QUESTION

Should TTM vs. no TTM be used for cardiac arrest?

POPULATION:	**Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest**
INTERVENTION:	**TTM [TTM studies targeting hypothermia at 32-34 C included in the systematic review]**
COMPARISON:	**No TTM [TTM studies targeting normothermia or fever prevention included in the systematic review]**
MAIN OUTCOMES:	**Survival to hospital discharge ; Favourable neurological outcome at hospital discharge or 30 days; Survival to 90 or 180 days; Favourable neurological outcome at 90 or 180 days**
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review. Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM CHH, JCR, KGH, RWN, CWC declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	TTM has been an important part of post-resuscitation care since 2002, when 2 RCTs reported improved outcomes among comatose OHCA patients who were cooled to 32-34 C for 12-24 h. These initial studies enrolled only patients with cardiac arrests from shockable rhythms. Since then, RCTs have reported conflicting results for the comparison of mild hypothermia with normothermia. The "TTM1 trial" in 2013 did not show a benefit with a target of 33°C compared to a target of 36°C. Since publication of TTM trial many settings have moved to targeting normothermia or possibly no temperature management Last ILCOR update was in 2015 (Donnino 2015) 4 RCTs since 2015 with 2 looking at hypothermia v normothermia/fever prevention. The HYPERION trial reported improved functional outcomes among post-cardiac arrest patients with non-shockable rhythms who were treated at 33oC compared with normothermia. The TTM-2 study reported no difference in outcomes when all rhythm OHCA patients were treated with 33 C compared with normothermia. In TTM2 trial protocol: In the normothermia arm the aim was early treatment of fever (greater than or equal to 37.8°C) using pharmacological measures and physical cooling when needed. For participants who developed a temperature of 37.8°C (trigger), a device was used and set at 37.5°C. Normothermia was defined in TTM2 as 36.5-37.7°C. pharmacological measures (acetaminophen), uncovering the patient, and lowering ambient temperature was used to maintain a temperature of ≤ 37.5 C (99.5 F) in the 'normothermia group/fever prevention group'. If the temperature was > 37.7 C (99.9 F) a cooling device was used and set at a target temperature of ≤ 37.5 C (99.5 F). [HACA - fever controlled, technique used not specified] Since publication of TTM trial many settings have moved to targeting normothermia or possibly no temperature management. There are concerns that this has led to worsened outcomes. Interventions and effectiveness of fever prevention in control groups was variable	TTM includes hypothermia at 32-34C 'No TTM' included normothermia/fever prevention 36.5-37.7C The term TTM is not helpful and using hypothermia TTM, normothermia, fever control is more useful .

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Evidence shows no difference, benefit or harm from hypothermia at 32-34 C**	Concerns raised with available data: 1. Target temperature achieved too late. Time to TTM target similar in most recent trials and observational studies 2. Select patient group of primary cardiac arrest and may not be generalisable to all post ROSC cardiac arrest patients. 3. No or very few patients with IHCA or non primary cardiac arrest.

32-34 v normothermia/fever prevention

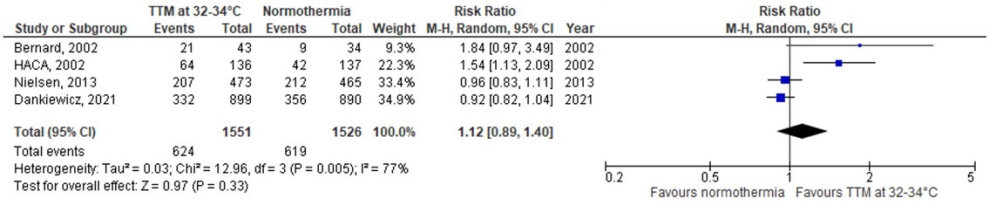
Outcomes	With no TTM	With TTM [32-34 C]	Difference	Relative effect (95% CI)
Survival to hospital discharge	460 per 1,000	**515 per 1,000** (423 to 621)	**55 more per 1,000** (37 fewer to 161 more)	**RR 1.12** (0.92 to 1.35)
Favourable neurological outcome at hospital discharge or 30 days	384 per 1,000	**499 per 1,000** (318 to 779)	**115 more per 1,000** (65 fewer to 395 more)	**RR 1.30** (0.83 to 2.03)
Survival to 90 or 180 days	435 per 1,000	**469 per 1,000** (387 to 565)	**35 more per 1,000** (48 fewer to 130 more)	**RR 1.08** (0.89 to 1.30)
Favourable neurological outcome at 90 or 180 days	363 per 1,000	**440 per 1,000** (331 to 585)	**76 more per 1,000** (33 fewer to 222 more)	**RR 1.21** (0.91 to 1.61)

