128	Systematic review and meta-analysis N= 6 RCTs (1412 patients)	Comparing conventional cooling methods versus no cooling (4 trials; n=437), we found that participants in the conventional cooling group were more likely to reach a favourable neurological outcome (RR 1.94, 95% CI 1.18 to 3.21); a 30% survival benefit (RR 1.32, 95% CI 1.10 to 1.65, 3 studies; n=383). The incidence of pneumonia (RR 1.15, 95% CI 1.02 to 1.30; 2 trials; N=1205) and hypokalaemia (RR 1.38, 95% CI 1.03 to 1.84; 2 trials; N= 975) was slightly increased among participants receiving therapeutic hypothermia, and no significant differences in reported adverse events between hypothermia and control groups were noted.	More recent updated systematic reviews and meta-analysis included.
Barbarawi M, Alabdouh A, Barbarawi O et al. (2020)	Systematic review and meta-analysis	Compared with standard care, patients with an	More recent updated systematic

Targeted temperature management in cardiac arrest patients with an initial non-shockable rhythm: a systematic review and meta-analysis. Shock; 54(5):623–30.	N=30 studies included (25 observational and 5 RCTs, n=10,703 patients, 4,023 had TTM and 6,680 had standard care). TSA was done on RCTs.	initial NSR cardiac arrest and received TTM (target of 32C –34C) had a significantly higher short-term survival (OR 1.44 95% CI 1.15–1.81; P = 0.002), long-term survival (OR 1.52 95% CI 1.03–2.26; P = 0.04), and CPC score of 1 to 2 (OR 1.63 95% CI 1.22–2.17; P = 0.0010). Sensitivity analyses by including only RCTs showed a trend, although not significant, toward better short-term survival (OR 1.25 95% CI 0.82–1.89; P = 0.30), long-term survival (OR 1.15 95% CI 0.80–1.66; P =0.46), and neurologic outcomes (OR 1.51 95% CI 0.81–2.80; P = 0.19). However, TSA done on the RCTs revealed that the results were inconclusive.	reviews and meta-analysis included. Study included expanded inclusion criteria, including retrospective and observational studies.
Bartlett ES, Valenzuela T, Idris A et al. (2020) Systematic review and meta-analysis of intravascular temperature management vs. surface cooling in comatose patients resuscitated from cardiac arrest.	Systematic review and meta-analysis N=12 studies RCTs and observational studies (with 1,573 patients who received IVTM; and 4,008 who received SCM).	Survival was 55.0% in the IVTM group and 51.2% in the SCM group [pooled risk difference 2% (95% CI - 1%, 5%)]. Good neurological outcome was achieved in 40.9% in the IVTM and 29.5% in the surface group [pooled risk	More recent review of RCTs included. This review also included observational studies which are prone to high risk of bias.

Resuscitation;146:82–95.		difference 5% (95% CI 2%, 8%)]. There was a 6% (95% CI 11%, 2%) lower risk of arrhythmia with use of IVTM and 15% (95% CI 22%, 7%) decreased risk of overcooling with use of IVTM versus SCM. There was no significant difference in other evaluated adverse events between groups.	
Bhattacharjee S, Baidya DK, Maitra S. Therapeutic hypothermia after cardiac arrest is not associated with favorable neurological outcome: a meta-analysis. J Clin Anesth. 2016;33:225–32.	Systematic review and meta-analysis N=1339 patients from 5 RCTs, and 1 quasi-randomised controlled trial comparing therapeutic hypothermia versus no therapeutic hypothermia in post-cardiac arrest patients.	Therapeutic hypothermia does not provide any benefit in favourable neurological outcome (P = .06; odds ratio, 1.80; 95% confidence interval [CI], 0.97-3.35; n = 1384), in survival at hospital discharge (P = .58; odds ratio, 1.16; 95% CI, 0.69-1.96; n = 1399), and in long-term survival (P = .36; odds ratio, 1.32; 95% CI, 0.73-2.39; n = 1292). Therapeutic hypothermia also increases incidence of pneumonia (P = .02; odds ratio, 1.30; 95% CI, 1.04-1.64; n = 1204; number needed to harm, 15).	More recent updated systematic reviews and meta-analysis included.
Calabro L, Bougouin W, Cariou A et al.	Systematic review and meta-analysis	When compared to surface cooling,	More updated systematic

