Meta-analyses with rare events should use adequate methods

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With great interest we read the meta-analysis of randomized clinical trials of Takagi et al. [1] on postoperative stroke risk in off-pump and on-pump coronary artery bypass grafting. Their work is a welcome update of the most recent meta-analysis on this topic by Sedrakyan et al [2].

Contrary to Sedrakyan et al., however, Tagaki et al. do not find a significant difference between off- and on-pump surgery (relative risk [95% CI]: 0.60 [0.34-1.06], p=0.08), whereas Sedrakyan et al. found 0.50 [0.27,0.93], p=0.03, for the relative risk. As an explanation, Tagaki et al. point to the methodical difficulties of dealing with studies reporting no events in both treatment groups. Whereas Sedrakyan removed these studies from analysis, Tagaki et al. obviously used a “0.5-correction”-rule, where 0.5 is added to the number of events as well as to the number of non-events in both groups (this is at least how we were able to reproduce their results).

However, we object to both ideas of dealing with studies with zero events. As those studies point to equal risk for both treatments (as Tagaki et al. noted correctly) deleting them, as Sedrakyan did, would probably overestimate the treatment effect. On the contrary, using the “0.5-correction”-rule, as Tagaki et al. did, adds 13 pseudo-events in the off-pump group and another 13 in the on-pump group. Thus, the analysis is performed with 59 pseudo-observed -- instead of 33 actually observed -- events, rendering the analysis also somewhat dubious.

We would rather recommend methods that adequately account for studies with zero observations. These methods have been proposed [3], are straightforward extensions of the familiar Mantel-Haenszel method [4], and standard software (e.g., SAS® PROC FREQ, CMH option, code is available from the authors on request) is

available for computation. We reanalysed the Tagaki data* and found an estimated relative risk of 0.376 [0.175, 0.807], p=0.0091. Note that this value compares very closely to the relative risk from the simple and most intuitive analysis performed by collapsing the data from the 32 studies into a simple four-fold table: 0.377 [0.176, 0.810], p=0.0092.

We therefore conclude that there is still significant evidence that the off-pump method is superior to reducing postoperative stroke risk after coronary baypass grafting, as compared to the on-pump method.

* Please do also note a printing error in table 1 of the Tagaki et al. study. Number of randomized patients in the off-pump group from the Lonn study should be “15”, not “60”. We performed all analyses with the corrected data set.

References

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