When TTM1 trial added (33 v 36) and 36 C included in definition of normothermia/no TTM, there was no difference in outcome.

Sensitivity analysis – TTM trial of 33 v 36 C added to no normothermia/fever prevention studies: there is no difference in outcome

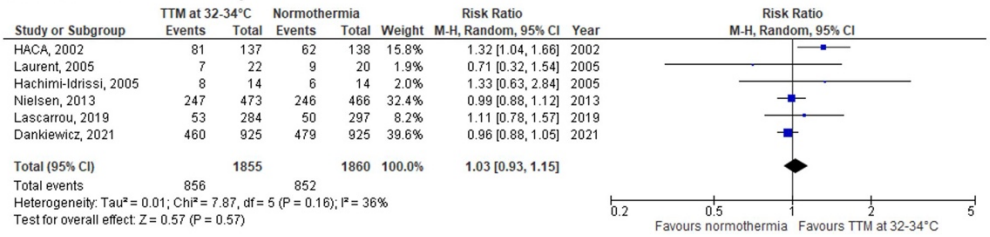
[TTM2 and HACA similar demographic?]

Favorable neurologic outcome at hospital discharge or 30 days



Debate as to whether TTM2 and RCT populations are different to real world practice.

Survival to 90 or 180 days



Paper on etiologies (Chen N, Callaway CW, Guyette FX, Rittenberger JC, Doshi AA, Dezfulian C, Elmer J; Pittsburgh Post-Cardiac Arrest Service. Arrest etiology among patients resuscitated from cardiac arrest. Resuscitation. 2018 Sep;130:33-40.] suggests significant proportion of patients have a non-cardiac arrest cause

Favorable neurologic outcome at 90 or 180 days

Active warming was used in the Hyperion control group - ? harmful

Prolonged sedation used in TTM2 control group up to 40 hours.

Concern that time to target temperature was too slow in the RCTs - seems reasonable compared to other RCTS/observational data where time for consent/randomisation did not have any impact

Trials assessing TTM at 32-34°C				
Trial	**Target**	**Time to randomization from ROSC**	**Time to target from randomization**	**Time from ROSC to target**
HACA, 2002[1]	32-34°C	105 min.*	NR	8 hours
Bernard, 2002[2]	33°C	NR	NR	2 hours**
Nielsen, 2013[3]	33°C	NR	≈ 3 hours to 34°C***	NR
Moler, 2015[4]*****	32-34°C	5.9 hours*	1.6 hours	≈ 7.5 hours
Lascarrou, 2019[5]	33°C	≈ 216 min.	317 min	≈ 8.9 hours
Lopez-de-Sa, 2018[6]	33°C	157 min.	≈ 1.5 hours***	≈ 4.1 hours
Dankiewicz, 2021[7]	33°C	≈ 111 min.	3 hours to 34°C	≈ 4.9
COACT*****	34°C	≈ 184 min.	= 1-2 hours***	≈ 4-5 hours

* Time to initiation of cooling from ROSC
** "In the hypothermia group, the core temperature decreased from 34.9°C 30 minutes after return of spontaneous circulation to 33.5°C 120 minutes after the return of spontaneous circulation"
*** NR. Estimated from figure.
**** Pediatric trial
***** Unpublished. Data from presentation.