(2019) Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: a systematic review and meta-analysis. Critical Care; 23:285, 1-12.	of RCTs and observational studies. 22 studies (n = 8,027 patients) were included.	core methods showed a lower probability of unfavourable neurological outcome (OR 0.85 [95% CIs 0.75–0.96]; p = 0.008) but not mortality (OR 0.88 [95% CIs 0.62–1.25]; p = 0.21). No significant heterogeneity was observed among studies. However, these effects were observed in the analyses of non-RCTs. A significant lower probability of both unfavourable neurological outcome and mortality were observed when invasive TTM methods were compared to non-invasive TTM methods and when temperature feedback devices (TFD) were compared to non-TFD methods. These results were significant particularly in non-RCTs.	reviews and meta-analysis included.
Nie C, Dong J, Zhang P et al. (2016) Pre-hospital therapeutic hypothermia after out-of-hospital cardiac arrest: a systematic review and meta-analysis. American Journal of Emergency	Systematic review and meta-analysis 5 studies	The pooled analysis revealed no differences in survival to hospital discharge, favourable neurological outcomes, and incidence of	More recent updated systematic reviews and meta-analysis included.

Medicine 34, 2209–2216		pulmonary oedema between the treatment group and control group. There were significant differences in body temperature at hospital arrival and the rate of re-arrest.	
Garrido CC, Gallego BR, Gracia JCS et al. (2021) The effect of therapeutic hypothermia after cardiac arrest on the neurological outcome and survival—a systematic review of RCTs published between 2016 and 2020. Int. J. Environ. Res. Public Health, 18, 11817, 1-17.	Systematic review N=17 randomised trials reporting on 5813 adults and 712 children were included.	Although therapeutic hypothermia is a safe technique with few adverse and manageable effects, it has not shown to improve survival rate and neurological status of adult nor paediatric patients. It is possible that its positive effect on neuroprotection could be achieved only by preventing hyperthermia although further investigation is needed.	More comprehensive and updated systematic reviews and meta-analysis added.
Hakim SM, Ammar MA, Reyad MS. (2018) Effect of therapeutic hypothermia on survival and neurological outcome in adults suffering cardiac arrest: a systematic review and meta-analysis. Minerva Anestesiol;84(6):720–30.	N=10 studies (7 RCTs, 2 retrospective, 1 cohort study) involving 3259 patients were included in meta-analysis.	Pooling all eligible studies showed a favourable effect for TH on survival and neurological recovery. However, sensitivity analysis for RCTs showed no benefit on either outcome, while observational trials showed benefit for neurological recovery with just marginally significant benefit	More recent updated systematic reviews and meta-analysis included.

		regarding survival. Studies including patients with shockable rhythms demonstrated benefit for both outcome measures, while those including patients with any rhythms demonstrated benefit for neurological recovery but not for survival. TH did not benefit patients with non-shockable rhythms. Trials using external cooling favoured TH regarding survival and neurological outcome but those using systemic cooling with or without external cooling did not show such benefit. When the overall incidence of complications was pooled, there was a statistically significant shift in odds ratio favouring normothermic management over TH.	
Hillerson DB, Laine ME, Bissell BD et al. (2022) Contemporary targeted temperature management: Clinical evidence and controversies. Perfusion 1-15.	Review describes the pathophysiology, physiologic aspects, clinical trial evidence, changes in post-cardiac arrest care, potential risks, as	the American Heart Association guidelines for post-cardiac arrest care recommend TTM in patients who remain comatose after ROSC. Recently, the TTM2	Review

