European Journal of Cardio-Thoracic Surgery 53 (2018) 708–713
doi:10.1093/ejcts/ezy004 Advance Access publication 23 February 2018

REVIEW

Cite this article as: Buccheri S, Sodeck GH, Capodanno D. Statistical primer: methodology and reporting of meta-analyses. Eur J Cardiothorac Surg 2018;53:708–13.

Statistical primer: methodology and reporting of meta-analyses†

Sergio Buccheri[a], Gottfried H. Sodeck[b] and Davide Capodanno[a,*]

[a] Cardio-Thoracic-Vascular Department, Azienda Ospedaliero-Universitaria 'Policlinico-Vittorio Emanuele', University of Catania, Catania, Italy
[b] Department of Emergency Medicine, Waehringer Guertel, Vienna, Austria

* Corresponding author. Cardio-Thoracic-Vascular Department, Azienda Ospedaliero-Universitaria 'Policlinico-Vittorio Emanuele', University of Catania, via Santa Sofia 78, 95100 Catania, Italy. Tel: +39-095-7436201; fax: +39-095-7436105; e-mail: dcapodanno@gmail.com (D. Capodanno).

Received 9 September 2017; received in revised form 11 December 2017; accepted 20 December 2017

Summary

In modern medicine, the results of a comprehensive and methodologically sound meta-analysis bring the most robust, high-quality information to support evidence-based decision-making. With recent developments in newer meta-analytic approaches, iteration of statistical paradigms and software implementations, network and patient-level meta-analyses have recently gained popularity alongside conventional pairwise study-level meta-analyses. However, pitfalls are common in this challenging and rapidly evolving field of statistics. In this regard, guidelines have been introduced to standardize, strengthen and homogenize different aspects of conducting and reporting the results of a meta-analysis. Current recommendations advise a careful selection of the individual studies to be pooled, mainly based on the methodological quality and homogeneity in study designs. Indeed, even if a reasonable degree of variability across study results (namely, heterogeneity) can be accounted for with proper statistics (i.e. random-effect models), no adjustment can be performed in meta-analyses violating the issue of clinical validity and similarity across the included studies. In this context, this statistical primer aims at providing a conceptual framework, complemented by a practical example, for conducting, interpreting and critically evaluating meta-analyses.

Keywords: Statistics • Meta-analysis • Clinical evidence

INTRODUCTION

In modern medicine, the results of a comprehensive and methodologically sound meta-analysis bring the most robust, high-quality information to support evidence-based decision-making. Frequently perceived as the result of mysterious statistical methodologies, *de facto*, a meta-analysis does not bring more complexity but rather a different way of looking at and analysing data.

In the surgical field, meta-analyses have been instrumental in appraising the clinical value and the comparative efficacy of different treatment strategies. As a paradigmatic example, the management algorithm for symptomatic severe aortic stenosis has been recently modified by the introduction of transcatheter aortic valve implantation. To date, a number of randomized clinical trials have compared the safety and efficacy of surgical aortic valve replacement and transcatheter aortic valve implantation. Unfortunately, all these trials are relatively modest sized and have been powered for composite clinical end-points so that robust and definitive answers on single hard end-points (i.e. mortality) cannot be drawn from single studies at this moment. By pooling the results of all available sources, a meta-analysis can address the current gaps in evidence while providing meaningful and directive clinical information. Indeed, pooling of the data increases the statistical power to detect differences in low-frequency events. In such a context, the advantages of a meta-analysis are intuitive and relevant not only from a clinical but also from a regulatory perspective.

In this context, this statistical primer is aimed at reviewing standards of methodology and reporting as well as common pitfalls in the interpretation of meta-analyses.

METHODOLOGY

Types of meta-analysis

Meta-analyses can widely differ with regard to their methodological and analytical aspects. The first relevant difference concerns the statistical framework used to conduct the analysis. For example, a frequentist or Bayesian approach can be employed for pooling the data [1, 2]. Data modelling on a frequentist framework is the conventional and standard methodology most widely used in the medical literature, while the Bayesian approach is gaining popularity. Basically, the 2 methods differ in their view and use of probability. Indeed, probability is also a subjective measure of belief in the Bayesian analysis (prior belief), rather than being only an observed frequency of events in an infinite number of repeated experiments as in the frequentist approach. To further clarify, supposing that a researcher is interested in

†Presented at the 31st Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 7–10 October 2017.