Other newer post-cardiac arrest trials				
Trial	**Target**	**Time to randomization from ROSC**	**Time to target from randomization**	**Time from ROSC to target**
Deye, 2015[8]	32-34°C	≈ 3.8 hours*	NR	Internal: 5.5 hours External: 8.5 hours
Kirkegaard, 2017[9]	32-34°C	NA	NA	≈ 5 hours
Lemkes, 2019[10]	NR	NA	NA	≈ 5 hours
François, 2019[11]	32-34°C	NA	NA	≈ 5-6 hours**

* Described as "Delay to start hypothermia"
** From cardiac arrest

Multicenter observational studies				
Study	**Target**	**Time to initiation of TTM from ROSC**	**Time to target from initiation**	**Time from ROSC to target**
Nielsen, 2009[12]	32-34°C	≈ 70 min.	NR	≈ 4 hours
Perman, 2015[13]	33°C	≈ 110 min.	≈ 200 min.	≈ 5 hours
Khera, 2018[14]	Multiple, median 34°C	160 min*	NR*	NR*
Sonder, 2018[15]	32, 33, or 34°C	Transferred: 214 – 378 min.** Non-transferred: 78 – 102 min.**	NR	Transferred: 7.6 – 8.4 hours** Non-transferred: 3.4 – 5.4 hours**
Sawyer, 2019[16]	33°C	213 min.***	89 min.	≈ 4.8 hours ***
Okazaki, 2019[17]	32-34°C or 35-36°C	≈ 110 min.****	NR	NR
Hifumi, 2020[18]	34°C	NR	180 min.	NR

* Reported as "Time from ROSC to TTM". Also state that time to TTM from hospital arrival is 84 min and that "Time from ED to hypothermia" was 138 minutes. Not clear what exactly is being reported.
** From cardiac arrest. Range depending on device. Reports time to 34°C
*** From cardiac arrest
**** "Door-to-TTM initiation"

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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● **Moderate** ● **Small** ○ Trivial ○ Varies ○ Don't know	**Range of TF opinion <u>small to moderate</u>** Task force mixed as to whether the level of harm caused by 33 C v normothermia/fever prevention is significant or trivial given no difference in overall outcomes. Majority of TF gave this as one of the reasons against the use of hypothermia Adverse events increased TTM2 in 33 C group – arrhythmia resulting in haemodynamic compromise 24% v 16% See table s.14 in TTM2 paper that lists specific arrythmia or complication. No difference in other complications - pneumonia, sepsis, bleeding, skin problems	Use of TTM at 32-34 C may delay prognostication and prolong sedative effects of drugs. Benefit from earlier trials (HACA, Bernard) could have been due to delay in prognostication caused by intervention, lack of standardised/delayed prognostication Unblinded reporting of complications. 10/17 voting TF members considered side effects a reason against hypothermia (including need for sedation, shivering) [7/11 non voting members also did so] Pointed out that control groups (normothermia/fever preventions) could have been harmed by

Table S14. All events reported as potential unexpected serious adverse events.