	well as controversies of TTM.	randomised controlled trial found no significant difference in neurologic function and mortality at 6-months between traditional hypothermia to 33°C versus 37.5°C. While TTM has been evaluated for decades, current literature suggests that the use of TTM to 33° when compared to a protocol of targeted normothermia does not result in improved outcomes. Instead, perhaps active avoidance of fever may be most beneficial.	
Hunter BR, O'Donnell DP, Allgood KL et al. (2014) No benefit to pre-hospital initiation of therapeutic hypothermia in out-of-hospital cardiac arrest: A systematic review and meta-analysis. Acad Emerg Med. 2014; 21(4):356–364.			More recent updated systematic reviews and meta-analysis included.
Kalra R, Arora G, Patel N et al. (2018) Targeted temperature management after cardiac arrest: systematic review and meta-analyses. Anesth Analg;126 (3):867–75.	Systematic review and meta-analysis Hypothermia versus normothermia compared in 5 RCTs with 1389 patients whereas pre-hospital hypothermia and	We observed no difference in mortality (RR; 0.88, 95% CI: 0.73–1.05) or neurological outcomes (RR; 1.26, 95% CI: 0.92–1.72) between the hypothermia and normothermia	More recent updated systematic reviews and meta-analysis included.

	in-hospital hypothermia were compared in 6 RCTs with 3393 patients.	strategies. Similarly, no difference was observed in mortality (RR; 1.00, 95% CI: 0.97–1.03) or neurological outcome (RR; 0.96, 95% CI: 0.85–1.08) between the pre-hospital hypothermia versus in-hospital hypothermia strategies.	
Karcioglu O, Topacoglu H, Dikme O et al. (2018) A systematic review of safety and adverse effects in the practice of therapeutic hypothermia. American Journal of Emergency Medicine; 36, 1886–1894.	Systematic review N=19 studies therapeutic hypothermia in patients resuscitated from OHCA.	There is a considerable incidence of side effects attributed to the procedure, for example, from life-threatening ventricular arrhythmias to self-limited consequences. Most studies analysed in this systematic review indicated that the procedure of TH has not caused severe adverse effects leading to significant alterations in the outcomes following resuscitation from OHCA.	More recent comprehensive updated systematic reviews and meta-analysis included.
Kim YM, Yim HW, Jeong SH et al. (2012) Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms?: A			More recent updated systematic reviews and meta-analysis included.

systematic review and meta-analysis of randomized and non-randomized studies. Resuscitation. 2012; 83(2):188– 196.			
Kim JG, Ahn C, Shin H et al. (2020) Efficacy of the cooling method for targeted temperature management in post-cardiac arrest patients: A systematic review and meta-analysis. Resuscitation, 148, 14-24.	Meta-analysis (4,401 patients from 2 RCT and 7 observational studies).	For mortality, the overall pooled analysis showed no statistically significant difference between ECD and SCD recipients (RR, 0.93; 95% CI 0.86-1.00; I 2 = 0%). Further, no statistically significant difference was observed between RCT (RR, 0.80; 95% CI 0.56-1.14; I 2 = 0%) and OS (RR, 0.94; 95% CI 0.85-1.04; I 2 = 18%) for in-hospital mortality. For good neurological status of survivors after TTM, the overall pooled analysis showed no statistically significant difference between ECD and SCD (RR, 1.08; 95% CI 0.99-1.18; I 2 = 71%). No statistically significant difference was found between ECD and SCD at hospital discharge in RCT (RR, 0.88; 95% CI 0.61-1.28; I 2 = 0%) and at 6	More recent updated systematic reviews and meta-analysis included.