Table 1: Characteristics and softwares for conducting different types of meta-analyses

Typology	Number of compared treatments	Type of studies included	Softwares for analysis			
			Type of analysis	Commercial	Free	R packages
Study-level meta-analysis	Two treatments	Randomized controlled trials	Frequentist	MedCalc, Comprehensive Meta-Analysis, SAS, STATA, SPSS[a]	RevMan, OpenMeta	Meta and Metafor
		Observational studies Combination of observational and randomized studies	Bayesian	SAS, STATA	OpenBUGS, JAGS, Stan	Bmeta, rjags, R2WinBUGS
Study-level network meta-analysis	More than 2 treatments	Randomized controlled trials	Frequentist	SAS, STATA		Netmeta
		Observational studies Combination of observational and randomized studies	Bayesian	SAS, STATA	OpenBUGS, JAGS, Stan	GEMTC, pcnetmeta
Patient-level meta-analysis	No restrictions	Individual characteristics of patients included in randomized controlled trials and observational studies		Standard statistical softwares		

[a]Free macros available at http://mason.gmu.edu/∼dwilsonb/ma.html [6].

finding out whether coronary artery bypass grafting using bilateral internal mammary arteries improves graft patency at 5 years with respect to the conventional approach of using arterial and vein grafts during interventions and if he wants to find this answer in a frequentist manner, he has to randomize a sufficient number of patients and collect their outcomes during the study follow-up. With these observations (repeated experiments), he will be able to calculate and subsequently infer the treatment option associated with the highest frequency (i.e. probability) of graft patency at 5 years. Now, suppose also that, based on the available evidence at the time of the study, he believes that panarterial bypass grafting may increase patency rates. Using a Bayesian approach, he can include this information (defined as prior belief) to refine his calculations. Similar to the frequentist approach, he will continue to enrol patients and observe their outcomes, but prior knowledge and his belief will be taken into account to finally assess the treatment modality with the highest probability of graft patency (i.e. the Bayesian posterior probability). In meta-analyses, the same conceptual framework of the above example holds true, but single studies in the literature represent the unit of analysis.

Meta-analyses can also differ on the number of therapeutic or treatment strategies that are compared. In conventional pairwise meta-analyses, 2 different strategies are compared ($n = 2$), while in network meta-analyses, multiple treatment options ($n \geq 3$) are simultaneously evaluated in terms of their comparative efficacy [3, 4]. Additionally, a network meta-analysis allows for ranking of different treatment options that have been evaluated in the network and, by combining direct and indirect evidence, also provides more robust estimates of the comparative treatment effect for therapeutic strategies that have rarely been investigated in a head-to-head manner in the literature.

Finally, methodological differences in meta-analyses depend on the type of data that are used in the analysis. Indeed, in a study-level meta-analysis, published reports in the literature are used to extract the total number of events and summary characteristics. On the contrary, patient-level meta-analyses [5] are conducted by merging data sets with individual characteristics of patients, thus allowing for a detailed assessment of time-to-event statistics (i.e. survival curves and landmark analysis), multivariable analyses to adjust for confounding and the evaluation of the consistency of results in clinically relevant subgroups. Table 1 summarizes the characteristics of different types of meta-analyses and the available softwares for analysis.

Study selection and quality issues in a meta-analysis

All published guidelines for conducting meta-analyses [7] advocate a rigorous screening of the literature, using different sources of evidence, as the crucial step before pooling the data. Preferentially based on a prespecified protocol, the selection of individual studies should be based on the methodological quality and homogeneity in study designs. Indeed, even if a reasonable degree of variability across study results (namely, heterogeneity) can be accounted for with proper statistics (i.e. random-effect models), no adjustment can be performed in meta-analyses, violating the issue of clinical validity and similarity across the included studies.