	Group	uSAE Category	Description	Meets critera for uSAE
1	Normothermia	Limb complication	Leg ischemia, treated by PTCA	No
2	Normothermia	Limb complication	Leg ischemia, no intervention possible	No
3	Normothermia	Tamponade	Cardiac tamponade, pacing wire perforation. Managed in OR	No
4	Normothermia	Bleeding	Splenic bleeding. Managed in the OR	No
5	Normothermia	Bleeding	Bleeding from femoral artery (PCI) requiring transfusion	No
6	Normothermia	Bleeding	Severe liver bleeding after CPR, managed in OR	No
7	Normothermia	Sepsis	Ventilator associated pneumonia and sepsis	No
8	Normothermia	Bradycardia	Temporary pacemaker needed	No
9	Normothermia	Bleeding	Major bleeding. Thoracostomy performed	No
10	Normothermia	Stroke	Major stroke after intervention	No
11	Normothermia	Other	Intravenous catheter not working resulting in inadequate sedation	No
12	Normothermia	Venous Thromboembolism	Cardiac arrest after removal of intravascular cooling device. Suspected PE	Yes
13	Normothermia	Venous Thromboembolism	Minor pulmonary embolism in patient with intravascular cooling device	Yes
14	Hypothermia	Hemodynamics	Overcooling, below 31 with severe hemodynamic instability, bradycardia and subsequent death	Yes
15	Hypothermia	Arrhythmia	Bradycardia, requiring adrenalin	No
16	Hypothermia	Arrhythmia	PEA-arrest, due to LVOT-obstruction	No
17	Hypothermia	Pneumothorax	Tension pneumothorax resulting in death	No
18	Hypothermia	Bleeding	Bleeding from femoral artery (PCI), stenting required	No
19	Hypothermia	Arrhythmia	Ventricular arrhythmia, needed CPR	No
20	Hypothermia	Arrhythmia	Hemodynamic instability and VT	No
21	Hypothermia	Bowel ischemia	Bowel ischemia resuting in death	No
22	Hypothermia	Arrhythmia	VT during rewarming (faster than according to protocol), resolved spontaneously	No
23	Hypothermia	Bradycardia	Bradycardia requiring atropine	No
24	Hypothermia	Vascular	Carotid/Jugular fistula as a result of ECCO2-cannulation - stented	No
25	Hypothermia	Vascular	Compartment syndrome needing decompression after ECCO2	No
26	Hypothermia	Tracheal injury	Tracheal injury during intubation	No
27	Hypothermia	Arrhythmia	Re-arrest, WPW syndrome, CPR required	No
28	Hypothermia	Bleeding	Liver bleeding after CPR - rewarming and transfusion	No
29	Hypothermia	Bleeding	Bleeding treated with FFP	No
30	Hypothermia	Coagulopathy	On warfarin with worsening coagulopathy during cooling. No bleeding. Rewarmed.	No
31	Hypothermia	Hypercapnia	Hypercapnia, transported for ECMO	No
32	Hypothermia	Bleeding	Minior intracranial bleed	No
33	Hypothermia	Cervical injury	Cervical fracture with complete medullar injury, resulting in death	No
34	Hypothermia	Bleeding	Massive bleeding during PCI, resulting in death	No
35	Hypothermia	Bleeding	Intracranial bleed, hematoma evacuated in the OR	No
36	Hypothermia	Bleeding	Liver bleeding, coiled by IR. Subsequent liver abscess	No
37	Hypothermia	Bleeding	Hemothorax, drained. Lung suture needed	No
38	Hypothermia	Bleeding	Major bleeding and shock due to rib fractures, intervention discontinued	No
39	Hypothermia	Vascular	Aortic dissection during surgery resulting in death	No
40	Hypothermia	Hemodynamics	Hemodynamic instability and low heart rate, rewarmed	No
41	Hypothermia	Sepsis	Septic shock	No
42	Hypothermia	Bleeding	Liver bleeding after CPR - treated medically	No
43	Hypothermia	Arrhythmia	New VF arrest, CPR performed	No
44	Hypothermia	Bradycardia	Bradycardia with ventricular bigeminy	No
45	Hypothermia	Bradycardia	Bradycardia treated with isoprenaline, intervention discontinued	No
46	Hypothermia	Arrhythmia	New VT-arrest, CPR performed, ROSC 1 min	No
47	Hypothermia	Venous Thromboembolism	Clot seen in IVC. Intravascular device used	Yes

prolonged sedation in TTM2 to match sedation in 33 C group, or active warming to achieve normothermia in HYPERION studies

Certainty of evidence

What is the overall certainty of the evidence of effects?

