QUESTION

Duration of TTM?

POPULATION:	**Adult patients with cardiac arrest**
INTERVENTION:	**TTM for a specific duration (e.g. 48 hours)**
COMPARISON:	**TTM at a different specific duration (e.g. 24 hours)**
MAIN OUTCOMES:	**Survival at 6 months ; Favorable neurological outcome at 6 months**
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	The optimal duration for TTM is unknown. It may depend on the likely severity of the hypoxic-ischaemic injury. There is just one RCT comparing 24 h versus 48 h TTM after OHCA [Kirkegaard 318 2017].	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	With 24 hours of TTM	With 48 hours of TTM	Difference	Relative effect (95% CI)
Survival at 6 months	659 per 1,000	**725 per 1,000** (633 to 837)	**66 more per 1,000** (26 fewer to 178 more)	**RR 1.10** (0.96 to 1.27)
Favorable neurological outcome at 6 months	636 per 1,000	**687 per 1,000** (592 to 795)	**51 more per 1,000** (45 fewer to 159 more)	**RR 1.08** (0.93 to 1.25)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The proportion of patients with 1 or more adverse events was significantly higher in the 48-hour group (97%) than in the 24-hour group (91%) (difference, 5.6%; 95% CI, 0.6%-10.6%; relative risk, 1.06; 95%CI, 1.01-1.12; P = .04). Significantly more patients had hypotension in the 48-hour group than in the 24-hour group (62% vs 49%; P = .013). There were no significant differences in the rates of pneumonia or bleeding between the groups; however, severe bleeding was more common in the 24-hour than in the 48-hour group (4% vs 1%; P = .03).	

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		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 24 hours of TTM	Risk with 48 hours of TTM				
Survival at 6 months	Study population		**RR 1.10** (0.96 to 1.27)	351 (1 RCT)	⨁⨁◯◯ LOW[a,b]	
	659 per 1,000	**725 per 1,000** (633 to 837)				
Favorable neurological outcome at 6 months	Study population		**RR 1.08** (0.93 to 1.25)	351 (1 RCT)	⨁⨁◯◯ LOW[a,b]	
	636 per 1,000	**687 per 1,000** (592 to 795)				

a. Risk of bias intermediate for the included trial
b. The 95% confidence interval includes no difference and potential benefit

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 or variability ● No important uncertainty or variability	People would value a good neurological outcome over death or severe disability.	

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	The point estimate for the primary outcome CCPC 1–2 at 6 months) favours TTM48 but it is not significantly different.	

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	The median ICU length of stay was longer in the 48-hour than in the 24-hour group (151 hours [IQR, 127-178 hours] vs 117 hours [IQR, 99-138 hours]; P < .001), but there was no significant difference in hospital length of stay. There were no significant differences between groups in the use of mechanical assist devices, tracheostomy, echocardiography, gastroscopy, or other operative procedures. Four patients in the 48-hour group had coronary artery bypass grafting compared with none in the 24-hour group.	

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	The additional period of cooling did appear to lead to an additional day of ICU care and this would be associated with additional cost.	

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	No studies included	

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	Any ICU providing 24 h of TTM should be able to provide 48 h of the therapy	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	If there was evidence of benefit, 48 h of TTM would be acceptable to most. Many are already providing 48–72 of TTM	May delay treatments decisions and increase cost

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Any ICU providing 24 h of TTM should be able to provide 48 h of the therapy	

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
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**			

	JUDGEMENT						
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 active prevention of fever for at least 72 hours in post-cardiac arrest patients who remain comatose [good practice statement].

Justification

- *Our TR is a good practice statement is based on trials controlling temperature for at least 72 h in those patients who remained sedated or comatose.*
- *One trial showed no difference between 24 and 48 hours of hypothermia (Kirkegaard 2017 3410)*
- *This could mean strategies such as 72 hours of active temperature control with avoidance of fever, or up to 24 hours of hypothermia followed by 48 hours of fever prevention if hypothermia treatment is used.*
- *We did not identify any RCTs of rewarming patients treated with hypothermia and note that a rate of 0.33 C/hour was used in TTM2 trial (Dankiewicz 2021 2283) , and 0.25 to 0.5 C/hour in the Hyperion study (Lascarrou 2019 2327).*

Research priorities

How long should temperature be actively controlled after cardiac arrest?