In this context, the PICO strategy represents a simple and useful framework to guide in the selection of a homogeneous group of studies to be pooled [8]. The PICO acronym stands for person, intervention, comparison and outcomes. During the literature review process, all these aspects should be carefully checked for consistency across candidate studies for inclusion in a meta-analysis. Also, the review process should be preferentially performed by 2 separate investigators, keeping careful track of the number and reasons for which studies have been excluded. Potential pitfalls at this stage (see points 1 and 2 in Table 2), such as the inclusion of studies with overlapping patient cohorts and the literature search restricted to a single database, should be avoided.

The quality of the selected studies is equally important. Restricting a meta-analysis to randomized controlled trials (RCTs)

increases the likelihood of reporting unbiased estimates. Indeed, randomization is protective against bias and minimizes the risk of confounding from known and unknown causes. On the contrary, observational studies are more prone to bias and, even if statistical adjustment may account for measured differences between groups, there is always the chance of bias due to unmeasured confounding. Unfortunately, the absolute number of RCTs with a similar design is generally scant in the medical literature and, actually, a trade-off between quality and inclusiveness exists in meta-analyses. Combining the results of observational studies and RCTs should be cautiously considered even when data from RCTs are either limited or insufficient. Moreover, when combining different types of studies, proper techniques should be employed to reduce the risk of reporting biased pooled estimates (i.e. down-weighting the evidence carried by observational studies as compared to RTCs). Figure 1 graphically summarizes a proposed sub-ranking of quality among different types of meta-analyses.

Table 2: Frequent issues and pitfalls encountered in meta-analyses

Common statistical pitfalls
Inclusion of studies with overlapping data (i.e. some patients contributing to the results of multiple studies)
Literature search limited to a single database[a]
Assessment of heterogeneity and inconsistency
Selection of random- versus fixed-effect model
Identification of proper outcome measure
Addressing different lengths of follow-up across studies
Accounting for differences in the design of included studies (RCTs versus observational)
Ignoring difference in the methodological quality across included studies
Exploring sources of heterogeneity (subgroup analysis and meta-regression)

[a]The following databases should be investigated for a comprehensive literature search: PubMed, Cochrane Library, Google Scholar, Embase, Scopus, ScienceDirect, Web of Science, major scientific or congress websites.

Statistical analysis: methodological background

After the literature screening and selection of studies has been completed, data are ready to be pooled. A sound statistical background may help to prevent common pitfalls encountered at this step (Table 2).

The goal of a comparative meta-analysis is to define a unique summary measure defined as effect size (ES), which gives information on the direction of the treatment effect (harmful or beneficial) and its magnitude. The ES is always complemented by a range of putative values because of uncertainty in estimation [i.e. confidence or credible interval in frequentist and Bayesian analyses (CI and CrI), respectively]. A CI/CrI expresses the amount of uncertainty (i.e. precision) around the ES and carries information on statistical significance. Wide CIs/CrIs reflect poor accuracy around the ES, while CIs/CrIs crossing 1 for relative risk-type effects or CIs/CrIs including 0 for continuous measures express a null treatment effect. The proper selection of the ES measure depends on the type of outcome that has to be summarized (time-to-event, dichotomous or continuous). For time-to-event data, the hazard ratio (HR) should be reported, while for dichotomous outcomes, the odds ratio, risk ratio or risk difference can be used as ES. Finally, when continuous outcomes are compared, the mean difference or the standardized mean difference can be employed.

Statistical heterogeneity and selection of a random- or fixed-effect model

The selection of a random- or fixed-effect model is a crucial step before pooling the data. This is based on the presence or absence

