Commentary: Trial sequential analysis: An upgrade to the meta-analysis worth learning

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Drs Chan and Harky present a clinically relevant and timely review of trial sequential analysis (TSA) during a meta-analysis using a recent study published in the Journal. The authors performed a secondary analysis of the meta-analysis by Woldendorp and colleagues. The TSA methodology suggested that the existing evidence was sufficient to reach a conclusion about a 100% increase in risk of stroke in patients with subclinical valve thrombosis (SCVT) and a 20% reduction in SCVT incidence in patients taking oral anticoagulation compared with those taking single or dual antiplatelet therapy. However, contrary to the published results of the meta-analysis, the TSA methods suggest data are insufficient to confirm or rule out a 20% increase in SCVT risk in patients taking single versus dual antiplatelet therapy.

The authors are to be commended for proving a well-written review tailored to the cardiothoracic community. TSA originates from sequential interim analysis of clinical trials, a topic surgeons rarely encounter. Yet the adaptation for meta-analysis is becoming increasingly popular and the additional information provided means it will likely continue to grow in use. As the authors mention, there are important limitations of TSA, including underlying publication bias and heterogeneity in studies identified for meta-analysis. A meta-analysis is only as good as the studies that go into it, and the same applies to TSA. Additionally, the authors point out the important consideration that investigators arbitrarily set the thresholds for relative risk reduction, which drives the outcome of the analysis. These parameters should use clinical background and knowledge to guide selection; however, it is up to the reader to critically review these selections and assess their validity. Finally, as the authors demonstrate with the first outcome of 100% increase in risk of stroke with SCVT, the threshold for conclusive level of evidence was reached after only 3 studies, so more studies were superfluous. Therefore, this methodology can help guide decisions for future research and resource allocation. A recent article by Storz-Pfennig using TSA methodology demonstrated that 8 of the 13 trials studied were identified as potentially unnecessary research.

The TSA methodology is being applied more frequently in cardiothoracic studies and will continue to be an important adjunct to meta-analysis. This timely article by Chan and Harky provides a straightforward description of the methodology and a relevant example that is pertinent for practicing cardiothoracic surgeons.

References
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. 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. Studies have shown that the risk of type 1 error could range from 10% to 30% of meta-analyses.

The presented article by Chan and Harkey, “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. The authors, using a post hoc TSA, performed an elegant reanalysis of data from the meta-analysis of Woldendorp and colleagues, which examined the associations among subclinical valve thrombosis (SCVT), stroke, and various antithrombotic strategies.

The reanalysis of the meta-analysis of Woldendorp and colleagues 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.