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Letter to the Editor

Meta-analyses of targeted temperature management in adult cardiac arrest studies – The big picture is dependent on study selection



To the Editor,

Correspondence on the article

Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW. Targeted Temperature Management in Adult Cardiac Arrest: Systematic Review and Meta-Analysis. *Resuscitation*. 2021;167,160–172.

In “Targeted temperature management (TTM) in adult cardiac arrest: Systematic review and meta-analysis”, the authors concluded that TTM 32–34 °C (TTM32-34) for 12–24 hours vs. normothermia did not result in a statistically significant improvement of neurological outcome.¹ This is shown in two Forrest plots, one with evaluation at hospital discharge or 30 days, and one at 90 or 180 days.

We are concerned about 1) Splitting and analysing of data for two different outcome assessment time points and 2) study selection. First, the recent large TTM2 trial, showing no difference between TTM32-34 and normothermia (Dankiewicz 2021) was included in both analyses, while three studies showing a beneficial effect of TTM32-34 (Bernard 2002, Lascarrou 2019, Hachimi-Idrissi 2005) were each included in only one analysis. Splitting the analysis in two different outcome evaluation time points reduced the number of eligible studies, and greatly reduced power. It was previously shown, in critical care randomized clinical trials (RCTs), that no influence of time point of outcome evaluation on pooled effect estimates is to be expected, and that splitting data to different time points is not required.² Secondly, the authors included one study (Laurent 2005), in which patients underwent haemofiltration in addition to cooling. The authors of a previous TTM Cochrane meta-analysis regarded inclusion of this work as introducing considerable clinical heterogeneity and did therefore not pool these data.³ Additionally, in the same Cochrane meta-analysis,³ the authors identified one additional study (Mori 2000), which was not included in the current meta-analysis.¹

Thus, we performed a meta-analysis, based on the previous Cochrane meta-analysis,³ pooling all available RCTs with outcome

evaluation within 6 months (see Fig. 1a). In this analysis, the pooled results showed a better neurological outcome with TTM32-34 compared to normothermia (RR 1.56, 95% CI 1.10 to 2.21). Even with the inclusion of the TTM-1 trial, comparing TTM33 with TTM36,³ to the analysis, the effect of TTM32-34 remained statistically significant (RR 1.27, 95% CI 1.02 to 1.58 (see Fig. 1b). If we exclude the Mori study, since it was only published as an abstract, the results show OR 1.43 (95% CI 1.01 to 2.02), $p = 0.04$, and RR 1.21 (95% CI 0.99 to 1.48), $p = 0.06$.

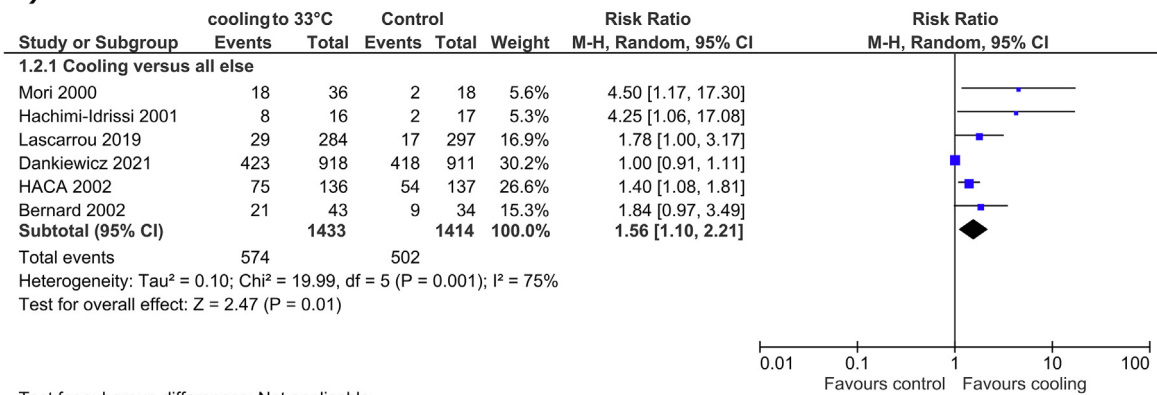
We suggest that a meta-analysis should pool all available RCTs on TTM32-34 versus normothermia for outcome evaluation at any time point in one analysis, carefully considering clinical heterogeneity. With these considerations, we believe the broader data may suggest a beneficial effect of TTM32-34 versus normothermia. In addition, delay and duration of cooling, methods used, non-blinded pragmatic trials, and selection of patients are of concern, the latter recently highlighted in two investigations suggesting a benefit of TTM32-34 vs TTM36 in patients with more significant post-arrest injury.^{4,5} We therefore believe the conclusion that TTM32-34 treatment is ineffective for all post-arrest patients is premature; we remain concerned about the one-size fits-all approach concerning neurological long-term outcome in patients with moderate to severe post-arrest disease.

