Editor’s Perspective

Recapitulation and Synthesis
Proliferation of Meta-Analysis in Structural Interventional Cardiology

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The highest ideal in medical practice is fully informed, evidence-driven practice. In pursuit of that ephemeral goal, clinical research in interventional cardiology is at an all-time high. One of the most rapidly growing domains of clinical research in interventional cardiology and other medical fields has been meta-research—systematic reviews and the meta-analyses they feed. In this journal alone, for example, 13 meta-analyses were published between 2013 and 2015, and 7 of the 112 original articles that appeared in 2015 fell into this category.1,2 Given the proliferation of such studies, in this journal and in the field more broadly, it seems an opportune moment to reflect briefly on their place in the evolving literature on structural interventions.

Although articles reporting the results of meta-analysis have become increasingly pervasive in recent years, the statistical methodology and discipline are not new, having been pioneered >40 years ago. Wielded judiciously and effectively, meta-analysis can be one of the most important tools available for integrating and demystifying clinical research. It is ideally suited for synthesizing data from multiple sources in the service of seeking clarity around important questions for which there is no clear answer—for example, when trials yield conflicting results, and there are multiple underpowered or unfocused studies. Targeted finely and executed expertly, meta-analysis can and should serve as some of the highest-level evidence for clinical decision making and for subsequent trial design. However, reality is not always in keeping with the ideal.

There is increasing evidence that the meta-analysis machine is bloated. In the cardiovascular literature, both the publication of meta-analyses and their relative contribution to the literature expanded dramatically during the first decade of this century, with the number of meta-analyses increasing >500% from 2000 to 2012 and the ratio of randomized trials to meta-analyses falling from >10:1 to <3:1.3 Although the sheer number of meta-analyses does not necessarily speak to appropriateness or necessity, there also seems to be increasing redundancy. For example, Siontis et al4 found that, for two thirds of medical meta-analyses published in 2010, there was at least 1, and often multiple, overlapping meta-analysis on the same topic. To be sure, meta-analyses on the same topic can differ in important respects and provide unique and complementary value, but discordance between overlapping studies can muddy, rather than clarify, the question, belying the purpose of a meta-analysis. In an effort to streamline the pipeline of meta-analyses, creating transparency and reducing redundancy, investigators at the Center for Reviews and Dissemination at the University of York developed PROSPERO, a Web-based system for registration of systematic reviews that was activated 5 years ago.5

Overlapping and redundancy are not the only concerning observations. Just as important, there is the issue of quality. As Berlin and Golub6 recently explored in an editorial in JAMA, the quality of synthesis generated through meta-analysis is subject to many important vulnerabilities, including heterogeneity among sources of evidence, methodological variability, and conduct by researchers without expertise. Recognizing the potential for inconsistency and misapplication, in 1996, an international group of investigators developed a set of guidelines for reporting meta-analyses, the Quality of Reporting of Meta-Analyses (QUOROM) statement. This was updated in 2009 as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA).7 Although PRISMA Reporting Items for Systematic reviews and Meta-Analyses is widely accepted and cited as a standard for performing and reporting meta-analyses, reference to these or similar guidelines in the Methods section of an article is no guarantee that they were followed with the expected degree of rigor. For example, many studies have documented that quality of published meta-analyses is highly variable, and even though quality has improved with the adoption of these standards, it remains poor in general.8–11

This is also true of network meta-analysis, a recent expansion of the meta-analysis concept that harnesses the principles of systems theory to provide a means of synthesizing data among multiple (ie, >2) types of treatment to facilitate and enhance comparison among an array of treatments.12 As Bafeta et al13,14 recently documented, although network meta-analysis brings unique and powerful potential to the analysis of complex clinical problems, the methodology and reporting of such studies are also beset by heterogeneity and variable rigor. Similar to standard meta-analysis, the lofty potential of this methodology does not insulate it from inappropriate or flawed application.

Examples of these concerning trends in the literature on structural interventional cardiology abound. Transcatheter aortic valve replacement (TAVR) has become one of the 21st century’s most emblematic examples of paradigm changing
technology. Concomitant with its proliferation, the literature surrounding TAVR has exploded, with >3400 articles indexed in Medline since 2011. Leaders in the field have wisely established standardized end point definitions and criteria that serve effectively to focus reporting of the various types and sizes of studies. This standardization has also facilitated and encouraged investigators to recapitulate and synthesize the primary literature. As clinical adoption of TAVR and related research has expanded, the metaresearch machine has followed closely, churning out at least 63 TAVR-centered meta-analyses (excluding those related to cost or cost-effectiveness) from 2011 to 2015, with an increasing number each year (Figure). Many of those focused on unique questions, but most were directly overlapping (Table). Keeping current in a rapidly evolving field is inevitably a challenge, and meta-analyses offer the potential to simplify digestion of the ever-expanding TAVR literature. To date, however, this potential has been limited by redundancy and inconsistency. Moreover, without invoking any particular analysis or topic within the TAVR sphere, or evaluating in depth the quality of this growing body of secondary literature, the rigor of these studies and their conformity to the PRISMA paradigm have been variable and, accordingly, invite a critical evaluation.

The phenomenon of proliferating and redundant metaresearch in structural interventional cardiology is not limited to the clinical success story of TAVR. In fact, it is even more striking with regard to patent foramen ovale closure, which holds so much nascent market promise but continues to struggle in its quest for legitimacy. Between 2012 and 2015, 20 systematic reviews and meta-analyses were published on the topic of device closure for stroke prevention in patients with a patent foramen ovale. These appeared in 14 different journals, and 4 were published in a single journal within a period of 6 months. With borderline statistical power in the 3 randomized trials on the topic, and the variability in findings among these and the multiple cohort studies that form the bulk of the literature, this is exactly the type of problem that is deserving of and potentially clarified through meta-analysis. But not 20 of them not surprisingly, there was no consensus among the conclusions reached by these meta-analyses, and instead of clarifying the issue, they have served only to obfuscate it further, as discussed in a recent study of the systematicity of systematic reviews and meta-analyses. As noted, although valid and valuable meta-analyses can overlap and even conflict with one another, there is no justification for such exuberant redundancy.

So what can we as editors and consumers of the literature do? Fundamentally, we should ask whether the question is well conceived and appropriately targeted for a meta-analysis,
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for while the technique may be powerful, the question must be on point. Beyond that, we can and should give critical attention to whether claims of adherence to the PRISMA statement are accurate and rigorous, to expect that meta-analyses in spirit and in fact conform to that reasonable set of standards. We should also recognize and expect that meta-analyses are registered in the PROSPERO registry, and that they acknowledge and specifically address overlapping with previous meta-research. Noting the potential for mixed quality and the proliferation of numerous, often overlapping and poor-quality meta-analyses, several authors have outlined considerations for reading meta-analyses critically and with the necessary insight, and for assessing quality, particularly in the case of overlapping studies. These are worth consideration and review by readers, article referees, and editors alike. To be sure, we should celebrate the potential of these methodologies to extend the insights that can be achieved through randomized trials, registries, and cohort studies, which have become indispensable, for good reason. But we must recognize that the synthetic clarity that meta-analysis can bring to questions clouded by conundrum and confounding is only as valuable as the question is astute and the methodology is precise. We must be both open to the revelation that meta-analysis can provide and attentive to the potential for misleading findings.

Disclosures

None.

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