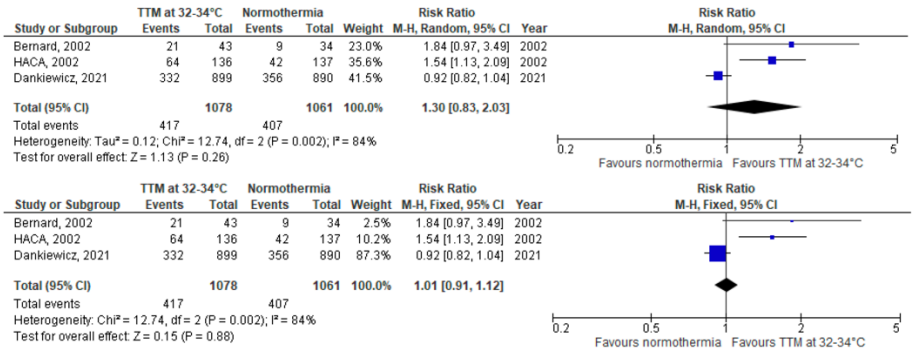
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Low certainty due to serious risk of bias and imprecision** Table below based on meta-analysis that used random effects model decided a priori	Concern that despite more data - we have lower certainty evidence than previous CoSTR In retrospect we have probably over stated the results of the HACA and Bernard studies as compared to the more recent TTM and Hyperion studies

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no TTM	Risk with TTM				
Survival to hospital discharge	Study population		**RR 1.12** (0.92 to 1.35)	2836 (5 RCTs)	⊕⊕◯◯ LOW[a,b,c]	
	460 per 1,000	**515 per 1,000** (423 to 621)				
Favourable neurological outcome at hospital discharge or 30 days	Study population		**RR 1.30** (0.83 to 2.03)	2139 (3 RCTs)	⊕⊕◯◯ LOW[a,c,d]	
	384 per 1,000	**499 per 1,000**				

		(318 to 779)				
Survival to 90 or 180 days	Study population		**RR 1.08** (0.89 to 1.30)	2776 (5 RCTs)	⨁⨁◯◯ LOW[a,c,d]	
	435 per 1,000	**469 per 1,000** (387 to 565)				
Favourable neurological outcome at 90 or 180 days	Study population		**RR 1.21** (0.91 to 1.61)	2753 (5 RCTs)	⨁⨁◯◯ LOW[a,b,c]	
	363 per 1,000	**440 per 1,000** (331 to 585)				

a. All included trials were assessed as having a intermediate risk of bias
b. Confidence interval includes both no difference and potential benefit
c. Although there were some inconsistency between the trials, we decided not to downgrade for this since the inconsistency was indirectly accounted for in the width of the confidence interval and the subsequent downgrading for imprecision
d. Confidence interval includes both benefit and harm

Task force discussion:
The point estimate of the random-effects meta-analysis favours hypothermia (a random effects meta-analysis was chosen a priori). However, the random effects model assigns a relatively higher weight per patient included to smaller studies; thus, the older, less methodologically robust studies published in 2002 had a greater influence on the point estimate than would be expected. When a fixed effect model is used the individual study weighting and point estimates and confidence intervals change e.g. for favourable outcome at 30 days (random effect top, fixed effects bottom:



Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty	All the outcomes assessed are judged critical by the ALS Task Force	

Outcomes	Importance	Certainty of the evidence (GRADE)
Survival to hospital discharge	CRITICAL	⨁⨁◯◯ LOW[a,b,c]
Favourable neurological outcome at hospital discharge or 30 days	CRITICAL	⨁⨁◯◯ LOW[a,c,d]

or variability ● No important uncertainty or variability	Survival to 90 or 180 days	CRITICAL	⊕⊕◯◯ LOW[a,c,d]	
	Favourable neurological outcome at 90 or 180 days	CRITICAL	⊕⊕◯◯ LOW[a,b,c]	

a. All included trials were assessed as having a intermediate risk of bias
b. Confidence interval includes both no difference and potential benefit
c. Although there were some inconsistency between the trials, we decided not to downgrade for this since the inconsistency was indirectly accounted for in the width of the confidence interval and the subsequent downgrading for imprecision
d. Confidence interval includes both benefit and harm

