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

Contents

Indications and current treatment....2
What the procedure involves....3
Outcome measures....3
Evidence summary....4
Population and studies description....4
Procedure technique....19
Efficacy....19
Safety....23
Validity and generalisability....26
Existing assessments of this procedure....27
Related NICE guidance....33
Interventional procedures....33
Technology appraisals....**Error! Bookmark not defined.**
Medical technologies....33
NICE guidelines....33
Professional societies....33
Company engagement....34
References....34
Methods....35
Other relevant studies....38

© NICE 2023. All rights reserved. Subject to Notice of rights.

Table 1 Abbreviations

Abbreviation	Definition
CI	Confidence interval
CPC	Cerebral Performance Categories
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
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). It 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

mechanical ventilation, and drugs such as adrenaline and amiodarone. The 2021 resuscitation guidelines contain information about basic and advanced life support.

Temperature control can also be described as targeted temperature management.

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 to prevent fever (by maintaining normothermia, a normal temperature of 36.5°C to 37.5°C) or induced to therapeutic hypothermia (cooled 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 protects against brain injury is unknown. Possible mechanisms include reductions in metabolic demand, release of excitatory neurotransmitters and inflammation after ischaemia.

Temperature control is doneusing surface techniques (for example, heat exchange cooling pads, cooling blankets and ice packs), internal techniques (for example, an endovascular cooling device) or a combination of these techniques. Core body temperature is monitored using a temperature probe (such as a bladder, rectal or nasopharyngeal temperature probe) and is controlled to a pre-set 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 together with intravenous sedation and muscle relaxants, to prevent and manage 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 18,825 patients from 6 systematic reviews and meta-analysis. There is an overlap between included primary studies (RCTs) within the 5 systematic reviews. So the actual number of patients in RCTs who had TTM with hypothermia were 2828 patients and those with normothermia were 1390 patients. Another systematic review with 6 observational studies included 1845 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 6 studies as the key evidence in table 2 and table 3, and lists other 38 relevant studies in table 5.

The 6 systematic reviews and meta-analyses were published between 2021-22. Five 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). Therefore, there is an overlap between included primary studies within the 5 systematic reviews. Only 1 systematic review and meta-analysis included

© NICE 2023. All rights reserved. Subject to Notice of rights.

observational studies (Yin 2022). One study did a network meta-analysis of different TTM strategies (Fernando 2021).

The SRs listed first authors from Canada, Denmark, USA, Italy and China.

All 5 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. 2 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 57-77 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.