		months in OS (RR, 1.03; 95% CI 0.99-1.09; I 2 = 32%).	
Liao X, Zhou M, Tang H et al. (2020) Effects of endovascular and surface cooling on resuscitation in patients with cardiac arrest and a comparison of effectiveness, stability, and safety: a systematic review and meta-analysis. Critical Care; 24:27, 1-18	Systematic review and meta-analysis N=20 studies with 4913 patients (4 RCTs and 16 cohort studies). 11 studies included IHCA patients and OHCA patients, and 9 studies only included OHCA patients.	Among adult patients receiving cardiopulmonary resuscitation, although there is no significant difference between the 2 cooling methods in the time from the start of cardiac arrest to achieve the target temperature, the faster cooling rate and more stable cooling process in EC shorten patients' ICU hospitalisation time and help more patients obtain good neurological prognosis compared with patients receiving SC. Meanwhile, although EC has no significant difference in patient outcomes compared with ArcticSun, EC has improved rates of neurologically intact survival.	Study included observational studies that are prone to high risk of bias.
Lindsay PJ, Buell D, Scales DC. (2018) The efficacy and safety of pre-hospital cooling after out-of-hospital cardiac arrest: a systematic review and meta-analysis. Critical Care (2018) 22:66	Systematic review and meta-analysis pre-hospital TH versus no pre-hospital TH in patients with OHCA. N= 10 trials (4220 patients)	There were no significant differences between the 2 arms for the primary outcome of neurological recovery (RR 1.04, 95% CI 0.93–1.15)	More recent updated systematic reviews and meta-analysis included.

		or the secondary outcome of survival to hospital discharge (RR 1.01, 95% CI 0.92–1.11). There was a significantly lower temperature at hospital arrival in patients receiving pre-hospital TH (MD− 0.83, 95% CI − 1.03 to − 0.63). Pre-hospital TH significantly increased the risk of re-arrest (RR 1.19, 95% CI 1.00 to 1.41). No survival differences were observed among subgroups of patients who received intra-arrest TH versus post-arrest TH or who had shockable versus non-shockable rhythms.	
Lusebrink E, Binzenhofer L, Kellnar A et al. (2022) Targeted temperature management in postresuscitation care after incorporating results of the TTM2 Trial. Journal of the American Heart Association; 2022; 11 (21); e026539	This contemporary review provides a comprehensive and structured synopsis on TTM. It discusses, in detail, the evidence from RCTs on outcome categories and complication rates related to different treatment regimens. Moreover, it provides a guide of how results from the TTM2 trial could change the	Targeted temperature management between 32°C and 36°C has been the main therapeutic strategies to improve neurological outcome in post-resuscitation care. This recommendation has been mainly based on 2 small, randomised trials published 20 years ago. Most recent data derived from	Systematic reviews added to table 2.

	standardized operational procedures for temperature management in our daily clinical practice.	the TTM2 (Targeted Hypothermia Versus Targeted Normothermia After Out-of-Hospital Cardiac Arrest) trial, which included 1861 patients, challenge this strategy. It showed no benefit of targeted hypothermia at 33°C over normothermia at 36°C to 37.5°C with fever prevention. Because temperature management at lower temperatures also correlated with an increased risk of side effects without any benefit in the TTM2 trial, a modification of the guidelines with harmonising temperature management to normothermia might be necessary.	
Mahmoud A, Elgendy IY, Bavry AA. (2016) Use of Targeted Temperature Management After Out-of hospital Cardiac Arrest: A Meta-Analysis of Randomized Controlled Trials. Am J Med; 129(5) 522-527.e522.	Systematic review and meta-analysis 6 trials with 1391 patients were included.	Targeted temperature management after resuscitation in patients who had an OHCA was associated with a nonsignificant reduction in mortality and poor neurological outcome. Lack of benefit was strongly influenced by inclusion of 1 study	More recent updated systematic reviews and meta-analysis included.

