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Letter to the Editors-in-Chief

The efficacy and safety of anticoagulation in cerebral vein thrombosis: A Systematic review and meta-analysis

Re-Abdulaziz Almulhim, Saad Fallatah, Ivo Abraham. Comparing incomparable with the wrong analytics: anticoagulation, disability, intracranial hemorrhage, and mortality in acute cerebral vein thrombosis. Thrombosis Research Volume 178, June 2019, Pages 110–111

We thank Almulhim et al. [1] for their correspondence about our article (TR-D-18-00302) [2].

They stated that pooling disability scores from different scales is controversial (e.g., Fig. 8), and we agree. However, we meant for our review to be clinically relevant and pragmatic for clinicians. While the scales score disability differently, overall, each patient can be broadly categorized into one of three categories: poor or severely disabled, partial or mild-moderately disabled, and completely recovered or lacking disability. Our interest centered around those with poor or severe disabilities, given that these outcomes are the most likely to be used by clinicians to tailor anticoagulation in the population of disabled persons [2]. We clearly explained that we used the definitions as stated in each individual study to determine those with severe disabilities. Given that both scaling systems are somewhat subjective and that individual patient data is not available, it is impossible to harmonize the two. However, the absence of heterogeneity for this specific analysis ($I^2 = 0\%$, $P = 0.8$) [2] provides reassurance that pooling the two disability scales is reasonable, particularly for patients with poor or severe disabilities.

To focus on the most clinically important outcomes (i.e., poor or severe disability), we stratified patients using a modified Rankin Scale (mRS) and included only those with scores of at least 4 from the study by Afshari and colleagues [3]. With an mRS score of at least 4, the patient has moderately severe disabilities (unable to walk without assistance and unable to attend to personal bodily needs without assistance) or severe disabilities (bedridden and incontinent, requiring constant nursing care and attention) [4]. These patients have significant disabilities. Unfortunately, the last sentence of the outcome paragraph in the Methods section contained an error: "severe disability of 4 or *less* based on modified Rankin score" should have read "severe disability of 4 or *more* based on modified Rankin score." This might have confused the readers.

We used the random-effects model for pooling analyses even though we realize this is controversial. While a fixed-effect model can be used when between-study variability (heterogeneity) is assumed to be absent, a random-effects model should be used when between-study variability or heterogeneity is suspected. It is important to note that our decision to use the random-effects model was made a priori as we suspected heterogeneity when we developed the review protocol. The studies used different types and doses of LMWHs, and different methods were used to establish CVT diagnoses. Furthermore, the disability scales used to assess disability differed between studies. Given our assumption of potential heterogeneity, the random-effects model was chosen. Please note that given most of the pooled analyses had low heterogeneity, the fixed-effect modeling shows similar results and the same conclusions. Therefore, use of a fixed- or random-effects model is not relevant in this systematic review and meta-analysis [5].

Finally, we agree with the last point raised by Almulhim et al. The sentence in Paragraph 5 of the Discussion section: "*Only in this review we were able to show that LMWH is associated with a statistically significant reduction in mortality*" should be deleted. This refers to additional analyses that were deleted from the original submission per the recommendations of our peer reviewers.

In conclusion, while Almulhim et al. brought out some important points, the clinical importance and conclusions of this important systematic review and meta-analysis are not changed.

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