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Letter to the Editor

Methodological concerns regarding "Clinical outcomes with vutrisiran in transthyretin amyloidosis: A systematic review and meta-analysis of randomized trials"

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Dear Editor,

We read with interest the meta-analysis by Ahmed et al. evaluating vutrisiran in transthyretin amyloidosis (ATTR) [1]. While the review addresses a clinically important question, we wish to raise several methodological concerns not addressed in the manuscript's limitations section.

In this paper, the authors included Adams et al. in the meta-analysis. However, this study has a placebo arm that which was not a randomized group; instead, it was an external group borrowed from another trial to compare the results. Using these kinds of external and historical control arms are well-documented to differ systematically from concurrent randomized controls even after apparent baseline balancing: a meta-analytic evaluation of external control arms across oncology trials estimated a residual hazard-ratio bias of 0.907 between randomized and matched external controls, despite careful construction [2]. Substituting or blending an external placebo into a pooled analysis therefore risks distorting both the point estimate and its heterogeneity statistics (I^2), and this concern warrants substantially more weight than the population-level heterogeneity the authors do acknowledge.

Secondly, HELIOS-B contributes data from two populations: the overall cohort (n=655, including tafamidis co-users) and a monotherapy subgroup (n=395). The authors use the monotherapy subgroup for mortality and fall risk, but switch to the overall population for adverse-event outcomes, without explanation. Since tafamidis co-administration was explicitly raised in the introduction as an open question affecting efficacy and safety, this undisclosed switching undermines comparability between the efficacy and safety conclusions and leaves the promised tafamidis subgroup analysis effectively unperformed.

Thirdly, the methods state a random-effects model was used throughout, yet the forest plot for risk of fall reports a fixed-effects (Mantel-Haenszel, fixed) model instead. No justification is given,

and it is unclear whether this deviation was pre-specified or post hoc, a concern heightened by the fact that fall risk was the only outcome reaching conventional statistical significance. Lastly, reference 10, cited to support the Cochrane RoB 2 description, is in fact a GRADE certainty-of-evidence methods paper. The correct source for RoB 2 is Sterne et al. [3], and this attribution should be corrected.

We commend the authors for undertaking this timely synthesis of a rapidly evolving area of ATTR therapeutics. However, addressing the points raised above would meaningfully strengthen the robustness and clinical interpretability of the pooled estimates. We hope these comments are received in the constructive spirit intended, and we look forward to future updates of this important work as longer-term data on vutrisiran become available.

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