		that used mild hypothermia in the control arm. These results indicate that only mild hypothermia may be needed to improve outcomes among patients presenting with an OHCA.	
Mishra BS, Patnaik R, Rath A et al. (2022) Targeted temperature management in unconscious survivors of post-cardiac arrest: A systematic review and meta-analysis of randomized controlled trials. Indian Journal of Critical Care Medicine; 26, 4, 506-513.	Systematic review and meta-analysis 11 RCTs with 5,305 adult comatose survivors of cardiac arrest who had TTM.	Pooled analysis of 11 RCTs, showed no difference in death caused by any origin in the hypothermia group compared to normothermia group (OR; 0.88, 95% CI: 0.39–1.16). No difference in poor neurological outcome was observed between the 2 groups (OR; 0.86, 95% CI: 0.66–1.12). Trial sequencing analysis for mortality and poor neurological outcome showed that number to achieve power to predict futility has been achieved in both the parameters.	Similar studies included.
Nielsen N, Friberg H, Gluud C et al. (2011) Hypothermia after cardiac arrest should be further evaluated—a systematic review of randomised trials with meta-analysis and trial	Systematic review with meta-analysis and TSA of RCTs evaluating MIH after cardiac arrest in adults.	The relative risk (RR) for death was 0.84 (95% confidence interval (CI) 0.70 to 1.01) and for poor neurological outcome 0.78 (95%	More recent updated systematic reviews and meta-analysis included.

sequential analysis. Int J Cardiol;151:333–341.	5 RCTs (478 patients) were included.	CI 0.64 to 0.95). For the 2 trials with least risk of bias the RR for death was 0.92 (95% CI 0.56 to 1.51) and for poor neurological outcome 0.92 (95% confidence interval 0.56 to 1.50). TSA indicated lack of firm evidence for a beneficial effect.	
Nolan JP, Soar J. (2022) Temperature control after cardiac arrest: friend or foe. Current opinion in critical care; 28 (3), 244-249.	Review	We suggest actively preventing fever by targeting a temperature 37.5 o C or less for those patients who remain comatose following ROSC after cardiac arrest.	Review
Osman M, Munir MB, Regner S et al. (2021) Induced Hypothermia in Patients with Cardiac Arrest and a Non-shockable Rhythm: Meta-analysis and Trial Sequential Analysis. Neurocritical care; 34 (1), 279-286.	meta-analysis and trial sequential analysis (TSA) comparing IHT with no IHT approaches in patients with CA and a non-shockable rhythm. N=9 studies (1 RCT and 8 observational studies) with 10, 386 patients were included.	There was no difference between both groups in terms of favourable neurological outcome (13% versus. 13%, RR 1.34, 95% CI 0.96–1.89, p=0.09, I^2=88%), survival at discharge (20% versus. 22%, RR 1.09, 95% CI 0.88–1.36, p=0.42, I^2=76%), or survival beyond 90 days (16% versus. 15%, RR 0.92, 95% CI 0.61–1.40, p=0.69, I^2=83%). The TSA showed from evidence supporting the lack of benefit of IHT in	More recent review included. This review included observational studies prone to high risk of bias.

		terms of survival at discharge.	
Patel JK, Parikh PB (2016). Association between therapeutic hypothermia and long-term quality of life in survivors of cardiac arrest: A systematic review. Resuscitation 103 (2016) 54–59.	Systematic review 9 studies with 801 patients. (6 prospective cohort studies, 1 retrospective study, 2 sub-studies of RCTs)	The included studies do not suggest any association between TH implementation in CA with long-term QoL in CA survivors. Further larger scale studies are needed to investigate the sustainability of TH effects long term in this patient population.	More recent updated systematic reviews and meta-analysis included.
Ramadanov N, Arrich J, Klein R et al. (2022) Intravascular versus surface cooling in patients resuscitated from cardiac arrest: A systematic review and network meta-analysis with focus on temperature feedback. Critical Care Medicine; 50 (6), 999-1009.	Network-meta-analysis of 14 studies (4 RCTs, 10 non-randomised observational studies) comparing intravascular cooling (IC), surface cooling with temperature feedback (SCF), and surface cooling without temperature feedback (SCnoF) in patients having TTM for CA.	IC compared with SCnoF was significantly associated with better neurologic outcome (OR, 0.6; 95% CI,0.49–0.74) and survival (OR, 0.8; 95% CI,0.66–0.96). IC compared with SCF, and SCF compared with SCnoF did not show significant differences in neurologic outcome and survival. The rankogram showed that IC had the highest probability to be the most beneficial cooling method, followed by SCF and SCnoF.	This review included observational studies that are prone to high risk of bias.
Schenone AL, Cohen A, Patarroyo G, et al. (2016) Therapeutic hypothermia after cardiac arrest: a	Systematic review and meta-analysis 11 studies (RCTs and observational	Use of TH after OHCA, even within an expanded use, decreased the mortality (OR 0.51,	Study included expanded inclusion criteria, including retrospective