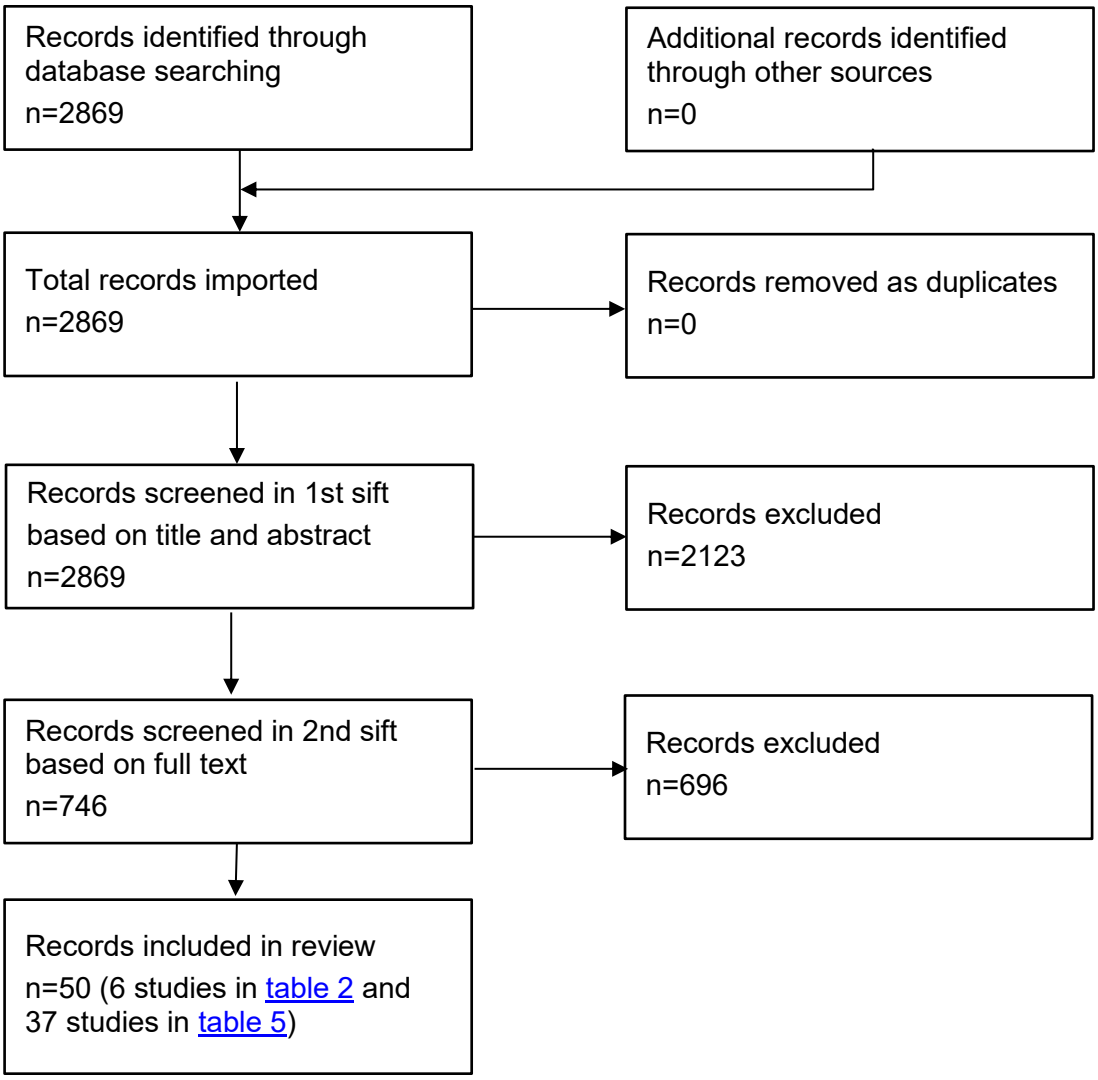
The quality of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. The level of evidence was judged to be low in 2 systematic reviews (Fernando 2021, Granfeldt 2021).

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

Table 2 presents study details.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Figure 1 Flow chart of study selection



© NICE 2023. All rights reserved. Subject to Notice of rights.

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

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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	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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Study no.	First author, date country	Studies/Patients (male: female)	Age	Study design	Inclusion criteria	Intervention and comparator	Follow up
					temperature (32.0 -34.0°C).		
6	Yin L 2022 China	Six 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

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) TTM with moderate hypothermia (33.0°C to 34.0°C) versus normothermia (OR 1.34, 95% CI 0.92–1.94)	**Adverse events** NWMA estimates (10 RCTs included, compared TTM with hypothermia with normothermia) <u>Arrhythmia:</u> TTM with deep hypothermia (31.0°C to 32.0°C): OR 3.58 (95% CI 1.77 to 7.26) TTM with moderate hypothermia (33.0°C to 34.0°C): OR 1.45 (95% CI 1.08 to 1.94)

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

First author, date	Efficacy outcomes	Safety outcomes
	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 deep hypothermia versus mild hypothermia (OR 1.01, [95% CI 0.47 to 2.14])	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: TTM with deep hypothermia (31.0°C to 32.0°C): Not available

© NICE 2023. All rights reserved. Subject to Notice of rights.

