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Letter to the Editors-in-Chief

Comparing incomparables with the wrong analytics: Anticoagulation, disability, intracranial hemorrhage, and mortality in acute cerebral vein thrombosis

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ABSTRACT

Significant progress has been made in the prevention and management of hypercoagulation. Unfractionated heparin (UF) and low molecular weight heparin (LMWH) are indicated for acute cerebral vein thrombosis with or without intracranial hemorrhage (ICH). A recent meta-analysis of four trials comparing UF and LMWH aimed to evaluate the efficacy and safety of both agents in terms of disability, intracranial hemorrhage, and mortality. However, several methodological aspects of the meta-analysis warrant further discussion. It appears that the disability outcome was not sufficiently harmonized by design or statistical standardization, some inputs could not be validated, incorrect statistical analyses were performed, major results could not be replicated, and conclusions were not supported by the statistical results. The conclusion of a statistically significant reduction in mortality is not supported by the data.

Four randomized controlled trials (RCTs) published between 1999 and 2015 [1–4] evaluated the efficacy and safety of unfractionated heparin (UF) and low molecular weight heparin (LMWH) in the management of acute cerebral vein thrombosis (aCVT) and were the subject of a recent meta-analysis [5]. Meta-analytic methods enable the estimation of the pooled risk of outcomes of interest across a set of studies – assuming the outcomes are harmonized by design or through statistical standardization, the inputs can be validated, the correct analytics are applied, the results can be replicated, and interpretations are consistent with the results. The meta-analysis by Al Rawahi and colleagues [5] includes violations of each of these assumptions and provides an opportunity to reiterate some key methodological aspects of pooled analyses.

In the meta-analysis that focused on the efficacy of low molecular weight heparin (LMWH) versus unfractionated heparin (UF) on the outcome of disability (Fig. 8 in Al Rawahi et al.) [5], the Misra et al. [3] study used the Barthel Index. This scale assesses ten *specific* physical activities of daily living in terms of the degree to which a person is able to perform each task independently, with some help, or is unable to do so. Items are scored separately and summed to a total ranging from 0 (total dependence) to 100 (total independence). In contrast, the Afshari et al. [4] study in this analysis employed the Modified Rankin Scale (mRS), a *global* rating scale ranging from perfect health (no symptoms; score 0), across several gradients of relative disability, to severe disability (requiring constant nursing care and attention, bedridden, incontinent; score 5) and death (score 6). The Barthel Index is quite objective, while the mRS is inherently subjective. Both scales define and operationalize disability differently, diverge in how scores are calculated, yield scores in opposite direction, and vary in how persons are classified as disabled. Al Rawahi et al. [5] did not harmonize the scoring nor the classification of disability. Instead, they adopted the disability classifications of the two studies with disregard for the differential scaling and without modification. Thus, both metrics and classifications are incompatible for use in a meta-analysis, invalidating the results summarized in Fig. 8 in the Al Rawahi et al. meta-analysis [5].

We also question the disability meta-analysis for another reason. Afshari et al. [4] treated the (ordinal) mRS as a continuous (interval) variable. As Al Rawahi et al. [5] state, “using the available means, standard deviations and total number of patients, we were able to estimate that 1 patient in each group would have had severe disability of 4 or less.” However, the mRS ranks severe disability as a score of 5, not a score of 4 or less, but Al Rawahi et al. [5] state that “a score of 4 or more was considered as severe disability”. We could not replicate either classification and, consequently, the disability findings could not be validated.

Two statistical models can be used in meta-analysis depending on how the effect size is defined [6]. A fixed effect model assumes that there is a true effect size that can be determined. In contrast, a random effects model allows the true effect sizes to vary as studies might be different from each other but are assumed to share a common effect size. Al Rawahi et al. [5] used random effect modeling, presumably to manage heterogeneity. With only two studies in each of the five meta-analyses (Figs. 4 through 8), fixed effect modeling is indicated because the estimate of the between-studies variance is likely to have poor precision. Further, a statistically non-significant test of heterogeneity should not be used as suggestive of a common effect size. The estimation of heterogeneity metrics Q and I^2 and the estimation of the overall effect in a random effect model is subject to bias when only 2 studies are available.

The authors used the RevMan5 software for analysis. Note that, in Fig. 6, the study by de Bruijn and Stam [2] had zero new intracranial hemorrhage (ICH) events in either arm. Clearly, this is a safety finding of major importance in anticoagulation because it would mean that no patients in either study arm experienced an ICH. However, the software used could not calculate a Mantel-Haenszel odds ratio (OR) because this requires that there be one non-zero rate; i.e., there should be at least 1 ICH in one of the arms - further underscoring the clinical importance of zero ICHs in either arm. It has been suggested to replace one zero with a close-to-zero value (e.g., 0.5), but this affects the ecological validity

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study ("half an ICH"?). By not managing the zero/zero result in the trial by de Bruijn et al. [2], the RevMan5 software dropped and ignored the data from this trial, leaving only the Einhäuple et al. [1] trial in the pooled analysis. Consequently, the analysis reverted to a repeat of the results of the Einhäuple et al. [1] study. While the RevMan5 software is unable to deal with zero/zero situations, other methods for estimating rare events are available, such as continuity corrections or estimating the Peto OR. In summary, Al Rawahi and colleagues applied incorrect analytics and thus biased if not invalidated the statistical results.

In meta-analyses such as the one being considered here, odds ratios (ORs) > 1 and with a confidence interval (CI) not crossing 1 signal an increased risk of a negative outcome. Conversely, while ORs < 1 with a confidence interval fully below 1 indicate a protective effect against a negative effect. In other words, inferring a significant protective effect of anticoagulation on mortality would require that a meta-analysis yielded a pooled OR < 1.00, the 95% CI was between zero and < 1.00 (i.e., not crossing unity), and the test for overall effect had a *p*-value < 0.05. According to Fig. 4, in the comparison of anticoagulation versus placebo the pooled OR estimate for mortality was 0.31 but the 95% CI extended from 0.07 to 1.45 and thus crossing unity. At 0.14, the *p*-value for the test of overall effect exceeded the statistical significance criterion of $p < 0.05$ and therefore confirmed the absence of statistical significance. Further, as Fig. 7 shows, the pooled OR estimate for mortality in the comparison of LMWH to UFH was 0.21 with a 95%CI extending from 0.02 to 2.44 and also crossing unity. The test for overall effect also yielded a statistically non-significant $p = 0.21$. Despite these statistically non-significant results, Al Rawahi et al. [5] concluded that they "were able to show that LMWH is associated with a statistically significant reduction in mortality". This statement is not supported by the statistical evidence and the claim of a mortality reduction benefit with any form of anticoagulation is incorrect.

In conclusion, we regret to bring these errors in the conduct, analysis, reporting, and interpretation to the attention of the research and clinical thrombosis communities. The conclusion of statistically significant reductions in mortality and disability is not warranted by the data. The only conclusion supported by this meta-analysis is that it failed to reject the null hypothesis of no benefit. In the end, it remains unknown whether (and which of) the agents of interest (UH or LMWH) were associated with increased or decreased disability, experiencing or not experiencing a new ICH, and dying or not dying.

Declaration of interests

None.

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