systematic review/meta-analysis exploring the impact of expanded criteria and targeted temperature. Resuscitation. 2016;108:102–10.	studies) reporting achieved temperature during TH after OHCA were included.	95%CI [0.41-0.64]) and improved the odds of good neurological outcome (OR 2.48, 95%CI [1.91-3.22]). No statistical heterogeneity was found for either mortality or neurological outcome. No differences in hospital mortality (p=0.86) or neurological outcomes at discharge (p=0.32) were found when pooled outcomes of 34 hypothermia arms grouped by cooling temperature were compared.	and observational studies.
Shrestha DB, Sedhai YR, Budhathoki P et al. (2022) Hypothermia versus normothermia after out-of-hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials. Annals of Medicine and Surgery 74 (2022) 103327	6 RCTs comparing therapeutic hypothermia (32–34 ◦C) with normothermia (≥36 ◦C with control of fever) in adult patients resuscitated after out-of-hospital cardiac arrest	There was no significant difference between the hypothermia and normothermia groups in mortality till 6 months follow up after out-of hospital cardiac arrest (OR 0.88, 95% CI 0.67–1.16; n = 3243; I 2 = 51%), or favourable neurological outcome (OR 1.31, 95% CI 0.93–1.84; n = 3091; I2 = 68%). Rates of arrhythmias were notably higher in the hypothermia group than the normothermia group (OR 1.43,	More comprehensive updated systematic reviews and meta-analysis included.

		95% CI 1.20–1.71; n = 3029; I 2 = 4%). However, development of pneumonia showed no significant differences across 2 groups (OR 1.13, 95% CI 0.98–1.31; n = 3056; I2 = 22%).	
Stagner Editor's Choice-Effects of targeted temperature management on mortality and neurological outcome: A systematic review and meta-analysis. European Heart Journal: Acute Cardiovascular Care 2018, 7(5) 467–477.	Systematic review, and meta-analyses. 6 RCTs 8 observational studies OHCA with SR- 2 RCTs, 1 quasi-RCT OCHA with NSR-5 observational studies. IHCA with any rhythm -2 observational studies. Optimal temperature for TTM-2 RCTs. Pre-hospital versus in-hospital-6 RCTs. Duration of TTM-1 RCT, 4 observational studies Endovascular versus surface cooling-1 RCT, 5 observational studies. TTM cooling methods with feedback temperature	Low-quality evidence supports the in-hospital initiation and maintenance of targeted temperature management at 32–36°C among adult survivors of OHCA with an initial shockable rhythm for 18–24 h. The effects of targeted temperature management on other populations, the optimal rate and method of cooling and re-warming, and effects of fever need further study.	More comprehensive updated systematic reviews and meta-analysis included.

	control compared to those without (that is, conventional cooling)-2RCTs, 4 observational studies. Gradual cooling (≤0.5°C/h) compared to rapid cooling (>0.5°/h)- 2 observational studies. Use of TTM compared to avoidance of fever-1 observational study rapid re-warming (≥0.5°C/h) compared to gradual re-warming -1 retrospective cohort study presence compared to absence of post-re-warming fever-6 observational studies.		
Suen KFK, Leung R, Lueng LP et al. (2017) Therapeutic hypothermia for asphyxia out-of-hospital cardiac arrest due to drowning: A systematic review of case series and case reports. THERAPEUTIC HYPOTHERMIA AND TEMPERATURE	13 studies (with 35 patients from case series and case reports)	Preliminary observation suggests that extended therapeutic hypothermia of 48–72 hours might help prevent reperfusion injury during the intermediate phase of post-cardiac arrest care to benefit patients of	More comprehensive updated systematic reviews and meta-analysis included.

