

CMB and intense blood pressure lowering in ICH: is there an additive effect?

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In a recent paper, Shoamanesh et al describe the joint effect of cerebral microbleeds (CMB) and intensive blood pressure reduction on hematoma expansion and functional outcome in intracerebral hemorrhage patients.¹ They report the interaction terms and corresponding p-values from which they conclude that the “response to (...) treatment did not differ in patients (...) with vs without CMB”. An intriguing finding but perhaps a slight change in perspective and methods would lead to other insights from these data.

For example, the authors focus perhaps too much on the non-significant nature of the different interaction terms. They do recognize that “there was a suggestion” of a joint effect on hematoma expansion but they also note that the power for these analyses is low, rendering the overall conclusion of no effect perhaps too definitive.

Also, the authors focus on *multiplicative interaction* while *additive interaction* is arguably more relevant in this case. Additive interaction quantifies how many individuals develop the outcome solely due to the combination of CMB and treatment status, on top of what can be expected based on the two individual effects.^{2,3} Several measures to quantify and test this excess in risk exist, like the relative excess risk due to interaction (RERI) measure. Interestingly, a review of the literature shows that the statistical significance of interaction analyses changes in 17% of trials when interaction is assessed on a different scale than originally reported.⁴

Also, the authors present odds ratios as estimates of relative risks. Not only are odds ratios poor estimates of the relative risk when the risk of outcome is high (here 20-30%), they are also non-collapsible. This can lead to differences between the marginal and conditional estimates, and therefore the measure of interaction can depend on the covariates that are being controlled for; risk differences as well as relative risks based on cumulative incidences do not suffer from non-collapsibility.^{3,5}

Unfortunately, the format in which the results are currently displayed do not allow some quick, back-of-the-envelope type, calculations to see whether these methodological tweaks would indeed lead to different insights or even conclusions. It is certain that the low power issue will not be resolved, and might even be exacerbated in a formal additive interaction analyses. Nonetheless, it would be useful to see the data in a format (e.g. 4x2 table) that allows us to see whether additive interaction could play a relevant role.

References

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