ALS TF has based these outcome priorities on:
Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD; COSCA Collaborators. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2018 Jun;127:147-163.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Research evidence limited - majority of TF support comparison given no difference with intervention and undesirable effects of intervention TF voting members (n=17): 'Normothermia' supported by 10/17 [No COI declared] Hypothermia or Normothermia 4/17 [3 with COI declared] Undecided/unclear 2/17 [1 COI declared] Did not respond 1/17 [1 COI declared] Non voting adhoc TF members 'Normothermia' 8/12 [1 COI] Hypothermia/Normothermia 2/12 [1 COI] Undecided 1/12 [no COI] Did not respond 2/12 [1 COI] Majority supported a recommendation against hypothermia but accepted that certain subpopulations of cardiac arrest patients (such as those with a non-cardiac cause of cardiac arrest or in-hospital cardiac arrest) may benefit from targeting hypothermia at 32-34 C, a more rapid induction of hypothermia, or a longer duration of temperature prevention and sedation remains unknown.	In 2015 we wrote an additional statement: 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.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	In TTM 2: All patients in 'hypothermia group' require cooling intervention versus 46% in 'normothermia' group	Cost of cooling will vary between settings and particular device/technique used to provide cooling Cost has not been formally assessed in our SR and meta-analysis. Costs of a 32-34 v normothermia approach are likely to vary according to setting Ice/fan/Surface devices - relatively easy to start

		Intravascular requires skills for insertion and invasive. Additional resource for 32-34 - sedation, cost, training, feedback device, more patients Task force opinion mixed on this issue as many units already use 33 C, and patients will still require close monitoring and intervention of fever prevention/normothermia target used. Concern from TF members that hypothermia leads to longer ventilation/delayed prognostication/ and that fewer patients require active cooling when normothermia or fever control targeted.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We have not identified recent studies on this issue	Post resuscitation care and TTM at any temperature target does require significant critical care resources to optimise outcome and costs will vary across settings. Additional cost of TTM over other post resuscitation care intervention will vary. Fewer patients require active cooling when normothermia or fever control targeted.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	We did not do a specific cost effectiveness analysis. We identified one modelling study. Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. Circ Cardiovasc Qual Outcomes. 2009;2(5):421-428.	No current cost effectiveness data.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No studies identified - probably varies	Both interventions require active temperature management and equity impact will vary. The cost and access to cooling devices and disposables will vary Post resuscitation care and TTM at any temperature target does require significant resources to optimise outcome

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No formal studies looked at regarding acceptability of hypothermia. Intervention is 32-34 and normothermia being used already Observational data suggests that some settings have moved from a target of 33 to normothermia/ or no temperature control.	Within ALS TF and different settings/regions there is considerable variation as to the acceptance of either intervention at 32-34 v normothermia Animal data of early/immediate post ROSC cooling show a consistent and strong protective effect across animal species and models. Reasons have been put forward as to why the largest and most recent RCTs have not managed

		to replicate animal data - cooling too late, too slow, wrong dose duration, wrong patient population. Some observational evidence or concerns that using 'normothermia' targets or switch from 32-34 to 36 C has been associated with worse outcomes. Most recent large observational study from UK does not suggest this and raises the issue that ICU risk models and risk adjustment cannot differentiate between therapeutic and pathological temperature changes when looking at observational data. Nolan JP, et al. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021 May;162:304-311.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Both intervention (hypothermia) and normothermia/fever prevention are feasible in most settings that care for post cardiac arrest patients and already use TTM.	TF considered that post resuscitation care is resource intensive, and temperature control is feasible in most settings that provide this care. Yes - in high resource settings. Hypothermia more challenging in low resource settings

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	**Moderate**	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

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

Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32-34ºC remains uncertain.

