Answer to Letter-to-the-Editor: Comments on an article published in the December 2025 AAB issue concerning evidence from meta-analysis and sebusequent large-scale randomized controlled trials in perioperative medicine

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We thank Dr. Himpe for his thoughtful comments on our article regarding the use of Trial Sequential Analysis (TSA) to better understand the apparent discordance between results from meta-analysis and from a subsequent large-scale randomized controlled trial[1].

Several important points were addressed indeed, many of which we feel supportive to our own concerns on the broader subject of evidence-based medicine. Firstly, we agree that TSA should not be seen as a superior statistical tool that claims the 'ultimate truth' in clinical research but rather as an adjunct to improve the interpretation of meta-analyses. It may represent a useful step away from the overly simplistic dichotomous interpretation of frequentist p-values, that inevitably comes with Type I and Type II errors. Such misinterpretations have long been a concern within the statistical community[2,3]. Trial Sequential analysis, however, is not without limitations and should not be regarded as an 'ultimate' solution[4]. Most importantly, it does not aid in the interpretation of effect size(s) or the uncertainty of these estimates. For conclusions regarding clinical relevance, these estimates -and not p-values- are paramount.

The notion that meta-analysis are complex endeavours that convey more information than the p-value of a statistical test alone is echoed in Dr. Himpe's second remark. Prior to statistical synthesis, a crucial part of any meta-analysis is the systematic search and the rigorous inclusion process for individual RCTs. An essential question is whether the included trials are sufficiently comparable and whether it is meaningful to pool them. Dr. Himpe focuses in particular on the meta-analysis by Pöpping[5] et al and the subsequent study by Du et al.[6] examining the effect of combined epidural-general anaesthesia versus general anaesthesia alone on survival, specifically questioning the difference in absolute mortality rates.

Heterogeneity among studies included in meta-analyses is not necessarily a weakness. It would be incorrect to assume that all included studies should be perfectly comparable or interchangeable. Some degree of variability in study population, intervention, and outcome is to be expected. Random-effects models explicitly account for such variability and thereby enhance the generalisability of the findings. The meta-analysis by Pöpping et al.[5] includes studies that differ in duration of follow-up, baseline mortality, and surgical populations. Mortality in the control groups ranged from 0% to 27%, while follow-up periods varied from 4 days to 1 year.

Dr. Himpe highlights the most extreme example in our analysis. The study by Du et al[6] reports a median follow-up of 66 months and a control-group mortality of 38% at that time point. Notably, based on the Kaplan-Meier survival curve they provide in their publication, the 1-year mortality was approximately 12%. The oncological surgical setting probably explains the high mortality observed at the end of the prolonged follow-up period. We acknowledge that, were the meta-analysis by Pöpping et al[5] to be updated, the inclusion of this study would likely be subject to extensive discussion. This further underscores that the interpretation of meta-analytic findings is far from straightforward and that results from both primary and sensitivity analyses require careful consideration.

Finally, we thank Dr. Himpe for pointing out the typographical error in Table V: indeed, the odds ratio in the study of Pöpping et al. was 0.69 instead of 0.96. In Table IV we also noticed that the numbers for Du et al were erroneously those to the 2x2 table; these have been corrected. We apologise for these mistakes that inadvertently entered the manuscript and are grateful for the opportunity to correct them.

We sincerely thank Dr. Himpe for his critical and constructive comments. We hope that this discussion further fuels the awareness about the risks of incorrect and overly simplistic interpretations of statistical results in general, and of meta-analyses in particular.

References

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