Declaration of Competing Interest

Wilhelm Behringer: Speakers honoraria BD Bard and Zoll
Benjamin Abella:

- Research Funding: Becton Dickinson, VOC Health
- Speakers honoraria: Becton Dickinson, Stryker, Zoll

a)



b)

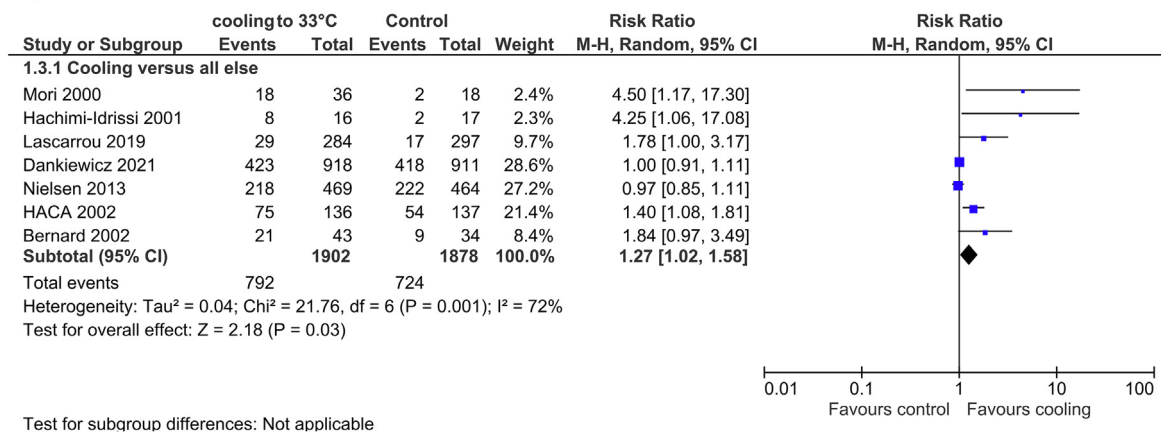


Fig. 1 – Meta-analyses of targeted temperature management (TTM). Random-effects meta-analyses of TTM at 32–34 °C (cooling to 33 °C) as compared to normothermia (control) for good neurologic outcome, reported within 6 months after cardiac arrest.

Kjetil Sunde: Speakers honoraria from BD Bard

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REFERENCES

1. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW. Targeted Temperature Management in Adult Cardiac Arrest: Systematic Review and Meta-Analysis. *Resuscitation* 2021;167:160–72.
2. Roth D, Heidinger B, Havel C, Herkner H. Different Mortality Time Points in Critical Care Trials: Current Practice and Influence on Effect Estimates in Meta-Analyses. *Crit Care Med* 2016;44:e737–41.
3. Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2016;2:CD004128.
4. Callaway CW, Coppler PJ, Faro J, et al. Association of Initial Illness Severity and Outcomes After Cardiac Arrest With Targeted Temperature Management at 36 degrees C or 33 degrees C. *JAMA Netw Open* 2020;3:e208215.
5. Nishikimi M, Ogura T, Nishida K, et al. Outcome Related to Level of Targeted Temperature Management in Postcardiac Arrest Syndrome of Low, Moderate, and High Severities: A Nationwide Multicenter Prospective Registry. *Crit Care Med* 2021;49:e741–50.

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