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Practical and updated guidelines on performing meta-analyses of non-randomized studies in interventional cardiology

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Abstract

The use of meta-analysis in medicine is widespread nowadays, particularly in the field of interventional cardiology. Meta-analysis is a statistical approach aiming to combine date from a large number of patients from randomized clinical studies and/or non-randomized registries so as to obtain a pooled estimate of the results and to answer specific research questions. It is important to take the correct methodological approach in order to reach unbiased conclusions. In this article, we provide an updated review of the methodological approaches needed to perform meta-analyses of non-randomized data, and we suggest a simplified check-list of items to be considered when attempting to deploy this kind of meta-analysis. (Cardiol J 2011; 18, 1: 3–7)

Key words: meta-analysis, non-randomized studies, interventional cardiology

Introduction

Meta-analysis is the use of statistical methods to summarize results of all relevant prior independent studies on a specified topic according to a predetermined and explicit method [1]. By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of healthcare than those derived from individual studies included within a review. They also facilitate investigations of the consistency of evidence and explore of differences across studies. Meta-analyses are often, but not always, important components of a systematic review procedure.

Meta-analyses of randomized clinical trials (RCT) are increasingly being employed in cardiovascular research. The strength of this meta-analytical approach is the collection of randomized trials, in which the study groups are created through randomization.

However, many topics in cardiovascular medicine are not suitable for randomization. In such cases, data are used that has come from non-randomized trials. This type of study, by definition, is subject to bias in terms of patient selection and treatment allocation. Participants are not randomly allocated to receive (or not) an intervention. They may choose which group they want to be in, or they may

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Table 1. Checklist of key issues in performing meta-analysis for non-randomized data.

Retrieving process of articles
1. Include in the manuscript a quality assessment of the studies collected for the meta-analysis
2. Assess the publication bias, and possibly include a Funnel Plot in the manuscript
Investigation of heterogeneity
3. Analysis of data
4. Include in the section of methods of the manuscript a pre-specification of potential agents of heterogeneity that might be used for subgroups analysis
5. Report (when possible) adjusted estimates for potential confounders by multivariate analysis
Interpretation of results
6. Report global and separate result estimates when combining randomized with non-randomized studies, whether heterogeneity is present, and the procedure used to investigate the source of this; eventually perform final sensitivity analysis
7. Discuss clearly the consistency of data, reporting strength and limits of the analysis performed

be assigned to a group by the researchers. For instance, the most important randomized studies in interventional cardiology have a mean ratio of eligible/randomized patients of about 10:1 [2, 3] and eligible but non-randomized patients are often enrolled in registries. Thus, meta-analyses of non-randomized studies are becoming more and more common.

This is particularly true in the field of interventional cardiology, where randomization is difficult, but where a large body of clinical databases and registries is often available. Furthermore, the evidence from clinical trials rarely answers all the important questions. For example, most trials are conducted to establish the efficacy/safety balance of a single agent in a particular clinical setting, but less commonly encountered adverse effects may only be detected in non-randomized observational studies and registries.

Randomization, whereby people receive all of the treatments and controls being tested in a random order, is the only means of controlling for unknown, and therefore unmeasurable, differences between comparison groups as well as those that are known and measured. This means that people receive one treatment, the effect of which is measured, and then 'cross over' into the other treatment group, where the effect of the second treatment (or control) is measured. Random assignment removes the potential for bias in the assignment of patients to one intervention or another by introducing unpredictability [4]. However, it is also possible to include in a meta-analysis the information from registries and observational studies, provided that the quality of the non-randomized data is good enough to apply the correct statistical procedures [1, 5].

Recently, a large number of interventional cardiology meta-analyses have been published with minor (and sometimes major) biases, which in some cases have led to incorrect inclusion of studies and a misleading interpretation of data [6].

In this work, we highlight and discuss some methodological points to be considered, in particular when dealing with the meta-analysis of non-randomized studies. These items are summarized in the check-list in Table 1.

Quality of studies retrieved

The first issue is the methodology to investigate the quality of the studies retrieved. In particular, meta-analyses of observational studies face the challenge of incorporating studies of varying quality, which can mask or even reverse the effect's direction. In other words, quality assessment of the studies offers an estimate of the likelihood of their results to express the truth [7].

Several scales have been created in an attempt to improve the quality investigation of reports, but unfortunately none of them is fully validated. The Newcastle-Ottawa Scale (NOS), a method for assessing the quality of non-randomized studies (case control studies, cohort studies and time interrupted series) in meta-analyses, is reasonably comprehensive and has been partly validated; it is the one actually recommended by the Cochrane Non-Randomized Studies Methods Working Group [5]. NOS assigns points on the basis of the selection process of the cohorts, or of the cases and of the controls (0–4 points), of the comparability of the cohorts or of the cases and of the controls (0–2 points), and of the identification of the exposure and of the outcomes of study participants (0–3 points).