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

Justification

- *This topic was prioritized by the ALS Task Force based on new RCTs of TTM since our previous systematic review, CoSTR (Callaway 2015 s84, Soar 2015 e71) and advisory statement in (Donnino 2015 2448, Donnino 2015 97) in 2015.*
- *All members of the Task Force agreed that we should continue to recommend active temperature control in post-cardiac arrest patients, although the evidence for this is limited.*
- *Further details of Task Force discussions are provided in the evidence to decision tables (ETDs).*

Defining Post-Cardiac Arrest Temperature Management Strategies

- *The term TTM on its own is not helpful and it is preferable to use the terms active temperature control, hypothermia, normothermia, or fever prevention. To provide additional clarity for interpreting future clinical trials, systematic reviews and CoSTRs we propose the following terms are used:*
    - *Hypothermic TTM (H-TTM) = active temperature control with the target temperature below the normal range.*
    - *Normothermic TTM = active temperature control with the target temperature in the normal range.*
    - *Fever prevention TTM (FP-TTM) = monitoring temperature and actively preventing and treating temperature above the normal range*
    - *No TTM = no protocolised active temperature control strategy.*

Hypothermia v normothermia or prevention of fever

- *The majority of the Task Force favored fever prevention for comatose patients following ROSC as opposed to hypothermia, based on the systematic review and because this intervention requires fewer resources and had fewer side effects than hypothermia treatment.*
- *The Task Force noted that in the TTM2 trial (Dankiewicz 2021 2283), pharmacological measures (acetaminophen), uncovering the patient, and lowering ambient temperature were used to maintain a temperature of ≤ 37.5 C (99.5 F) in the normothermia/fever prevention group. If the temperature was > 37.7 C (99.9 F) a cooling device was used and set at a target temperature of ≤ 37.5 C (99.5 F). 95% of patients in the hypothermia group and 46% in the fever prevention group received temperature control with a device.*
- *We chose prevention of fever as opposed to normothermia in the treatment recommendation.*
- *The Task Force acknowledged that the systematic review found no difference in overall outcomes between patients treated with hypothermia and normothermia or fever prevention.*

- *Several members of the Task Force were keen to leave open the option to use hypothermia (33°C). The discussions included:*
    - *No trials have shown that normothermia is better than hypothermia.*
    - *Among non-shockable cardiac arrest patients, the Hyperion trial (Lascarrou 2019 2327) showed better survival with favorable functional outcome in the hypothermia group (although 90-day survival was not significantly different and the Fragility Index was only 1).*
    - *Although our systematic review did not find evidence favoring TTM with hypothermia in multiple subgroups, there remained a view that some populations of cardiac arrest patient could potentially benefit from hypothermia treatment at 32-34 C. Specifically, the largest TTM studies (TTM1 and TTM2) have mainly included cardiac arrests with a primary cardiac cause and this may not reflect the total population of post cardiac arrest patients treated (Chen 2018 33).*
    - *There was a suggestion that we should only advocate fever prevention for those with a primary cardiac arrest in the main treatment recommendation – our systematic review did not find any evidence supporting targeting hypothermia in patients with a cardiac arrest due to other causes.*
    - *Concerns were raised that the TTM2 trial cooling rates were too slow and that the time to target temperature was outside the therapeutic window. In animal studies rapid induction of hypothermia after ROSC is required for a beneficial effect (Arrich 2021 47). The time to target temperature in TTM-2 is consistent with virtually all other human observational studies and RCTs including those where there was no delay caused by the need for consent/randomization (see ETD). Of the RCTs included, only the Bernard study (Bernard 2002 557) had a rapid time (2 hours after ROSC) to achieve target temperature (33.5 C). It remains possible that there is a therapeutic window within which hypothermia is effective that has not been rigorously tested in randomized clinical trials.*