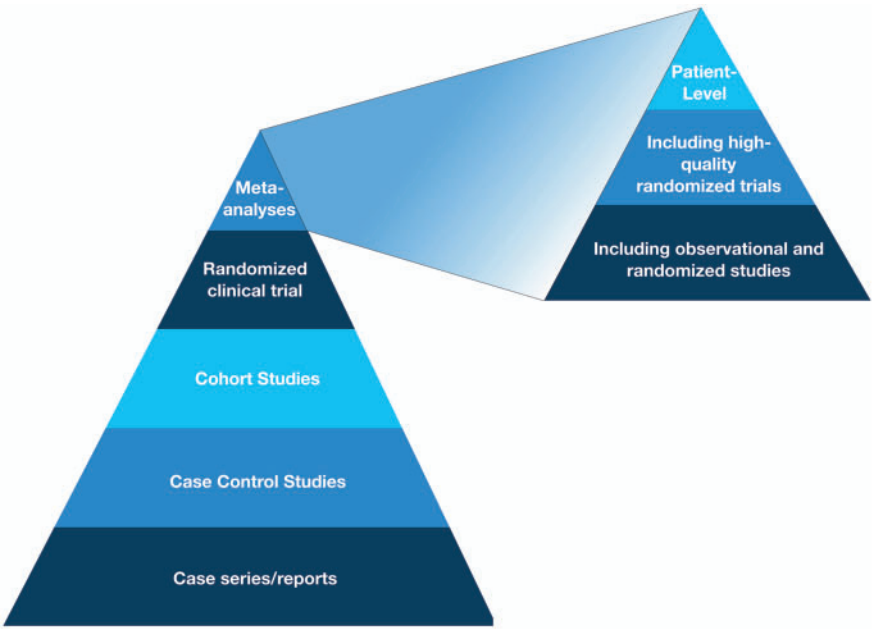

Figure 1: Proposed sub-ranking of evidence in meta-analyses. Because of several advantages in the estimation of the treatment effect, patient-level meta-analyses are ranked at the top of the pyramid of evidence in meta-analyses.

of statistical heterogeneity, defined as the amount of variability across study results included in the meta-analysis [9]. Sources of heterogeneity arise from methodological, clinical and random variability across studies. Historically, a relevant source of heterogeneity the in cardiothoracic surgery meta-analysis literature came from inconsistent definitions of the same clinical end-point between studies. The use of standardized definitions endorsed by international scientific societies may be instrumental in overcoming this methodological shortcoming [10].

Heterogeneity is quantified by the Cochrane's Q statistic and the I^2 value [11]. The Q statistic has a χ^2 distribution, and the *P*-value obtained with this test informs on the presence of heterogeneity (*P*-values <0.1 are considered indexes of significant heterogeneity). The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance (I^2 values between 25% and 50% are considered indexes of moderate heterogeneity, while values above 50% are the expression of severe heterogeneity). In addition, other methods can be used to investigate the presence of heterogeneity while complementing the results of the above-mentioned statistical tests. In particular, visual inspection of forest plots to check the presence of severe asymmetry in treatment effect estimates, specific plots to explore heterogeneity (radial or L'Abbé plots) [12], sequential exclusion of individual studies to understand the individual contribution of a single study to the total amount of heterogeneity, meta-regression and subgroup analyses (see later) can all be employed to fully apprise the presence of heterogeneity in a meta-analysis. When heterogeneity is found, a random-effect model has to be preferred because the variability in results across studies is accounted in the model. The DerSimonian and Laird method is a standard approach in random-effect meta-analyses, but it has been questioned when the number of studies is modest. In this case, the Knapp–Hartung random-effect model should be preferred [13]. Conversely, a fixed-effect model should be used when heterogeneity is low or absent. Of note, pooling in the presence of extreme heterogeneity should be avoided because the risk of reporting inaccurate and biased pooled treatment effect estimates becomes too high.

Accounting for the different lengths of follow-up across studies

One of the most important but often neglected aspects in meta-analyses is the proper management of studies with different lengths of follow-up. Pooling the results at a constant time interval across selected studies should be the default and preferred strategy, but this approach is often not practicable because the length of follow-up often varies across studies. Because the comparative treatment effects of different interventions may diverge over time (i.e. due to the increased number of events accruing with time), totally ignoring time-dependent effects of an intervention may lead to biased estimates. Different approaches can be used to overcome this issue. First, a simple yet effective strategy is that of assessing the relationship existing between the length of follow-up and the ES measures (i.e. by meta-regression analysis). If no association is found, pooling studies with a different follow-up is assumed to be reasonable. However, this approach can be inaccurate if the number of studies included in the meta-regression analysis is small. Alternatively, pooling the HR measures can represent an alternative option because the HR measure is independent of time. Unfortunately, the HR measure is not uniformly reported across studies and randomized trials. Some methods have been developed to overcome this issue. The first is based on digitized survival curves and inverted Kaplan–Meier equations to obtain individual patient time-to-event data [14]. A second method uses different mathematical equations to obtain the log HR from published studies [15]. A nice example of the digitized survival curve method has been recently reported [16]. Finally, specific statistical models (i.e. Poisson regression analysis) can aptly account for the varying length of follow-up between studies [17].