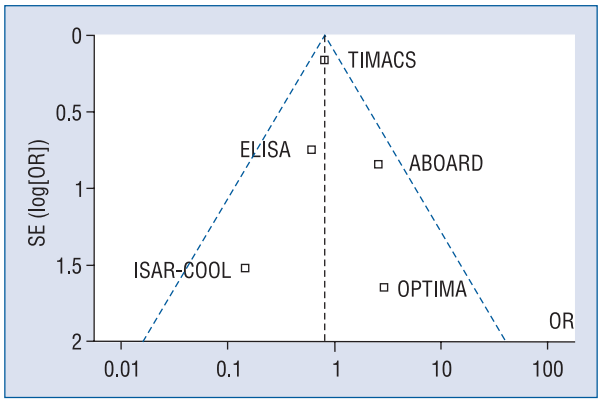

Figure 1. Example of publication bias plot without evidence of bias producing a symmetrical plot; the squares are the studies with related name [8].

Publication bias

Another potential confounder, especially in the setting of non-randomized studies, is publication bias. Studies with negative results can take longer to be published. Results which do not conform to the desired outcome may never even be published.

A related term, the 'file drawer problem', refers to the tendency for negative or inconclusive results to remain unpublished by their authors. We always recommend an investigation of this bias. It can be done through a graphical test such as the Funnel Plot, which is created by plotting the estimated treatment effect against the study size. A practical example can be found in the study by Navarese et al. [8] on the early as opposed to delayed invasive approach in acute coronary syndrome (Fig. 1).

A symmetrical plot around a chosen measurement indicates no publication bias. An asymmetrical funnel indicates a relationship between treatment effect and study size (possibility of publication bias or a systematic difference between smaller and larger studies) and may also arise from measuring an inappropriate effect. An indication of publication bias would be the absence of small studies with small effects in the Funnel Plot's lower left-hand corner [9]. An asymmetrical Funnel Plot requires investigation of its possible causes. Furthermore, there have been several suggestions in the literature of how to translate the graphical approach of the Funnel Plot into a statistical model. It is possible to evaluate Funnel Plot asymmetry by statistical tests such as Begg's method and Egger's test. Begg et al. [10] proposed an adjusted rank correlation method to examine the association between the effect estimates and their variances. Egger et al. [11] introduced a linear regression approach in which the standardized effect size is regressed into a measure of precision. The greater the regression coefficient, the greater the evidence for small study effects.

Because each of the two approaches looks for an association between treatment effect (e.g. log odds ratio) and its standard error in each study, these are the statistical version of the graphical Funnel Plot test.

Analysis of data

Clinical and statistical heterogeneity of studies included is another issue of concern in dealing with meta-analysis of non-randomized studies. Heterogeneity may either arise from systematic differences between studies (e.g. confounders) or from random differences between effect sizes. So an accurate analysis of data searching for heterogeneity must be employed. The commonly used test of heterogeneity in meta-analysis is Cochran's Q test, a non-parametric statistical test of whether k treatments have identical effects (considering $k > 2$ experimental treatments). The test is based on a weighted least-squared statistic and compares the study-specific estimates of the effect measure with an estimate of the common homogeneous effect measure. Q distribution approximately resembles χ^2 distribution. The statistical power is very low, implying that heterogeneity may be present even if Q statistic is not significant at conventional levels of significance [12]. As a response to this, while a two-tailed $p = 0.05$ is used for cut-off for hypothesis testing of effect, a two-tailed $p = 0.1$ is conventionally recommended for heterogeneity [13].

Therefore, it would be useful to combine this test with a more reliable one. The statistical inconsistency test (I^2) has been recently introduced [14]. It is computed as $[(Q - df)/Q] \times 100\%$, where Q is the χ^2 statistic and df is its degrees of freedom. I^2 values of 25% suggest low inconsistency, 50% moderate inconsistency, and 75% severe inconsistency. If heterogeneity is present, a random effect model to build up the meta-analysis is more appropriate than a fixed effect model [12, 13]. Reviewers may formally explore possible reasons for heterogeneity, inspecting the Forest Plot or using advanced techniques such as meta-regression which employs meta-analytic methods to explore the impact of covariates on the main effect measure [15].

An example of a methodological approach potentially misleading due to heterogeneity of the data is the work of Brilakis et al. [16]. In this case, the authors compared drug-eluting stents (DES) *vs* bare

