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Commentary: Not all meta-analyses can be trusted

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Systematic reviews and meta-analyses are widely viewed as the gold standard within the hierarchy of evidence-based medicine. These studies directly impact clinical guidelines and influence the way we practice medicine. However, clinicians may be unaware of the risk for introduction of random error, that is, type 1 error, when meta-analyses are small and underpowered, potentially inflating estimates of treatment effect.¹ This risk may be further increased as evidence continues to accumulate and meta-analyses are updated over time, ultimately resulting in spurious data that can negatively affect how we deliver clinical care.² Studies have shown that the risk of type 1 error could range from 10% to 30% of meta-analyses.²⁻⁴

The presented article by Chan and Harkey,⁵ “Trial Sequential Analysis in Meta-analyses: A Clinically Oriented Approach With Real World Example,” provides a detailed introduction for the clinician to trial sequential analysis (TSA), an analytic method aimed at minimizing the chance of type 1 error in meta-analyses, by adjusting the test statistics accordingly as new trials or more data are added.⁵ The authors, using a post hoc TSA, performed

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TSA, a statistical tool for critical data analysis and confirmation, minimizes risk of type 1 error. TSA helps clinicians critically appraise data when considering applications to clinical practice.

an elegant reanalysis of data from the meta-analysis of Woldendorp and colleagues,⁶ which examined the associations among subclinical valve thrombosis (SCVT), stroke, and various antithrombotic strategies.

The reanalysis of the meta-analysis of Woldendorp and colleagues⁶ using TSA confirmed a 100% increase in the risk of stroke in patients with SCVT and a 20% reduction in the incidence of SCVT in patients taking oral anticoagulants, as opposed to single antiplatelet therapy or dual antiplatelet therapy. Of note, with TSA, the observed 20% increase of SCVT in patients taking single antiplatelet therapy as opposed to dual antiplatelet therapy could not be considered conclusive because of underpowered data. As noted by the authors, the important limitations to TSA include susceptibility to bias and heterogeneity. In fact, the conclusion regarding the superiority of oral anticoagulants to antiplatelet therapies must be interpreted with caution, because significant heterogeneity was detected.

TSA appears to be a strong, although complex, statistical tool that allows for the critical analysis and confirmation of data with the goal of minimizing the risk of type 1 error.

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When appropriate, and with cautious attention to inherent limitations, TSA can complement available statistical models and help clinicians critically appraise the available data when considering applications to clinical practice.

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Commentary: Seeing the faces in Rubin's vase

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As surgeons increasingly turn to the published literature to guide clinical practice, Chan and Harky¹ provide a timely tutorial on analyzing meta-analysis data using trial sequential analysis (TSA). TSA is essentially the same statistical methodology as interim analysis, which allows investigators in clinical trials to analyze data as it accumulates in “real time” rather than having to wait for a final accounting of all anticipated results.^{2,3} The authors showcase TSA using a recently published meta-analysis by Woldendorp and colleagues on subclinical valve thrombosis (SCVT), stroke, and different antithrombotic strategies in patients who underwent transcatheter valve insertion.⁴ Using the 12 studies from the original publication, the investigators reconfigure the data from forest plots into TSA diagrams. Although the information is essentially the same, a distinctly new perspective

Rubin's vase: a vase with embedded faces.

CENTRAL MESSAGE

Surgeons should be familiar with the principles and caveats of trial sequential analysis, an emerging statistical methodology that offers a unique view of meta-analysis data.

emerges. With TSA, one can visualize the contribution of each individual study, added over time, in the march toward a finite answer.

In the case of the association of SCVT with stroke, the TSA diagram presented in the didactic suggests we ponder this question no further; the statistical significance boundary, set to query whether SCVT was associated with at least a 100% increase in stroke compared with normal leaflet motion, was crossed several studies ago. Additional investigation is unlikely to alter conclusions. However, investigators interested in differences between antithrombotic regimens of dual- versus single-antiplatelet therapy can see that, for a relative risk reduction (RRR) of 20%, the strength of the currently available data renders this question

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