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Meta-analysis of non-randomized studies in interventional cardiology: a critical appraisal

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Abstract

Utilisation of meta-analysis is becoming more and more common in interventional cardiology. The aim of this statistical approach is to collect a large number of patients from randomized clinical studies and non-randomized registries in order to obtain a pooled estimate of the results.

Nevertheless, simply pooling these results without a correct methodological approach can easily lead to biased conclusions. In this report we analyse the possible methodological drawbacks of such an approach and we suggest a simplified check-list of items to be considered in the effort of building-up a meta-analysis from non-randomized studies.

Key words: meta-analysis, randomized controlled trials, non-randomized studies, methodological drawbacks

Background

The meta-analysis is a systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all the relevant prior studies on a specified topic according to a predetermined and explicit method [1]. Meta-analyses of randomized clinical trials (RCT) are employed with increasing frequency in clinical and in particular in cardiovascular research. The strength of this meta-analytical approach is the collection of randomized trials, in which treatment allocation is assigned randomly to patients.

However a lot of topics of cardiovascular medicine are not suitable to randomization and a methodology to employ data arising from non-randomized trials (which are for definition subject to bias in terms of patient selection and treatment allocation) would be of great interest. For instance, the most important randomized studies about 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 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 common adverse effect may only be detected in non randomized observational studies and registries.

Randomization is the only means of controlling for unknown and unmeasured differences between comparison groups as well as those that are known and measured. Random assignment removes the potential of bias in the assignment of patients to one intervention or another by introducing unpredictability [4]. However, including in a meta-analysis also information from registries and observational studies is possible, at the condition 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 were published with minor and sometimes major biases, which in some case leaded to incorrect inclusion of studies and misleading interpretation of data [6].

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

Figure 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, include possibly the 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, if heterogeneity is present and the procedure used to investigate the source of this. Eventually perform final sensivity analysis
7) Discuss clearly the consistency of data, reporting strength and limits of the analysis performed

in the check-list shown in figure 1.

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Quality of studies retrieved

First issue is the methodology to investigate quality of the studies retrieved. In particular, meta-analyses of observational studies face the challenge of incorporating studies with various levels of quality. Incorporating studies of various quality levels can mask or reverse effect direction. In other words quality assessment of the studies offers an estimate of the likelihood that their results will express the truth [7]. Several scales were created in the effort to improve quality investigation of the reports but unfortunately none of them is fully validated. The "Newcastle-Ottawa Scale" (NOS) for assessing the quality of non-randomized studies in meta-analyses is quite comprehensive and has been partly validated; this is the one actually recommended by the Cochrane Non-Randomized Studies Methods Working Group [5].

Publication bias

Another potential confounder, especially in the setting of non randomized studies, is that of "publication bias". Studies with negative results can take longer to be published and results not conforming to the desired outcome may not even be reported. The investigation of this bias can be performed through a graphical test such as the Funnel Plot, which is created by plotting the estimated treatment effect against the study size. A symmetrical plot around a chosen measurement indicates no publication bias. An indication of publication bias would be the absence of small studies with small effects in the Funnel Plot's lower left-hand corner [8]. Furthermore, several methods have been suggested in the literature that translate the graphical approach of the Funnel Plot into a statistical model. It is possible to statistically evaluate the Funnel Plot asymmetry by statistical tests as Begg's method and Egger's test. Begg et al. [9] proposed an adjusted rank correlation method to examine the association between the effect estimates and their variances. Egger et al., [10] introduced a linear regression approach in which the standardized effect size is regressed is into a measure of precision; the greater the value of 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 versions of the graphical test Funnel Plot.

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. Thus 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. 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 is approximately distributed as a chi-squared 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 [11]. As a response to this, while

a 2-tailed p=0.05 is used for cut-off for hypothesis testing of effect, a 2-tailed p=0.1 is conventionally recommended for heterogeneity [12].

So it would be useful to combine this test with another that is more reliable. In order to address this the statistical inconsistency test (I2) has been recently introduced [13]. It is computed as [(Q – df)/Q] x 100%, where Q is the chi-squared statistic and df is its degrees of freedom. I2 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 [11,12]. Reviewers may formally explore possible reasons for heterogeneity, inspecting the Forrest 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 [14].

An example of methodological approach potentially misleading research results due to heterogeneity of the data is the work of Brilakis et al.[15]. In this case the authors compared drug eluting stents (DES) vs bare metal stents (BMS) in a particular subset of "off-label" indications for DES, saphenous graft disease (SVG). In this particular clinical subset only 1 small RCT was available in the literature when Brilakis et al. addressed the problem. To overcome this limitation the authors performed a meta-analysis combining the unique RCT with 5 retrospective cohort studies, observing a lower incidence of MACE (death, MI, or ischemia-driven target SVG revascularization) in DES patients. As a pitfall of this analysis, even if significant heterogeneity was found among the 6 studies used, they used a Fixed Effect model for the meta-analysis. Furthermore no subsequent analysis was performed to explain this heterogeneity.

Subgroups analysis

Even though studies may be 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 the researchers would define these subgroups prior to carrying out the meta-analysis based on clinical elements (e.g. drug treatment or disease condition) in order to avoid post-hoc data manipulation.

Confounders

Confounders and bias are other 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 reporting "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 simple combining "raw" and biased values [1,5].

Results of the Meta-analysis

In the review that comprises both randomized and not randomized studies; summary results should be presented separately for each of these two broad categories. They have to report if heterogeneity is present and the procedure used to investigate the sources of this.

Sensitivity analysis, by removing studies one at time and comparing the pooled estimates obtained with the original meta-analysis, is another way to evaluate the reliability of data.

Consistency of data

In the discussion section, the authors should discuss 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. [16]. In this study the authors addressed the problem of comparing the safety and efficacy (DES) among more generalized "real-world" patients (were "off-label" use of DES is frequent) and those enrolled in pivotal randomized controlled trials.

The authors performed two separate meta-analysis of DES versus BMS, one for the RCTs and another for the observational studies. Also separated unadjusted and adjusted estimates were reported in the analysis and highest quality estimate available was chosen for the overall meta-analysis. In RCTs, DES (compared with BMS) were associated with no detectable differences in overall mortality or myocardial infarction, even if there was a clear advantage for DES in target vessel revascularization. In observational studies, DES were associated with significant reductions in mortality, myocardial infarction and target vessel revascularization. The authors concluded that DES are safe and efficacious in both on-label and off-label use, issue supported by the lower mortality observed in observational studies.

Conclusive Comments

In conclusion, scientific literature of meta-analysis of non-randomized trials in interventional cardiology has grown up in recent years; however the building process often suffered from several

incorrect procedures for the inclusion-interpretation of data, potentially leading to biased estimates and confounding results. This would represent a limit for the application of the pooled estimates of the meta-analysis in the real world of "public health". It might be recommendable to follow the guidelines reported and the simplified check-list that we have provided when dealing with meta-analysis of non-randomized studies. We think the check-list of items we propose and have discussed is a simple and useful tool which can help the clinical researcher to improve his or her meta-analysis of non randomized studies. The particular field of interventional cardiology needs to strictly adhere to such rules if the researchers want to improve the validity and subsequent reliability of their meta-analyses.

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