    - *There was a unanimous desire to leave open the opportunity for further research on post-cardiac arrest hypothermia, not least because animal models have shown consistent and convincing evidence of benefit.*
    - *Finally, there are concerns that poor implementation of temperature control may lead to patient harm - for example the publication of the TTM trial in 2013 (Nielsen 2013 2197) may have led to some clinicians abandoning temperature control after cardiac arrest which in turn was associated with worse outcomes (Bray 2017 39, Salter 2018 1722, Nolan 2021 304). Whether this was caused by abandoning the use of temperature control is uncertain.*
- *In our meta-analysis we decided to use a random effects model a priori (as opposed to fixed effects). The point estimates of the random-effects meta-analysis favors hypothermia. However, the random effects model assigns a relatively higher weight to smaller studies; thus, the smaller and older less methodologically robust studies published in 2002 (Bernard 2002 557, HACA 2002 549) had a greater influence on the point estimate than would be expected based on the trial sizes.*
- *We chose the term 'comatose' instead of 'unresponsive' to define the population of patients who do not wake up after ROSC. Another option considered was 'unconscious' – in the TTM2 trial this was defined as not being able to obey verbal commands and no verbal response to pain after sustained ROSC. The Task Force acknowledges that patients are unconscious and sedated after ROSC for a number of reasons in addition to a hypoxic ischemic brain injury including the need for airway protection with a tracheal tube, lung injury, and to facilitate interventions.*
- *We have made no comments on sedation use or its duration but noted that in the TTM2 trial, patients in the normothermia/fever prevention arm were sedated for 40 hours to ensure a similar duration of sedation to the hypothermia arm.*
- *Although there was no direct evidence in our systematic review, the Task Force made a good practice statement supporting the avoidance of active warming of patients who have passively become mildly hypothermia (e.g. 32-36) immediately after ROSC there was concern that this may be a harmful intervention. The Task Force noted that in the TTM2 trial, patients in the normothermia/fever prevention arm with an initial temperature above 33 C were not actively warmed. The Task Force noted that in the Hyperion trial (Lascarrou 2019 2327), patients allocated to normothermia whose temperature was below 36.5 C at randomization were warmed at 0.25 - 0.5 C/hour and then maintained at 36.5 - 37.5 C.*
- *There was discussion about the definitions of normothermia and fever. Among a diverse cohort of 35,488 hospital patients the 99% range for normal temperature was 35.3-37.7°C, and 95% range was 35.7 to 37.3 C (Obermeyer 2017 j5468). Whether these ranges can be generalized to the adult post cardiac arrest patient population is uncertain.*

Alternate temperature comparisons

- *In addition, in our systematic review and meta-analysis we looked at comparisons between 33 v 36 C (Nielsen 2013 2197), 32 v 34 C (Lopez-de-Sa 2018 1807, Lopez-de-Sa 2012 2826), 33 v 34 C (Lopez-de-Sa 2018 1807) and 33 v 32 C (Lopez-de-Sa 2018 1807). There was no difference between control and intervention groups for all these comparisons and the certainty of evidence was low for all comparisons.*
- *The comparison between 33 v 36 C (Nielsen 2013 2197) was included in a sensitivity analysis of 33 C v normothermia/fever prevention, as 36 C falls within the normothermia temperature range – this did not change the point estimates in favor of either group.*

Research priorities

- *There are no RCTs of no TTM versus fever prevention TTM.*
- *There are few RCTs of TTM after eCPR.*
- *There are no large RCTs of TTM after in-hospital cardiac arrest.*
- *Is there a therapeutic window within which hypothermic TTM (H-TTM) is effective in the clinical setting?*
- *If a therapeutic window exists, are there clinically feasible cooling strategies that can rapidly achieve therapeutic target temperatures within the therapeutic window?*
- *Is the clinical effectiveness of hypothermia dependent on providing the appropriate dose (target temperature and duration) based on the severity of brain injury?*
- *Are there unidentified subsets of post-cardiac arrest patient who would benefit from H-TTM as currently practiced?*
- *Is TTM using a cooling device with feedback more effective than TTM without a feedback controlled cooling device?*