



Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Letter to the Editor

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



To the Editor,

Drs. Behringer, Abella, and Sunde are concerned about our decision to conduct separate meta-analyses for outcomes at different time points and about the selection of trials for inclusion in the meta-analyses.¹ The systematic review group and the Advanced Life Support Task Force *a priori* decided that outcomes would be analysed separately at hospital discharge/30 days and after hospital discharge/30 days. The selection of trials for each analysis was based on the available data. As stated in the manuscript, trials reported only as abstracts were not included. We did not include abstracts, as it is impossible to thoroughly evaluate a trial and perform bias assessment based on an abstract. We decided to include the Laurent et al. trial as we considered it unlikely that hemofiltration would be an effect modifier for the relationship between cooling and outcomes. We are not aware of a biological rationale nor data to support such a relationship.

The meta-analysis provided by Behringer, Abella, and Sunde in [Figure 1b](#) is similar to eFigure 3 in our manuscript.² The differences are 1) inclusion of the Mori et al. trial, 2) inclusion of outcomes at hospital discharge from Bernard et al., and 3) exclusion of the Laurent et al. trial.

As noted above, we do not agree with #1 and #3. In [Fig. 1a](#), we have added the small Bernard trial to eFigure 3 from the manuscript. The result is a risk ratio of 1.15 (95 %CI: 0.97, 1.37) instead of 1.11 (95 %CI: 0.94, 1.31) in the original figure. We note that there are some differences in the included numbers for the trials by Hachimi-Idrissi et al. and Nielsen et al. Specifically, the numbers of events are reported as 8/16 and 2/17 for the Hachimi-Idrissi trial and 218/469 and 222/464 for the Nielsen trial. We have reassessed the numbers and believe that those included in our meta-analysis are correct. Specifically, the results from the Hachimi-Idrissi et al. trial are presented in Table 2 in the original manuscript.³ For the Nielsen et al. trial, it appears that Behringer, Abella and Sunde have used Cerebral Performance Category score to define neurological outcomes, whereas we have used the modified Rankin Scale. We used the modified Rankin Scale given the

recent recommendation from ILCOR.⁴ Lastly, we note that the authors write “Hachimi-Idrissi, 2001” but presumably mean “Hachimi-Idrissi, 2005”.

We note two important considerations regarding the above meta-analysis and the interpretation of the results.

- (1) The weights in the meta-analysis are agnostic to the quality of the trials. The most recent trials (i.e., Nielsen, Lascarrou, and Dankiewicz) clearly have a lower risk of bias than the previous trials. Furthermore, the external validity of these newer multi-centre trials is likely higher.
- (2) The random effects approach used above puts relatively more weight on smaller trials. A fixed effects approach gives a different result ([Fig. 1b](#)).

The authors refer to two observational studies. As noted in the systematic review, we did not include observational studies due to a high risk of bias from potential immortal time bias and confounding and given the number of randomised trials.

Taken together, we do not believe that the above results change our conclusions.

CRediT author statement

Lars Anderson: Writing – original draft.
 Asger Granfeldt: Writing – review & editing.
 Mathias Holmberg: Writing – review & editing.
 Jerry Nolan: Writing – review & editing.
 Jasmeet Soar: Writing – review & editing.

Declaration of Competing Interest

JN is Editor-in-Chief of Resuscitation.
 JS is an Editor of Resuscitation.
 AG, MH and LA declare no conflicts of interest.

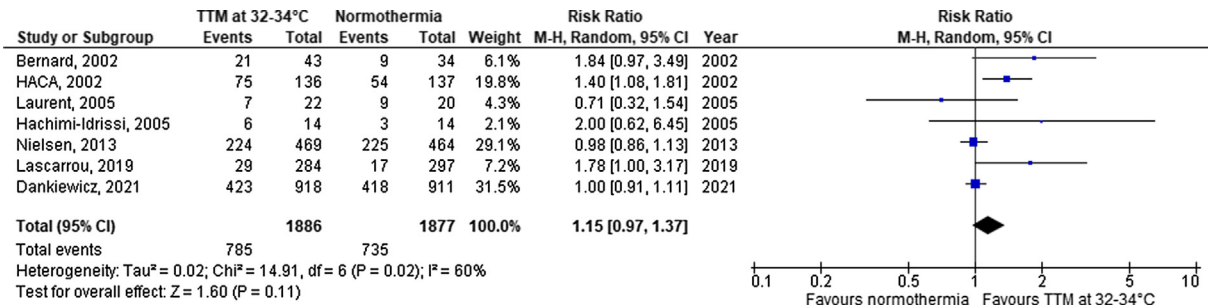


Fig. 1a – Random-effects meta-analysis.

