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Discordances originated by multiple meta-analyses on interventions for myocardial infarction: a systematic review

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Abstract

Objectives: To clarify the impact of multiple (covering the same population, intervention, control, and outcomes) systematic reviews (SRs) on interventions for myocardial infarction (MI).

Study Design and Setting: Clinical Evidence (BMJ Group) sections and related search strategies regarding MI were used to identify multiple SRs published between 1997 and 2007. Multiple SRs were classified as discordant if they featured conflicting results or interpretation of them.

Results: Thirty-six SRs (23.5% of 153 on the treatment or prevention of MI) were classified as multiple and grouped in 16 clusters [ie, at least two SRs with the same PICO (population, condition/disease, intervention, control) and at least one common outcome] exploring angioplasty, angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelets, β-blockers, and stents. Complete agreement on statistically significant differences between interventions was found in 7 of 10 clusters with a shared composite outcome. Agreement was reduced when single outcomes were considered. Despite substantial variation and limited agreement in reporting of major outcomes, SRs agreed in their conclusions on the superiority of either the intervention or control in 14 of 16 clusters. Sources of minor discrepancies were found in terms of study and outcome selection, subgroup analyses, and interpretation of findings.

Conclusion: Multiple SRs agreed in their qualitative conclusions but not on reporting and on analyses of hard outcomes. Discordance on significance of treatment effects was due to a combination of variation in design with inclusion of different studies and lack of precision for single hard outcomes compared with a composite outcome. Such inconsistencies among SRs could potentially slow the translation of

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SRs' results to clinical and public health decision making and suggest the need for a broader methodological and clinical agreement on their design.

Keywords: Cardiovascular agents; Dissent and disputes; Evidence based medicine; Meta-analysis; Myocardial infarction; Policy making

1. Introduction

The number of systematic reviews (SRs) published has risen in the past decade with approximately 2,500 new publications indexed annually on MEDLINE [1]. This increases the likelihood of finding multiple overlapping reviews [2] that present conflicting results.

The term ''systematic'' implies that the process and methodology of generating a review, in addition to being exhaustive, are valid, transparent, and well reported such that other independent researchers following the same methods can replicate the same results and, therefore, arrive at the same conclusions [3,4]. In 1997, Jadad et al. [5] first addressed the issue of how to appraise discordant evidence originating from multiple but similar SRs. Similar SRs have the same objective but might differ at the level of the results or their interpretation. In such cases, the review featuring the most comprehensive literature search, explicit and reproducible selection of studies, and a quality assessment of the primary studies should be preferred. There are some examples of discordant SRs that have generated controversy [6–8]. One emblematic case study explored the results of 10 multiple SRs focused on the role of acetylcysteine in the prevention of contrast-associated nephropathy [9]. Five reviews recommended routine use of acetylcysteine, whereas the others were more cautious and called for further trials. There exists little empirical evidence about the multiplicity cumulative phenomenon.

The aim of this article was to assess the scientific validity and reproducibility of results in multiple SRs examining the health effects of interventions for a cardiovascular disease such as myocardial infarction (MI). We focused on a cohort of SRs published between January 1997 and December 2007. These SRs are the potential, key drivers of actual clinical practice and can help elucidate the impact of discordances on practice for cardiovascular diseases.

2. Methods

We have described the rationale, design, and methods in detail in a previous publication [10]. Briefly, the eligibility of studies was assessed, independently, by two reviewers across all phases in accordance to standard rules and implementing ad hoc forms. Disagreements were resolved by consensus; arbitration with a third reviewer was possible when necessary. We kept double entry of all details to ensure data quality.

Our study was carried out in six phases.

Phase 1. We carried out a systematic search process starting from Clinical Evidence search strategy process, as described elsewhere [10]. Clinical Evidence is the BMJ Group medical textbook synthesizing biomedical evidence on a wide range of globally important clinical conditions [11]. We focused on the MI Clinical Evidence chapter presenting interventions encompassing the primary and secondary prevention on MI. The Clinical Evidence search strategy was based on strategy process and outputs developed a priori and performed by BMJ Evidence Centre information specialists (Clinical Evidence Study design search filters, available at http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html). The search strategy was adapted to MI prevention and applied to MEDLINE, Embase, and Cochrane Register of Controlled Trials (Central) to capture all potential overlapping SRs. We checked, also, the reference list of all selected SRs to identify other relevant SRs.

Phase 2. We screened the titles and abstracts to identify SRs investigating the efficacy of treatments for coronary artery disease, including both pharmacological and procedural interventions. We included publications that mentioned the terms ''systematic review'' or ''meta-analysis'' in the title or abstract or reported to have searched at least one bibliographic database. We searched SRs published from January 1997 to December 2007 in English, Italian, Spanish, or French.

Phase 3. We extracted information from the title and abstract to identify potential, multiple SRs. Potential multiplicity was defined as at least two independent SRs sharing the same population condition/pathology and intervention, irrespective of differences in outcomes and controls. Reasons for exclusion, such as duplicate publication or narrative nature of review, were documented.

Phase 4. We accessed the full text of reviews, analyzing the overlap between controls and outcomes. Thus, we identified clusters of at least two SRs with the same PICO (population, condition/disease, intervention, control and at least one outcome) and objective. These were classified as clinically homogeneous (ie, multiple SRs). SRs considering several drugs or interventions could have been grouped in more than one cluster.

Phase 5. We completed an analytical characteristic report for each SR within a cluster, determining the clinical features, design (eg, inclusion criteria), methods, and the publication history. We used the checklist by Oxman and Guyatt [4] to assess the quality of included SRs. When a previous review was cited, we abstracted the authors' rationale for repeating the review, if reported [12].