Supplemental digital content

Targeted temperature management after cardiac arrest: a systematic review and meta-analysis with trial sequential analysis.

1. **PRISMA Checklist**
2. **Grade of evidence**
3. **Trial sequential analysis – Survival at longest follow up**
4. **Trial sequential analysis – Neurological outcome**
5. **Risk of bias assessment**
6. **Funnel plot – Survival at longest follow up**
7. **Funnel plot – Neurological outcome**

Table S1. PRISMA Checklist

ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6-7

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	10 and Supplemental
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8-9
Study characteristics	17	Cite each included study and present its characteristics.	8 and table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10 and Supplemental
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-9 Figure 2 and 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-9-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-9 Figure 2 and 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-9-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplemental
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-12
	23b	Discuss any limitations of the evidence included in the review.	13
	23c	Discuss any limitations of the review processes used.	13
	23d	Discuss implications of the results for practice, policy, and future research.	11-12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2

Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	On request

Section and Topic	Item #	Checklist item	Location where item is reported

Table S2. Grade of evidence

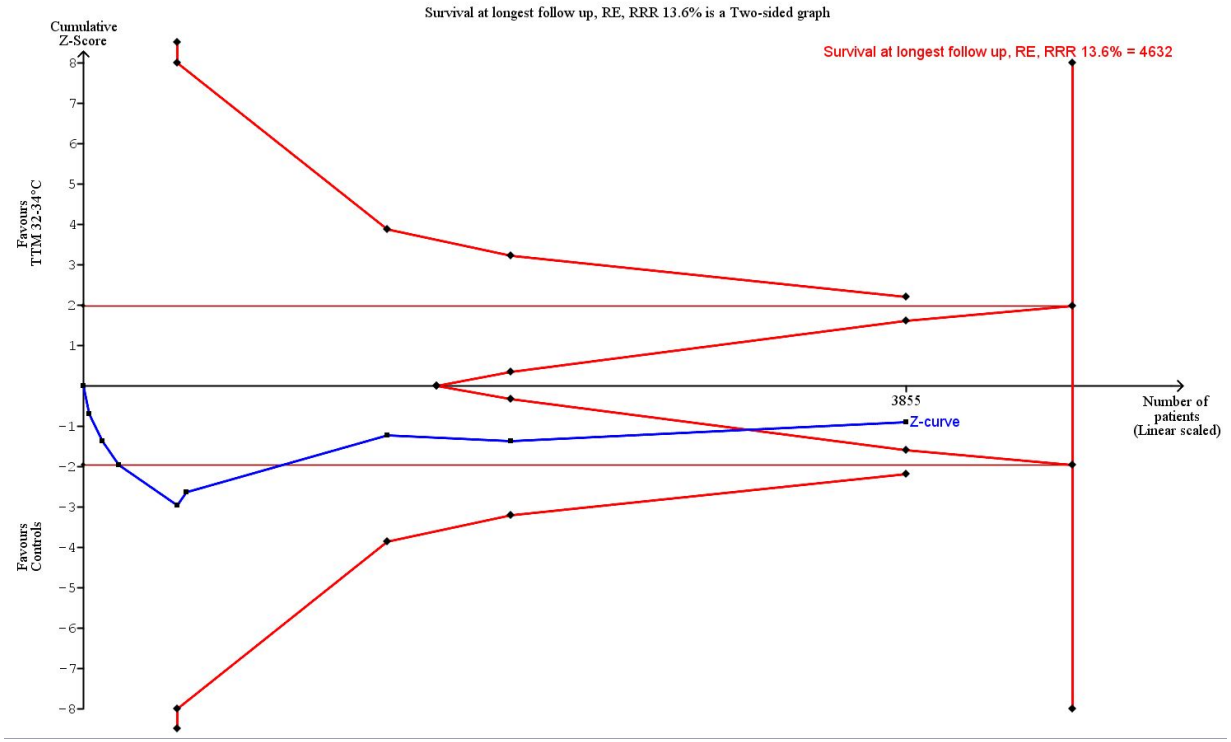
Question: TTM 33 °C compared to Normothermia for post-resuscitation care

Setting: Cardiac Arrest patients admitted to Intensive Care Unit

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TTM 33 °C	Normothermia	Relative (95% CI)	Absolute (95% CI)		
Survival (follow up: median 180 days)												
8	randomised trials	not serious	serious	not serious	not serious	none	396/953 (41.6%)	365/949 (38.5%)	**RR 1.07** (0.96 to 1.19)	**27 more per 1.000** (from 15 fewer to 73 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Good neurological outcome (follow up: median 180 days)												
8	randomised trials	not serious	serious	not serious	not serious	none	345/948 (36.4%)	302/946 (31.9%)	**RR 1.35** (0.98 to 1.87)	**112 more per 1.000** (from 6 fewer to 278 more)	⊕⊕⊕◯ MODERATE	CRITICAL