First author, date	Efficacy outcomes	Safety outcomes
	TTM with mild hypothermia versus moderate hypothermia (OR 1.02, [95% CI 0.79 to 1.32	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). **Timing of initiating TTM**	

© NICE 2023. All rights reserved. Subject to Notice of rights.

First author, date	Efficacy outcomes	Safety outcomes
	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)	

© NICE 2023. All rights reserved. Subject to Notice of rights.

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%.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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%.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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%.	

© NICE 2023. All rights reserved. Subject to Notice of rights.

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:	

© NICE 2023. All rights reserved. Subject to Notice of rights.

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%. <u>Neurological outcome</u> 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.	

© NICE 2023. All rights reserved. Subject to Notice of rights.

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 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 to2.11]; 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).

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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).

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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).

Safety

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).

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). Arrhythmia was more common among patients receiving TTM with deep hypothermia (OR 3.58, 95% CI 1.77 to 7.26) and with moderate hypothermia (OR145, 95% CI 1.08 to 1.94) compared with normothermia, GRADE high certainty; Fernando 2021).

© NICE 2023. All rights reserved. Subject to Notice of rights.

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).

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).

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).

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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).

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).

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Validity and generalisability

- All 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.
- 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.
- There are no RCTs evaluating TTM in adult IHCA; only observational studies were assessed.
- There is no long-term data greater than 6 months.
- 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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Existing assessments of this procedure

International guidance

The **International Liaison Committee on Resuscitation (ILCOR): International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations – for adult advanced life support (2020)** includes updated recommendations on targeted temperature management. This is based on the systematic review on temperature management after cardiac arrest (Granfeldt 2021). These remained unchanged from 2015 and include the following:

'We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom temperature control is used (strong recommendation, moderate-quality evidence). Whether certain subpopulations of cardiac arrest patients may benefit from lower (32°C – 34°C) or higher (36°C) temperatures remains unknown, and further research may help elucidate this.

We recommend TTM as opposed to no TTM for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence).

We suggest TTM as opposed to no TTM for adults with OHCA with an initial non-shockable rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence).

We suggest TTM as opposed to no TTM for adults with IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence).

© NICE 2023. All rights reserved. Subject to Notice of rights.

We suggest that if TTM is used, duration should be at least 24 hours (weak recommendation, very low-quality evidence).

We recommend against routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation, moderate-quality evidence).

We suggest prevention and treatment of fever in persistently comatose adults after completion of TTM between 32°C and 36°C (weak recommendation, very low-quality evidence).'

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:

© NICE 2023. All rights reserved. Subject to Notice of rights.

- ‘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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.'

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.'

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

References

1. Fernando SM, Di Santo P, Sadeghirad B, et al. Targeted temperature management following out-of-hospital cardiac arrest: a systematic review and network meta-analysis of temperature targets. Intensive Care Med 2021; 47:1078–1088.
2. Granfeldt A, Holmberg MJ, Nolan JP, et al., International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force. International Liaison Committee on Resuscitation Advanced Life Support Task Force. Targeted temperature management in adult cardiac arrest: systematic review and meta-analysis. Resuscitation 2021; 167:160–172.
3. Elbadawi A, Sedhom R, Baig B, et al. Targeted hypothermia vs targeted normothermia in survivors of cardiac arrest: a systematic review and meta-analysis of randomized trials. Am J Med. 2021;6:66. 50.
4. Sanfilippo F, La Via L, Lanzafame B et al. Targeted temperature management after cardiac arrest: a systematic review and meta-analysis with trial sequential analysis. J Clin Med. 2021;10(17):66.
5. Zhu Y-B, Yao Y, Ren Y et al. (2022) Targeted temperature management for cardiac arrest due to non-shockable rhythm: A systematic review and meta-analysis of randomized controlled trials. Frontiers in Medicine; 9: 910560.
6. Yin L, Xie D, He D et al. (2022) Survival to hospital discharge and neurological outcomes with targeted temperature management after in-hospital cardiac arrest: a systematic review and meta-analysis. Ann Palliative Med;11(1):68-76.
7. Adult advanced life support 2020 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 156 (2020) A80
8. Panchal AR, Bartos JA, Cabanas JG et al. (2020) Part 3: Adult Basic and Advanced Life Support. 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation;142 (suppl 2):S366–S468.