Addressing differences in the typology and methodological quality of the included studies

As reported above, the quality of a meta-analysis mirrors the methodological quality of the included studies. Addressing such differences is of crucial importance for the reliability of the pooled estimates. First, if either observational studies or RCTs have been included, separate analyses should be performed (i.e. by subgroup analysis) to assess the consistency of ES estimates between different types of studies. Additional techniques for handling and combining different sources of evidence into a meta-analysis have also been developed by down-weighting the information carried by observational studies [18]. Finally, a further stratification of the methodological quality in RCTs and observational studies should be performed using dedicated scales (Cochrane collaboration tool, Jadad and GRACE scales), and consistency of results should be then verified in analyses restricted to studies of high methodological quality.

Investigating sources of heterogeneity and publication bias

Even if statistical heterogeneity is accounted for in a random-effect model, investigating its sources among clinical and methodological characteristics of the included studies should be performed using either subgroup or meta-regression analyses. Results of these exploratory analyses should be cautiously interpreted and generalized [19]. Finally, the assessment of publication bias should be performed by visual inspection of funnel plot asymmetry and complemented by objective statistics (trim-and-fill method and Begg's and Egger's tests). Publication bias can be viewed as a 'literature distortion', depending on the selective publication of studies with significant results (e.g. impactful findings) as compared to studies with neutral/inconclusive results. In the absence of publication bias, scatters inside a funnel plot [with each scatter representing the estimated treatment effect (*x*-axis) against the standard error/precision (*y*-axis)] should be symmetrically distributed. Shortcomings of performing pooled analyses in the presence of publication bias are evident because treatment effect estimates will be inflated rather than being balanced.

REPORTING

Standards for the reporting of meta-analyses have been advocated and promoted by experts and international cardiovascular societies. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and its extension on network and individual patient meta-analyses currently represent the standards to homogenize and improve the methodological