MANAGEMENT, 7, 4, 210-222.		drowning-associated asphyxia OHCA. No conclusive recommendation could be made about the duration of and the time of onset of therapeutic hypothermia.	
Rout A, Singh S, Sarkar S et al. (2020) Meta-analysis of the usefulness of therapeutic hypothermia after cardiac arrest. Am J Cardiol;133:48–53.	Systematic review and meta-analysis RCTs comparing TH (32°C to 34°C) with controls (normothermia or temperature ≥36°C) in comatose patients who sustained cardiac arrest. N=8 RCTs with a total of 2,026 patients (TH n = 1,025 and control n = 1,001) were included.	Irrespective of initial rhythm, TH was associated with significant reduction in poor neurological outcomes (RR 0.87, 95% CI 0.77 to 0.98; p = 0.02) without any difference in mortality (RR 0.94, 95% CI 0.85 to 1.03; p = 0.17). In patients with initial shockable rhythm compared with control, TH reduced mortality (RR 0.85, 95% CI 0.73 to 0.99; p = 0.04) and poor neurological outcomes (RR 0.81, 95% CI 0.67 to 0.99; p = 0.04). Whereas, in patients with initial non-shockable rhythm, TH was associated with decreased poor neurological outcomes after excluding 1 trial (RR 0.95 95% CI 0.91 to 1.00; p = 0.05).	More recent updated systematic reviews and meta-analysis included.

Song L, Wei L, Zhang L et al. (2016) The role of targeted temperature management in adult patients resuscitated from non-shockable cardiac arrests: an updated systematic review and meta-analysis. Biomed Res Int. 2016:2350974. doi: 10.1155/2016/2350974	Systematic review and meta-analysis of 25 trials (with 5715 patients from RCTs and observational studies) on TTM compared to normothermia for patients resuscitated from non-shockable cardiac arrest.	Pooled data showed that TTM not only associated with improved short-term survival (RR = 1.42, 95% CI: 1.28–1.57) and neurological function (RR = 1.63, 95% CI: 1.39–1.91) but also associated with improved long-term survival (RR = 1.64, 95% CI: 1.27–2.12) and neurological recovery (RR = 1.42, 95% CI: 1.07–1.90) in observational cohort studies. However, more frequent infectious complications were reported in hypothermia-treated patients (RR = 1.46, 95% CI: 1.26–1.70) and the quality of the evidence ranged from moderate to very low.	Study included observational studies which are prone to high risk of bias.
Stanger D, Mihajlovic V, Singer J, et al. (2018) Effects of targeted temperature management on mortality and neurological outcome: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care; 7(5):467–77.	Systematic review and meta-analysis (6 RCTs and 8 observational studies).	Overall, low-quality evidence demonstrated that targeted temperature management at 32–36°C, compared to no targeted temperature management, decreased mortality (risk ratio 0.76, 95% confidence interval 0.61–0.92) and poor neurological	Recent and updated systematic reviews and meta-analysis included.

