

Disorganized Systematic Reviews and Meta-analyses: Time to Systematize the Conduct and Publication of These Study Overviews?

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Introduction

- Since initial publication in 1979, meta-analyses and systematic reviews are becoming more and more popular
- Evidence frequently incorporated in guidelines and clinical decision making
- Increase statistical power and ability to discover potentially meaningful findings when studies are combined
- Identify gaps and methodological flaws in existing medical and public health literature
- Assist in identifying possible sources of heterogeneity between investigations
- Generate important future research directions

Introduction Cont.

- Useful in avoiding redundant research
 - For example, a SR of 64 published trials revealed that the role of aprotinin in reducing the risk of bleeding in patients undergoing cardiac surgery could have been established after the 12th published trial, thereby avoiding the extensive funding and effort devoted to the subsequent conduct of 52 additional clinical trials

Downside?

- Logarithmic increase in publications has been accompanied by redundant publications
 - Survey in 2010 showed approx. two-thirds of meta-analyses are followed by a redundant meta-analysis

Redundant publications are usually thought of as research reported by the same investigator and sent to 2 or more different journals

Purpose of Report

- Review the published literature and identify examples of redundant and disorganized systematic reviews and analyze one example in detail
- Provide recommendations that could help improve the conduct and publication of SR's

Methods

- Searched Medline using the search term “meta-analysis” as publication type during the past 20 years
- Search performed at 2 time points: 1994 and 2014
- Identified examples using a modified strategy described by Konstantinos et al
 - Case study: redundant meta-analyses involving the use of transcatheter closure devices for patent foramen ovale vs medical therapy in patients with cryptogenic stroke
- Searched citations using Medline, Embase, Web of Science, Cochrane Library, and conference proceedings using the following search terms: patent foramen ovale, inter-atrial shunt, transcatheter closure, and cryptogenic stroke
- Critically examined potential reasons to explain the redundancy and disorganization

Results

Magnitude of Redundant Systematic Review and Meta-analysis Publications

- Medline search (via Pubmed): 8000 new MA's or SR's are being indexed annually in Medline every year
 - 24 new MA's daily
- Number of MA's published annually has increased more than 20-fold during the period 1994 (n = 386) to 2014 (n = 8203)
- Identified at least 10 topics that were the subject of a minimum of 10 MA's

Table 1 Examples of Overlapping Systematic Reviews and Meta-analyses

Topic	No. of Overlapping Systematic Reviews and Meta-analyses
Comparison of laparoscopic and open surgery for colorectal cancer	27
Vitamin D supplements and fracture	24
Transcatheter patent foramen ovale closure vs medical therapy for cryptogenic stroke	17
Efficacy and safety of new oral anticoagulants in atrial fibrillation	15
Prevention of colorectal cancer	13
Pharmacological treatment in fibromyalgia	12
Percutaneous coronary intervention vs coronary artery bypass graft surgery in patients with left main coronary artery disease	12
Statins for prevention for atrial fibrillation	11
Anterior cruciate ligament reconstruction comparing hamstring autograft with bone-patellar tendon bone autograft	11
Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes in clopidogrel users	11
Antiepileptics for refractory epilepsy	8
Intracoronary vs intravenous administration of abciximab	8

Results

Case Study

- Using the example of foramen ovale closure: 17 MA's using published information from only 3 RCT's
 - Among these 17 MA's, 13 were published over a short duration of 6 months

Table 2 Examples of Redundant Meta-analysis on a Single Topic: Transcatheter Patent Foramen Ovale Closure vs Medical Therapy for Cryptogenic Stroke

