Assessing the quality of evidence supporting patent foramen ovale closure over medical therapy after cryptogenic stroke

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This commentary refers to ‘Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials’, by Y. Ahmad et al., pp. 1638–1649.

We read the recent article by Ahmad et al. with interest. This systematic review and meta-analysis compared patent foramen ovale (PFO) closure to medical therapy for patients with cryptogenic stroke. After pooling data from five studies, the authors concluded that PFO closure is superior to medical therapy (hazard ratio 0.32, 95% confidence interval 0.13–0.82, $I^2 = 73\%$), and called for updated guidelines reflecting these findings.

When appraising the methodological rigor of the evidence, the authors concluded that the overall quality of individual trials was either ‘intermediate’ or ‘high’ and they did not provide an evaluation of their overall confidence in the body of evidence. In the approach recommended by GRADE, included trials should be dichotomized as high or low risk of bias according to the Cochrane framework. We applied this framework based on the information provided in Table 2; our judgements differed from those made by the study authors (Figure 1). In the PC, REDUCE, and RESPECT trials, the number of patients who were lost to follow-up in the intervention arm were large and exceeded the fragility index. Hence, we disagree that these trials were at low risk of attrition bias. We agree with Ahmad et al. that the open-label CLOSE, CLOSURE, and REDUCE trials were at risk of detection bias due to non-blinded adjudication. In consequence, each of the five trials in this meta-analysis is at risk of detection bias, attrition bias, or both biases; this places them at high overall risk of bias. Ahmad et al. also failed to consider other factors that affect quality of evidence. In the GRADE framework, summary findings based on randomized controlled trials start as high quality evidence but can be downgraded based on five categories—risk of bias, imprecision, inconsistency (also known as heterogeneity), indirectness, and publication bias. The summary data presented by the review authors is therefore of low quality, requiring downgrading for serious risk of bias, and substantial heterogeneity ($I^2 = 73\%$).

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In summary, before drawing strong conclusions regarding the efficacy of PFO closure after cryptogenic stroke, clinicians need to consider not only the pooled effect estimate, but also the methodological quality of the included studies and potential sources of heterogeneity in treatment effect. Ultimately, assessing confidence in the estimates of effect with a systematic approach—such as GRADE—helps clinicians appreciate whether they should apply the findings in their practice.

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References