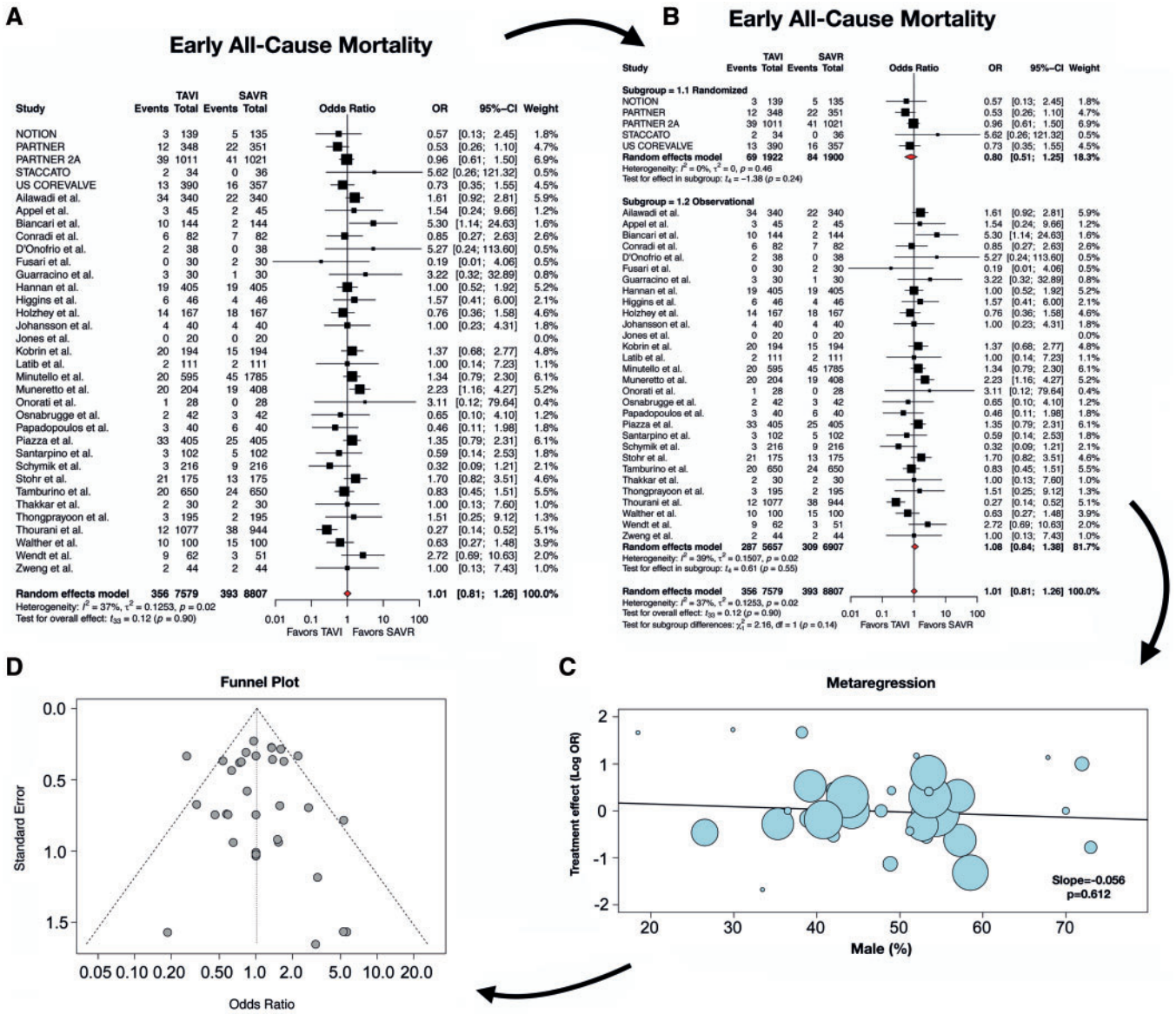

Figure 2: A practical example of a comparative meta-analysis of early mortality in TAVI versus surgery studies. (**A)** The pooled results of RCTs and observational studies are shown. (**B**) The results are consistent between RCTs and observational studies. (**C**) A bubble plot from meta-regression analysis exploring whether the percentage of male patients included in each study acts as a treatment effect modifier. (**D**) The funnel plot with symmetrical distribution of studies and no concerns as regards publication bias are shown. CI: confidence interval; OR: odds ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

quality of meta-analyses [20–22]. The PRISMA checklist is shown in Supplementary Material, Fig. S1. A corresponding PRISMA checklist should be provided with every published meta-analysis. Also, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines should be considered when reporting meta-analyses of observational studies [23].

EXAMPLE

An example of the practical advantages of using a meta-analysis to inform and guide surgical practice has been presented in the introduction of this article (e.g. comparing mortality in transcatheter aortic valve implantation versus surgery). We can address our initial aim by conducting a conventional pairwise study-level meta-analysis, with the OR used as the ES measure. Building on this, the forest plot for mortality (at 30 days), obtained with the Knapp–Hartung random-effect model, is shown in Fig. 2A. Data used in the analysis are based on Gargiulo *et al.* [24]. The random-effect model has been selected because moderate heterogeneity is present (37% by I^2 statistic). Moreover, because our meta-analysis has included both observational and randomized studies, a subgroup analysis based on a separate analysis of RCTs and observational studies has been performed and is shown in Fig. 2B. Of note, the *P*-value for interaction is not significant ($P = 0.14$), showing, therefore, that the ES is consistent between RCTs and observational studies. Figure 2C shows the results of meta-regression analysis (bubble plot) as a graph, investigating whether the percentage of male patients included in each study acted as a treatment effect modifier. This relationship was not statistically significant ($P = 0.612$). A funnel plot with symmetrical distribution of studies (no concerns for publication bias) is shown

in Fig. 2D. The Egger's and Begg's tests also showed no concerns as regards publication bias. The R command used for analysis is provided in the Supplementary Material, Appendix S1.