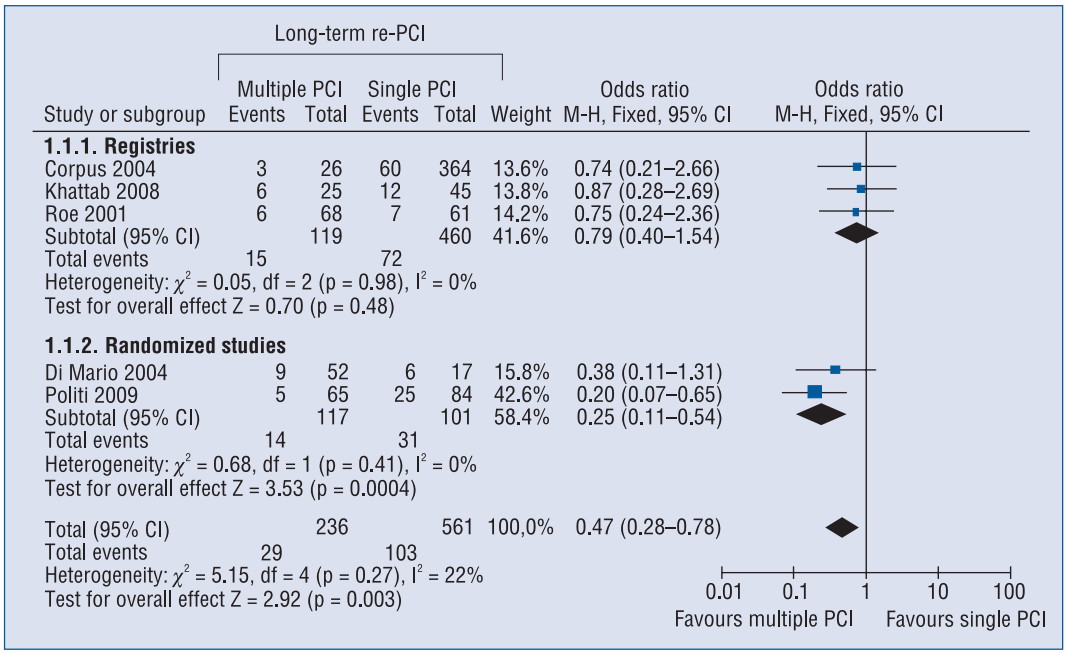

Figure 2. Forest plot of a meta-analysis with subgroups (randomized and non-randomized studies) [17].

metal stents (BMS) in a particular subset of "off-label" indications for DES, saphenous vein graft disease (SVG). In this particular clinical subset, only one small RCT was available in the literature when Brilakis et al. [16] addressed the problem. To overcome this limitation, the authors performed a meta-analysis combining the unique RCT with five retrospective cohort studies, observing a lower incidence of major adverse cardiac events (death, myocardial infarction, or ischemia-driven target SVG revascularization) in DES patients. As a pitfall of this analysis, even if significant heterogeneity was found among the six studies used, they employed the Fixed Effect model for the meta-analysis. Furthermore, no subsequent analysis was performed to explain this heterogeneity.

Subgroups analysis

If the studies are too heterogeneous to be combined sensibly, it is possible that groups of studies are similar, and a decision to combine them may be justified [5]. However, researchers should define these subgroups prior to carrying out the meta-analysis based on clinical elements (e.g. drug treatment or disease condition) to avoid *post-hoc* data manipulation. An example might be derived from the recent study by Navarese et al. [17] where a prespecified analysis for randomized and non-randomized data was applied in the setting of a meta-analysis regarding the multivessel *vs* culprit vessel approach in ST-elevation myocardial infarction (Fig. 2).

Confounders

Confounders and bias are major concerns with non-randomized studies. The MOOSE Group recommends formal assessment and reporting of confounders in reviews of non-randomized studies [1]. In randomized and controlled trials, the exposed and unexposed groups tend to be comparable with respect to confounding variables, while in the non-randomized studies, the reporting of 'crude' estimates without considering potential confounders can lead to biased and heterogeneous results.

So, reporting the highest quality adjusted estimate may be a better strategy than simply combining 'raw' and biased values [1, 5].

Results of the meta-analysis

In a review that comprises both randomized and non-randomized studies, summary results should be presented separately for each of these two broad categories. They must say whether heterogeneity is present and specify the procedure used to investigate its sources. Sensitivity analysis, by removing studies one at a time and comparing the pooled estimates obtained with the original meta-analysis, is another way of evaluating the reliability of data.

Consistency of data

In the 'discussion' section, authors should discuss the strengths and limitations of their meta-analysis. An interesting example of the approach discussed in our review can be found in the recent paper by Kirtane et al. [18]. Here, the authors addressed the problem of comparing the safety and efficacy of DES among a more generalized, real-world population of patients (where off-label use of DES is frequent) and those enrolled in pivotal randomized controlled trials. The authors performed two separate meta-analyses of DES *vs* BMS, one for the RCTs and one for the observational studies. Also, separate unadjusted and adjusted estimates were reported in the analysis and the highest quality estimate available was chosen for the overall meta-analysis. In RCTs, DES (compared to BMS) was associated with no detectable differences in overall mortality or the rate of myocardial infarction occurrence, despite a clear advantage for DES in target vessel revascularization. In observational studies, DES were associated with significant reductions in mortality as well as rates of myocardial infarction occurrence and target vessel revascularization. The authors concluded that DESs are safe and efficacious in both on-label and off-label use, a conclusion supported by the lower mortality observed in observational studies.

Conclusive comments

In conclusion, the scientific literature on meta-analysis of non-randomized trials in interventional cardiology has expanded in recent years. However, the building process has several times been hindered by incorrect procedures of inclusion/interpretation of data, potentially leading to biased estimates and confounding results. This would limit the application of the pooled estimates of the meta-analysis in the real world of public health.

It might be advisable to follow the guidelines reported and the simplified check-list that we suggest when dealing with meta-analysis of non-randomized studies. We think the check-list of items we propose is a simple and useful tool which could help clinical researchers improve their meta-analyses of non-randomized studies.

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