		outcome (risk ratio 0.73, 95% confidence interval 0.60–0.88) among adult survivors of OHCA with an initial shockable rhythm. Targeted temperature management use did not benefit survivors of IHCA nor OHCA survivors with a non-shockable rhythm. Moderate-quality evidence demonstrated no benefit of pre-hospital targeted temperature management initiation. Low-quality evidence showed no difference between endovascular versus surface cooling targeted temperature management systems, nor any benefit of adding feedback control to targeted temperature management systems. Low-quality evidence suggested that targeted temperature management be maintained for 18–24 h.	
Szarpak L, Filipiak KJ, Mosteller L et al. (2021) Survival,	Systematic review and meta-analysis	The survival to hospital discharge did not differ	More recent and comprehensive updated

neurological and safety outcomes after out-of-hospital cardiac arrests treated by using pre-hospital therapeutic hypothermia: A systematic review and meta-analysis. American Journal of Emergency Medicine 42, 168–177.	OHCA treated using pre-hospital therapeutic hypothermia N= 11 studies with 4891 patients.	between PTH and control group (RR 1.02; 95%CI 0.93 to 1.12). Among 4891 participants (2466 in PTH group and 2425 in control group), 1087 participants (564 versus 523) had a favourable neurological outcome. Pulmonary oedema occurred in 320 cases in PTH group and 273 in control group with significant heterogeneity (RR 0.90, 95%CI 0.59–1.38; I2 = 80%). The pooled results showed a significant difference in rearrests between the PTH and control group (RR 1.19; 95%CI 1.00 to 1.42).	systematic reviews and meta-analysis included.
Villablanca PA, Makkiya M, Einsenberg E, et al. (2016) Mild therapeutic hypothermia in patients resuscitated from out-of-hospital cardiac arrest: A meta-analysis of randomized controlled trials. Ann Card Anaesth; 19 (1):4–14.	Meta-analysis of 6 RCTs MTH in 1400 patients successfully resuscitated from OHCA.	Overall survival was 50.7%, and favourable neurological recovery was 45.5%. Pooled data demonstrated no significant all-cause mortality (OR, 0.81; 95% CI 0.55-1.21) or neurological recovery (OR, 0.77; 95% CI 0.47-1.24).	More recent updated systematic reviews and meta-analysis included.
Yu T, Longhini F, Wu R et al. (2015) The role of the induction of mild	Systematic review comparing mild hypothermia (32-	Mild hypothermia demonstrated no significant	More recent updated systematic

hypothermia in adult patient outcomes after cardiac arrest: Systematic review and meta-analysis of randomized controlled studies. J Int Med Res; 43(4):471–482.	34℃) with normothermia or hypothermia other than mild hypothermia after cardiac arrest, in adults with ROSC. N=7 RCTs were included.	beneficial effects in terms of overall mortality or neurological outcomes. In addition, no significant outcome differences were observed between the pre- and in-hospital subgroups.	reviews and meta-analysis included.
Zhang XW, Xie JF, Chen JX, et al. (2015) The effect of mild induced hypothermia on outcomes of patients after cardiac arrest: a systematic review and meta-analysis of randomised controlled trials. Crit Care; 19:417.			More recent updated systematic reviews and meta-analysis included.
Zhang Q, Qi Z, Liu B et al. (2018) Predictors of survival and favorable neurological outcome in patients treated with targeted temperature management after cardiac arrest: A systematic review and meta-analysis. Heart & Lung 47 (2018) 602-609.	Systematic review and meta-analyses of 17 studies.	Favourable neurological outcome was associated with significantly higher odds of an initial shockable rhythm (OR: 7.63, 95%CI: 6.51-8.96), bystander CPR (OR: 1.44, 95%CI: 1.14-1.82), male (OR: 1.39, 95%CI: 1.20-1.61). Survival was associated with higher odds of an initial shockable rhythm (OR: 4.88, 95%CI: 3.18-4.79), higher odds of bystander CPR (OR: 1.71, 95%CI: 1.05-2.77). No significant association was	More comprehensive updated systematic reviews and meta-analysis included.

		found between survival and male. In adult patients treated with TTM, initial shockable rhythm, bystander CPR and male sex were associated with a higher likelihood of favourable neurological outcome. Initial shockable rhythm and bystander CPR were associated with a higher likelihood of survival.	