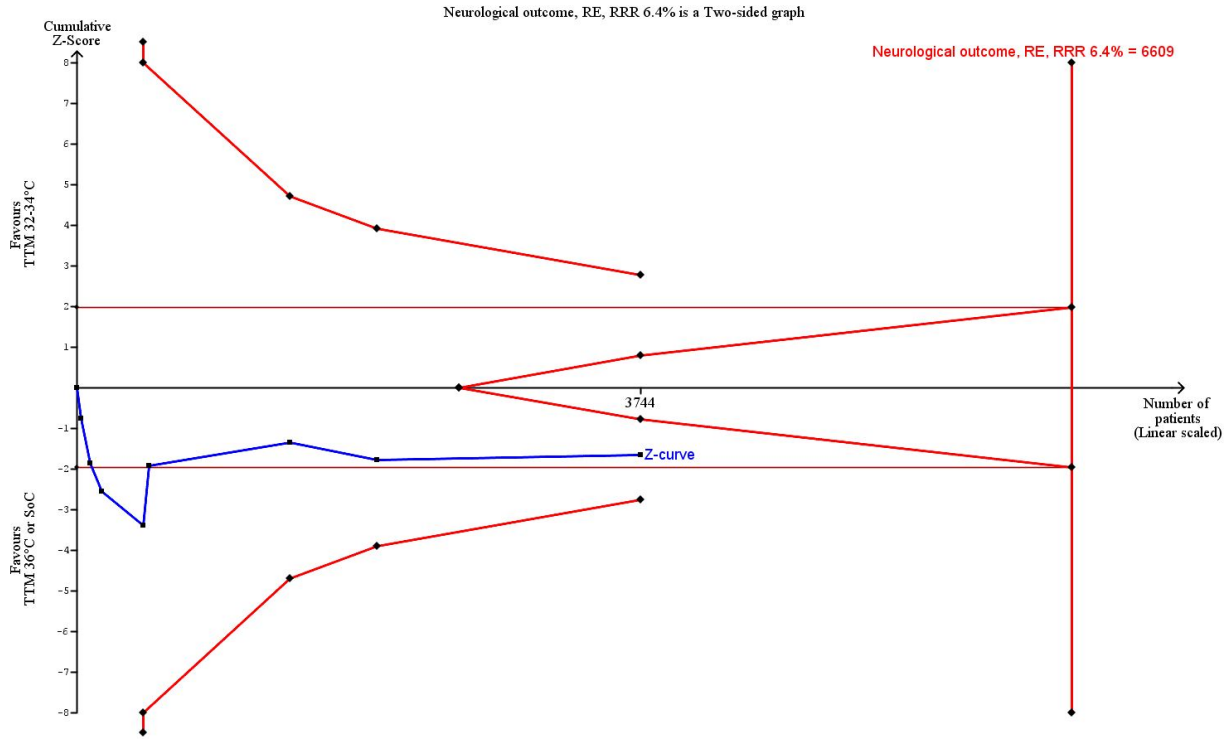
CI: Confidence interval; RR: Risk ratio

Figure S1. Trial Sequential analysis – Survival at longest follow up



RE=random effect, RRR=Relative risk reduction.

Figure S2. Trial Sequential analysis – Neurological outcome



RE=random effect, RRR=Relative risk reduction.

Table S3. Risk of bias assessment

Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Dankiewicz et al 2021	hypothermia	normothermia	survival with good neurological outcome	1	Low	Low	Low	Low	Low	Low
Lascarrou et al 2019	hypothermia	normothermia	survival with good neurological outcome	1	Low	Low	Low	Low	Low	Low
Nielsen et al 2013	hypothermia	normothermia	survival with good neurological outcome	1	Low	Low	Low	Low	Low	Low
Laurent et al 2005	hypothermia	normothermia	survival with good neurological outcome	1	Low	Some concerns	Low	Low	Some concerns	Some concerns
Hachimi-idrissi et al 2001	hypothermia	normothermia	survival with good neurological outcome	1	Some concerns	Low	Low	Low	Some concerns	Some concerns
Holzer et al 2002	hypothermia	normothermia	survival with good neurological outcome	1	Low	Low	Low	Low	Low	Low

Bernard et al. 2002	hypothermia	normothermia	survival with good neurological outcome	1	Low	Low	Low	Low	Some concerns	Some concerns
Hachimi-idrissi et al 2005	hypothermia	normothermia	survival with good neurological outcome	1	Some concerns	Low	Low	Low	Some concerns	Some concerns

Figure S3. Funnel plot – Survival at longest follow up

Figure S4. Funnel plot – Neurological outcome