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EDITORIAL

When Is It Appropriate to Publish a Meta-Analysis in Cardiovascular Drugs and Therapy?

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The method of meta-analysishas been in existence for hundreds of years in various scientific disciplines, but it was only in the twentieth century that clinical scientists began to address medical questions by combining results from different randomized clinical trials and observational studies [1]. The method of summarizing results from different studies has become the formalized method known as meta-analysis, which has been defined as "a statistical analysis of results from separate studies, examining sources of differences in results among studies, and leading to a quantitative summary of the results if the results are judged sufficiently similar or consistent to support such synthesis [2]." This is especially important when the sample size for individual studies is small leading to uncertainty about the effect size and wide confidence intervals pertaining to the treatment. The statistical methods for conducting meta-analyses have evolved over time and continue to do so.

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It is evident that numerous meta-analyses have significantly advanced the knowledge and treatment of many medical conditions, including diseases of the heart. From 30 years ago, the Fibrinolytic Therapy Trialists Collaborative Group combined several studies of lytic treatment of acute myocardial infarction to conclude that this therapy was beneficial in specific subgroups of patients (patients presenting with ST elevation in the anterior or lateral leads and patients with bundle branch block, but not in patients without ST elevation or ST elevation limited to the inferior leads) [3]. This has led to the formulation of the guidelines for emergent reperfusion therapy in patients with ST elevation acute myocardial infarction. More recently, a meta-analysis examining randomized trials of new anticoagulation agents for non-valvular atrial fibrillation demonstrated that these new oral anticoagulants reduced stroke, intracranial hemorrhage, and death, and had overall bleeding risks similar to warfarin, but are associated with higher gastrointestinal bleeding rates compared to warfarin [4]. An earlier meta-analysis found little difference between the new agents and warfarin [5]. Also, a number of meta-analyses conducted over the past 10 years have reported differing results for the value of closure devices versus medical treatment for patent foramen ovale [6, 7]. These examples demonstrate the advantages of meta-analysis in assessing medical and surgical treatments for a variety of cardiovascular conditions. In addition, citing a meta-analyses instead of the original studies reduces the number of references, which is important for journals that limit the numbers of references.

The vast resources of the internet including the existence of extensive medical research databases such as PubMed and the ready availability of statistical software packages have led to the increasing use of meta-analyses. There has been significant growth in the use of meta-analyses. According to PubMed, in 2000, only 1167 of 663,892 (0.2%) of publications mentioned meta-analysis,

whereas in 2022, 26,141 of 1,263,506 (2.1%) publications mentioned meta-analysis. As above mentioned, meta-analysis involves the statistical combination of results from 2 or more studies. It can be used to address questions that cannot be answered by single studies and can also be employed to reconcile conflicting results from different studies and to assess more precisely the effect size from an intervention. However, results from meta-analyses can be misleading if specific study designs, within-study biases, variation across studies, and reporting biases are not considered [8].

The purpose of this editorial is to assess when it is appropriate to submit a meta-analysis for *Cardiovascular Drugs and Therapy*.

For a manuscript to be considered for publication, it should contain significant new information, whether it is new data (original research) or new insight or summary of existing data (reviews, meta-analyses, editorials, and letters to the editors). The first meta-analysis on a topic can be of value; however, repeat meta-analyses on the same topic should provide new information, not merely repetitions with an increased number of included studies and/or patients.

First and of most importance, whether to perform a meta-analysis depends on aligning the synthesis with the research question [9]. If a similar meta-analysis has been published, it may not be worth the effort to repeat what has already been done, especially if the results of the new meta-analysis are similar to the earlier one (unless more granular data are available, such as access to individual patient data to update the findings of a previously published aggregate data meta-analysis). If a new study investigating a question addressed in a previous publication is submitted, the authors should explain in the submission letter what their manuscript adds on top of a previously published one(s) [10].

Second, the new meta-analysis may clarify questions raised in the initial studies or may provide a more precise estimate of the treatment effect.

Third, for the research question to be of interest to a wider audience, it is preferable that it be broader than the questions addressed by the individual studies. Although this does not rule out meta-analyses which address the same questions the primary studies examined. It is also desirable that studies with different results be included. This does not eliminate including studies with similar results, but it is likely that such meta-analyses will not be as interesting to the journal readership (especially if this is not the first meta-analysis on the topic).

Fourth, high-quality studies are usually needed to perform meta-analyses. For studies to be combined, there must be sufficient information about the study design (randomized versus observational), characteristics of the patient population, and outcome measures, including their definitions and metrics used for reporting, so that all studies share a common metric. We believe that only meta-analyses with correct statistical methods should be published.

Fifth, there should be a sufficient number of studies with adequate numbers of subjects. This is particularly important for estimating the between studies variance, which has implications for many aspects of the meta-analysis. It is also important for assessing heterogeneity or variation across studies, for conducting sub-group analyses, and for evaluating secondary endpoints. If sufficient number of patients are enrolled in the studies of interest, only two studies may be needed to conduct the meta-analysis. For example, in a meta-analysis of empagliflozin and dapagliflozin, two studies were sufficient to demonstrate the efficacy of sodium-glucose co-transporter-2 (SGLT2) inhibition in improving the secondary endpoints of renal outcomes and reducing all-cause and cardiovascular death in patients with heart failure reduced ejection fraction [11].

If all the included studies are showing similar results, it is not expected that the meta-analysis will show novel findings, justifying its publication (if similar meta-analyses have already been published). This is also true if several small studies are combined with one large study that dominates the results. However, if the meta-analysis focuses on secondary outcome(s) that each of the original studies are not powered to assess, there is a justification for a meta-analysis. This was the case with the meta-analysis of SGLT2 inhibitors in which the 2 separate randomized trials could not show a statistically significant effect on mortality, although the combined primary end point of mortality and hospitalization for heart failure was consistently reduced. Only a meta-analysis was sufficiently powered to show a significant effect. It is also appropriate to use meta-analysis for examining differential effects in subgroups (older versus younger, females versus males, etc.).

In summary, a meta-analysis will receive relatively low priority for publication in *Cardiovascular Drugs and Therapy* if (1) a similar meta-analysis has been published and there is no clear explanation as to the incremental value of the new analysis compared to the previous ones, (2) includes studies with similar results, (3) includes low-quality studies, and (4) has a small number of studies with inadequate numbers of subjects.

In short, we hope to publish meta-analyses in *Cardiovascular Drugs and Therapy* that present new information and include high-quality studies with sufficient numbers, report results for sub-groups, and assess secondary outcomes. Sub-group analysis and assessing secondary outcomes are especially important if results for the primary outcome are consistent across the individual studies. Meta-analysis is warranted if it offers definite conclusions when the results of its individual component studies are not definitive or if a more precise estimate of the effect size of the intervention

is needed. If the results are not statistically significant and the conclusion is that further studies are needed, the priority for publication is lower. Coincidentally, our criteria for publishing meta-analyses are similar to those from another publication in JAMA Network Open [10]. For those interested in performing a meta-analysis, the Cochrane website provides important guidance. (https://training.cochrane.org/handbook/current/chapter-10).

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Declarations

Competing Interests The authors declare no competing interests.

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