QUESTION

Should prehospital cooling vs. no prehospital cooling be used for cardiac arrest?	
POPULATION:	**Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest**
INTERVENTION:	**TTM induction before a specific time point (e.g. prehospital or intra-cardiac arrest, i.e. before return of spontaneous circulation (ROSC))**
COMPARISON:	**TTM induction before a specific time point (e.g. prehospital or intra-cardiac arrest, i.e. before return of spontaneous circulation (ROSC))**
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	Animal data suggest that following hypoxic-ischaemic injury, neuroprotection from targeted temperature is more likely to be effective if started early after return of spontaneous circulation (ROSC) or even before ROSC. Following out-of-hospital cardiac arrest (OHCA) , early cooling implies the need to start TTM prehospital. Given the high mortality from OHCA any benefit from earlier initiation of TTM would result in a substantial increase in lives saved. Eleven trials have assessed timing of TTM initiation: • Ten trials have compared prehospital with no prehospital cooling for patients with out-of-hospital cardiac arrest. • Six trials tested post-cardiac arrest rapid intravenous cold fluid infusion • Two trials tested intra-cardiac arrest intravenous cold fluid infusion • Two tested intra-cardiac arrest intra-nasal cooling	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Meta-analysis of prehospital vs. no prehospital cooling showed that prehospital cooling did not result in improved survival to hospital discharge (risk ratio: 1.01 [95%CI: 0.92, 1.11]) or survival to hospital discharge with a favorable neurologic outcome (risk ratio: 1.00 [95%CI: 0.90, 1.11]).	*We are aware of 2 recent meta-analyses (Taccone 2021 196; Annoni 2021 365) that suggest in the subgroup of the intra-arrest-intranasal studies initial shockable OHCA intranasal intra-arrest cooling is associated with favorable neurological outcome at hospital discharge.*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prehospital cooling	Risk with prehospital cooling				
Survival to hospital discharge	Study population		**RR 1.01** (0.92 to 1.11)	4808 (10 RCTs)	⨁⨁⨁◯ MODERATE[a]	
	242 per 1,000	**244 per 1,000** (223 to 269)				
Favorable neurological outcome at hospital discharge	Study population		**RR 1.00** (0.90 to 1.11)	4666 (9 RCTs)	⨁⨁⨁◯ MODERATE[a]	
	218 per 1,000	**218 per 1,000** (196 to 242)				

a. All included trials were assessed as having a intermediate risk of bias

There was no indication of effect measure modification according to the cooling method (P = 0.61 and P = 0.40 for the two outcomes).

Trials of intra-arrest cooling did not result in a difference in ROSC/admission alive (risk ratio: 0.95 [95%CI: 0.84, 1.07].

A meta-analysis of two studies of intra-nasal cooling showed a risk ratio of favourable neurological outcome of 1.37 [95%CI: 0.97, 1.94]

Our review (random effect)s: OR 1.37 (0.97, 1.94), 54/163 vs. 40/167
Taccone ("as treated"): RR: 1.43 (1.01, 2.02), 54/158 vs. 40/167
Taccone ("ITT"): RR: 1.26 (1.00, 1.56), 56/165 vs. 40/167
Annoni: OR: 1.62 (1.00, 2.64), 56/154 vs. 41/156

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	One study of prehospital IV cold fluid post-ROSC compared with delaying TTM until admission to hospital showed that the intervention was not associated with improved neurological outcome (Kim 2014 45). But the intervention had a higher rate of re-arrest prehospital and a higher incidence of pulmonary oedema on the initial chest x-ray. One study of intra-arrest infusion of cold saline showed no improvement in survival to discharge (Bernard 2016 797). For patients with an initial shockable cardiac rhythm, there was a decrease in the rate of return of a spontaneous circulation in patients who received cold saline compared with standard care (41.2% compared with 50.6%, P=0.03).	*The rapid infusion of large amounts of cold fluid immediately after achieving ROSC and in the prehospital setting could theoretically be harmful, as indicated by increased rates of rearrest and pulmonary edema in the largest of the included studies (Kim 2014 45). Any potential harm from this therapy may relate specifically to the prehospital setting, where there may be less control over the environment, fewer personnel, and reduced monitoring capabilities.*

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		

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a. All included trials were assessed as having a intermediate risk of bias

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	Patients value survival with favourable neurological outcome over long term 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	Given the lack of benefit from prehospital cooling and harmful effects in some studies the balance probably favours no routine prehospital cooling of patients.	Time taken to get to hospital. Passive cooling due to ambient temperature vs. active cooling.

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	Prehospital cold fluids requires cold storage facilities on EMS vehicles. Intra-nasal cooling is associated with additional cost although we have not analysed the additional cost in detail.	

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 did not identify cost studies	

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 identify cost-effectiveness studies for prehospital cooling	

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	Depending on the cooling technique selected, prehospital cooling would not be available to all EMS systems	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Given the lack of beneficial effect and likely increased cost, the intervention is unlikely to be acceptable to stakeholders	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	It is feasible but the precise feasibility varies with the technique used.	

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

[unchanged from 2015-2020 TR]

Justification

· Our TR for prehospital cooling is unchanged from our 2015 recommendation.
· We found no evidence that any method of prehospital cooling improved outcomes.
· The rapid infusion of large amounts of cold fluid immediately after achieving ROSC and in the prehospital setting could theoretically be harmful, as indicated by increased rates of rearrest and pulmonary edema in the largest of the included studies (Kim 2014 45). Any potential harm from this therapy may relate specifically to the prehospital setting, where there may be less control over the environment, fewer personnel, and reduced monitoring capabilities.
· We have not made a treatment recommendation about intra-arrest cooling for OHCA. We are aware of 2 recent studies (Taccone 2021 196; Annoni 2021 365) that suggest in the subgroup of the intra-arrest-intranasal studies initial shockable OHCA intranasal intra-arrest cooling is associated with favorable neurological outcome at hospital discharge.

- *Our review (random effect)s:* *OR 1.37 (0.97, 1.94), 54/163 vs. 40/167*
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Research priorities

Is there a therapeutic window for hypothermia treatment after cardiac arrest?