FURTHER READING

Readers are also invited to refer to recently published meta-analyses in the *European Journal of Cardio-Thoracic Surgery* and the *Interactive CardioVascular and Thoracic Surgery* for further examples of good quality experimental methodology and reporting on cardiothoracic meta-analysis literature [25, 26]. Also, the *Cochrane Handbook for Systematic Reviews of Interventions* may offer a straightforward and comprehensive overview of proper methodology and reporting in meta-analyses, also focusing on specific issues such as the inclusion of observational studies [27].

CONCLUSIONS

Meta-analyses are powerful tools to evaluate the available evidence and draw useful information to guide therapeutic decision-making in everyday clinical practice. Simple methodological rules and a tailored, step-by-step statistical approach should be considered to preserve the reliability and clinical value of this methodology.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Copetti M, Fontana A, Graziano G, Veneziani F, Siena F, Scardapane M *et al*. Advances in meta-analysis: examples from internal medicine to neurology. Neuroepidemiology 2014;42:59–67.

[2] Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health 2008;11:956–64.

[3] Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med 2011;9:79.

[4] Chaimani A, Salanti G, Leucht S, Geddes JR, Cipriani A. Common pitfalls and mistakes in the set-up, analysis and interpretation of results in network meta-analysis: what clinicians should look for in a published article. Evid Based Ment Health 2017; doi: 10.1136/eb-2017-102753 [Epub ahead of print].

[5] Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221.

[6] Lipsey MW, Wilson DB. Practical Meta-Analysis. Sage Publications, 2001.

[7] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[8] Uman LS. Systematic reviews and meta-analyses. J Can Acad Child Adolesc Psychiatry 2011;20:57–9.

[9] Fletcher J. What is heterogeneity and is it important? BMJ 2007;334:94–6.

[10] Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T *et al*. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2017;52:408–17.

[11] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[12] Anzures-Cabrera J, Higgins JP. Graphical displays for meta-analysis: an overview with suggestions for practice. Res Synth Methods 2010; doi:10.1002/jrsm.6.

[13] IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 2014;14:25.

[14] Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

[15] Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.

[16] Giacoppo D, Colleran R, Cassese S, Frangieh AH, Wiebe J, Joner M *et al*. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis. JAMA Cardiol 2017;2:1079.

[17] Guevara JP, Berlin JA, Wolf FM. Meta-analytic methods for pooling rates when follow-up duration varies: a case study. BMC Med Res Methodol 2004;4:17.

[18] McCarron CE, Pullenayegum EM, Thabane L, Goeree R, Tarride J-E, Rogers S. Bayesian hierarchical models combining different study types and adjusting for covariate imbalances: a simulation study to assess model performance. PLoS One 2011;6:e25635.

[19] Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21:1559–73.

[20] Vrabel M. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Oncol Nurs Forum 2015;42:552–4.

[21] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777.

[22] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G *et al*. Preferred reporting items for a systematic review and meta-analysis of individual participant data. JAMA 2015;313:1657.

[23] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

[24] Gargiulo G, Sannino A, Capodanno D, Barbanti M, Buccheri S, Perrino C *et al*. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a systematic review and meta-analysis. Ann Intern Med 2016;165:334.

[25] Sá MP, Cavalcanti PE, Santos HJ, Soares AF, Miranda RG, Araújo ML *et al*. Flow capacity of skeletonized versus pedicled internal thoracic artery in coronary artery bypass graft surgery: systematic review, meta-analysis and meta-regression. Eur J Cardiothorac Surg 2015;48:25–31.

[26] Giglio M, Dalfino L, Puntillo F, Rubino G, Marucci M, Brienza N. Haemodynamic goal-directed therapy in cardiac and vascular surgery. A systematic review and meta-analysis. Interact CardioVasc Thorac Surg 2012;15:878–87.

[27] Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Cochrane Book Series. 2008; doi:10.1002/9780470712184.fmatter.