© NICE 2023. All rights reserved. Subject to Notice of rights.

9. Perkins GD, Grasner JT, Semeraro F et al. European Resuscitation Council Guidelines 2021: Executive summary. Resuscitation 161.1-60.

10. Nolan JP, Deakin CD, Soar J et al. (2021) Resuscitation Council (UK): Resuscitation guidelines. Post Resuscitation care.

11. Nolan JP, Sandroni C, Böttiger BW et al. (2022) European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med. 2021;47(4):369–421

Nolan JP, Sandroni C, Andersen LW, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Resuscitation 2022; 172; https://doi.org/10.1016/j.resuscitation.2022.01.009.

12. ANZCOR Guideline 11.8 – Targeted Temperature Management (TTM) after Cardiac Arrest. Australian Resuscitation Council. 2016, 1-8.

13. Kumar D, Tran K, Premji Z. (2022) Temperature Management in Patients After Cardiac Arrest. CADTH Health Technology Review 2, 2 (accessed 2022 December 7).

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 30-08-2022: 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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

- 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)	30/08/2022	1946 to August 29, 2022
MEDLINE In-Process (Ovid)	30/08/2022	1946 to August 29, 2022
MEDLINE Pubs ahead of print (Ovid)	30/08/2022	August 29, 2022
EMBASE (Ovid)	30/08/2022	1974 to 2022 August 29
EMBASE Conference (Ovid)	30/08/2022	1974 to 2022 August 29
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/08/2022	Issue 8 of 12, August 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/08/2022	Issue 8 of 12, August 2022
International HTA database (INAHTA)	30/08/2022	-

Trial sources searched April 2022

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

Websites searched April 2022

- National Institute for Health and Care Excellence (NICE)
- NHS England

© NICE 2023. All rights reserved. Subject to Notice of rights.

- 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 following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

Strategy used:

1	Hypothermia, Induced/	21,660
2	Cold Temperature/	54,122
3	TTM.tw.	1,630
4	(Target adj4 temperat* adj4 manage*).tw.	191
5	((Therapeut* or Protect* or Induc*) adj4 hypother*).tw.	9,937
6	(temperature adj4 (manage* or target*) adj4 (cool* or chill* or reduce* or low* or cold*)).tw.	277
7	(control* adj4 normoth*).tw.	562
8	(Intravascular adj4 cool*).tw.	95
9	((Cool* or chill*) adj4 (device or blank*)).tw.	968
10	or/1-9	81,550
11	Heart Arrest/	31,643
12	Cardiopulmonary Resuscitation/	20,610
13	((cardiac* or heart* or postcard*) adj4 arrest).tw.	36,300
14	(cardiopulmon* adj4 resuscitat*).tw.	15,313
15	Out-of-Hospital Cardiac Arrest/	6,405
16	(out of hospital adj4 (cardiac* or heart*) adj4 arrest*).tw.	6,814
17	or/11-16	62,450
18	10 and 17	4,468
19	Thermogard.tw.	9
20	RhinoChill.tw.	15
21	Medicool.tw.	0
22	Arctic Sun.tw.	34
23	coolgard.tw.	23
24	or/19-23	77
25	18 or 24	4,503
26	Animals/ not Humans/	5,007,751
27	25 not 26	3,716
28	limit 27 to english language	3,368
29	limit 28 to ed=20170101-20220930	1,173

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

(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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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

© NICE 2023. All rights reserved. Subject to Notice of rights.