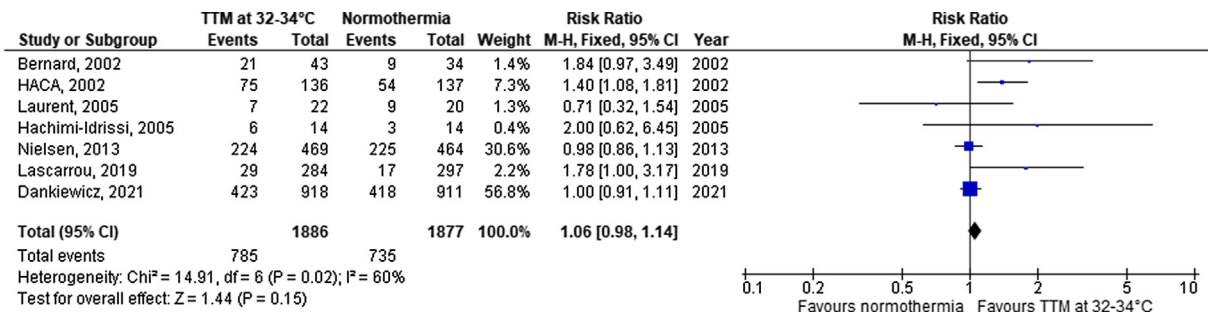


Fig. 1b – Fixed-effects meta-analysis.

REFERENCES

- Behringer W, Abella BS, Sunde K. Meta-analyses of targeted temperature management in adult cardiac arrest studies – the big picture is dependent on study selection! *Resuscitation* 2021.
- Granfeldt A, Holmberg MJ, Nolan JP, et al. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. *Resuscitation* 2021;167:160–72.
- Hachimi-Idrissi S, Zizi M, Nguyen DN, et al. The evolution of serum astroglial S-100 beta protein in patients with cardiac arrest treated with mild hypothermia. *Resuscitation* 2005;64:187–92.
- Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. *Resuscitation* 2018;127:147–63.

Asger Granfeldt

Department of Anesthesiology and Intensive Care Medicine,
Aarhus University Hospital, Aarhus,
Denmark

Mathias J. Holmberg

Research Center for Emergency Medicine,
Department of Clinical Medicine,
Aarhus University Hospital and Aarhus University,
Aarhus, Denmark

Department of Cardiology, Viborg Regional Hospital, Viborg,
Denmark

Jerry P. Nolan

University of Warwick, Warwick Medical School, Coventry, United
Kingdom
Royal United Hospital, Bath, United Kingdom

Jasmeet Soar

Southmead Hospital, North Bristol NHS Trust, Bristol, United
Kingdom

Lars W. Andersen*

Department of Anesthesiology and Intensive Care Medicine, Aarhus
University Hospital, Aarhus, Denmark

Research Center for Emergency Medicine, Department of Clinical
Medicine, Aarhus University Hospital and Aarhus University, Aarhus,
Denmark

Prehospital Emergency Medical Services, Central Denmark Region,
Denmark

* Corresponding author at: Research Center for Emergency Medi-
cine, Department of Clinical Medicine, Aarhus University Hospital,
Palle Juul Jensens Boulevard 99, Bygning J, Plan 1, 8200 Aarhus N,
Denmark.

E-mail address: lwandersen@clin.au.dk

Received 6 October 2021

<https://doi.org/10.1016/j.resuscitation.2021.10.018>

© 2021 Elsevier B.V. All rights reserved.