	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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

	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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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.	
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 that used mild hypothermia in the control arm. These results indicate that	More recent updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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 sequential analysis. Int J Cardiol;151:333–341.	Systematic review with meta-analysis and TSA of RCTs evaluating MIH after cardiac arrest in adults. 5 RCTs (478 patients) were included.	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% CI 0.64 to 0.95). For the 2 trials with least risk of bias the RR for death was	More recent updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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 terms of survival at discharge.	More recent review included. This review included observational studies prone to high risk of bias.
Patel JK, Parikh PB (2016). Association between therapeutic	Systematic review 9 studies with 801 patients. (6	The included studies do not suggest any	More recent updated systematic

© NICE 2023. All rights reserved. Subject to Notice of rights.

hypothermia and long-term quality of life in survivors of cardiac arrest: A systematic review. Resuscitation 103 (2016) 54–59.	prospective cohort studies, 1 retrospective study, 2 sub-studies of RCTs)	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.	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/meta-analysis exploring the impact of expanded criteria and targeted temperature.	Systematic review and meta-analysis 11 studies (RCTs and observational studies) reporting achieved temperature during TH after OHCA were included.	Use of TH after OHCA, even within an expanded use, decreased the mortality (OR 0.51, 95%CI [0.41-0.64]) and improved the odds of good neurological outcome (OR 2.48,	Study included expanded inclusion criteria, including retrospective and observational studies.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Resuscitation. 2016;108:102–10.		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.	
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, 95% CI 1.20–1.71; n = 3029; I 2 = 4%). However, development of pneumonia showed	More comprehensive updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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 control compared to those without (that is, conventional cooling)-2RCTs, 4	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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

	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 MANAGEMENT, 7, 4, 210-222.	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 drowning-associated asphyxia OHCA. No conclusive recommendation	More comprehensive updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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	Systematic review and meta-analysis of 25 trials (with 5715 patients from RCTs and observational	Pooled data showed that TTM not only associated with improved short-term survival (RR = 1.42, 95%	Study included observational studies which are prone to high risk of bias.

© NICE 2023. All rights reserved. Subject to Notice of rights.

from non-shockable cardiac arrests: an updated systematic review and meta-analysis. Biomed Res Int. 2016:2350974. doi: 10.1155/2016/2350974	studies) on TTM compared to normothermia for patients resuscitated from non-shockable cardiac arrest.	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.	
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 outcome (risk ratio 0.73, 95% confidence interval 0.60–0.88) among adult survivors of OHCA with an initial	Recent and updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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, neurological and safety outcomes after out-of-hospital cardiac arrests treated by using pre-hospital therapeutic hypothermia: A	Systematic review and meta-analysis OHCA treated using pre-hospital therapeutic hypothermia N= 11 studies with 4891 patients.	The survival to hospital discharge did not differ between PTH and control group (RR 1.02; 95%CI 0.93 to 1.12). Among 4891 participants (2466 in PTH group and	More recent and comprehensive updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

systematic review and meta-analysis. American Journal of Emergency Medicine 42, 168–177.		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).	
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 hypothermia in adult patient outcomes after cardiac arrest: Systematic review and meta-analysis of randomized controlled	Systematic review comparing mild hypothermia (32-34℃) with normothermia or hypothermia other than mild hypothermia after	Mild hypothermia demonstrated no significant beneficial effects in terms of overall mortality or neurological outcomes. In addition, no	More recent updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

studies. J Int Med Res; 43(4):471–482.	cardiac arrest, in adults with ROSC. N=7 RCTs were included.	significant outcome differences were observed between the pre- and in-hospital subgroups.	
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 found between survival and male. In adult patients treated with TTM, initial shockable rhythm, bystander	More comprehensive updated systematic reviews and meta-analysis included.

© NICE 2023. All rights reserved. Subject to Notice of rights.

		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.	

© NICE 2023. All rights reserved. Subject to Notice of rights.