Authors	Publication Time	Primary Endpoint	Type of Analysis	Results	Secondary Outcomes	Studies Included	Type of Meta-analysis
Kwong et al ¹²	October 2013	Stroke TIA All-cause mortality	Random	Stroke OR 0.65 (0.36-1.20) TIA HR 0.77 (0.45-1.32) Mortality OR 0.65 (0.23-1.85)	New-onset AF Bleeding	CLOSURE I RESPECT PC TRIAL	Individual studies
Ntaios et al ¹³	October 2013	Stroke	Fixed	Stroke OR 0.64 (0.37-1.10)	TIA Death MI New-onset AF	CLOSURE I RESPECT PC TRIAL	Individual studies
Moreno et al ¹⁴	November 2013	Composite endpoint of death and recurrent vascular events	Random	Composite endpoint HR 0.67 (0.44-1.00)	AF Bleeding	CLOSURE I RESPECT PC TRIAL	Individual studies
Nagaraja et al ¹⁵	November 2013	Stroke TIA	Random	Stroke OR 0.65 (0.36-1.19) TIA OR 0.77 (0.41-1.43)	AF Major vascular complications	CLOSURE I RESPECT PC TRIAL	Individual studies
Pineda et al ¹⁶	November 2013	Composite of stroke and TIA	Random	Composite endpoint OR 0.70 (0.47-1.05)	Stroke and TIA individually	CLOSURE I RESPECT PC TRIAL	Individual studies
Hakeem et al ¹⁷	November 2013	Composite of stroke, death, and fatal stroke	Random	Composite endpoint RR 0.70 (0.48-1.06)	Adverse events	CLOSURE I RESPECT PC TRIAL	Individual studies
Riaz et al ¹⁸	December 2013	Composite of stroke, TIA, and death	Random	Composite endpoint HR 0.66 (0.43-1.01)	AF Bleeding	CLOSURE I RESPECT PC TRIAL	Individual studies
Khan AR et al ¹⁹	December 2013	Stroke	Fixed	HR 0.67 (0.44-1.00)	—	CLOSURE I RESPECT PC TRIAL	Individual studies
Salas-Gutierrez et al ²⁰	2013	Composite of stroke, TIA, and death	Random	Composite endpoint RR 0.72 (0.49-1.06)	—	CLOSURE I RESPECT PC TRIAL	Individual studies
Chen L et al ²¹	February 2014	Composite of stroke and TIA	Fixed	Composite of stroke and TIA RR 0.70 (0.47-1.04)	Death	CLOSURE I RESPECT PC TRIAL	Individual studies
Capodanno D et al ²²	March 2014	Stroke	Random	For RCTs, stroke HR	New-onset AF	CLOSURE I	Individual studies

- 11 were published in cardiology journals
- 2 were published in neurology journals

Table 2 Continued

Authors	Publication Time	Primary Endpoint	Type of Analysis	Results	Secondary Outcomes	Studies Included	Type of Meta-analysis
Spencer FA et al ²³	March 2014	Stroke	Random	Stroke RR 0.61 (0.34-1.07)	—	CLOSURE I RESPECT PC TRIAL	Individual studies
Wolfrum et al ²⁴	March 2014	Stroke	Random	For RCTs, stroke RR 0.66 (0.37-1.19) For observational studies, stroke RR 0.37 (0.20-0.67)	Bleeding Death AF	CLOSURE I RESPECT PC TRIAL And 11 observational	Individual studies
Pandit A et al ²⁵	April 2014	Stroke	Fixed	Stroke HR 0.62 (0.36-1.07)	—	CLOSURE I RESPECT PC TRIAL	Individual studies
Pickett CA et al ²⁶	August 2014	Composite of stroke, death, and TIA	Random	Composite endpoint HR 0.67 (0.44-1.01)	Bleeding AF	CLOSURE I RESPECT PC TRIAL	Individual studies
Udell JA et al ²⁷	October 2014	Composite of stroke and TIA	Random	Composite endpoint RR 0.73 (0.50-1.07)	AF	CLOSURE I RESPECT PC TRIAL	Individual studies
Stortecky S et al ²⁸	January 2015	Stroke	Random	Stroke RR 0.39 (0.17-0.84)	TIA AF All-cause mortality	CLOSURE I RESPECT PC TRIAL Hornung et al	Networking

In "Results" column, values in parentheses are 95% confidence intervals.

AF = atrial fibrillation; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; TIA = transient ischemic attack.

Results

Case Study Cont.

- 3 published RCT's were quite similar
 - All 3 trials failed to demonstrate the superiority of percutaneous closure over the use of medical therapy using the intention-to-treat analysis

Table 3 Study Characteristics of 3 Randomized Controlled Trials on Transcatheter Patent Foramen Ovale Closure vs Medical Therapy for Cryptogenic Stroke

Trial Name	N	Follow-Up (y)	Age (y)	Primary Endpoint	Endpoint Outcomes, n (Closure vs Medical)	Outcome Measure
CLOSURE	909	2.0	46.0	Composite of stroke or TIA and death	23 vs 29	HR 0.78 (0.45-1.35)
PC	414	4.1	44.5	Composite of death, nonfatal stroke, TIA, and peripheral embolism	7 vs 11	HR 0.63 (0.24-1.62)
RESPECT	980	2.1	45.9	Composite of death, nonfatal and fatal stroke	9 vs 16	HR 0.49 (0.22-1.11)

Values in parentheses are 95% confidence intervals.
HR = hazard ratio; TIA = transient ischemic attack.

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Values in parentheses are 95% confidence intervals.
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- Results and interpretation of the RCT results in the meta-analyses, using data from the same 3 trials, were quite diverse
- Authors from 9 studies concluded that there was no benefit of transcatheter patent foramen ovale closure vs medical therapy, whereas the authors from 4 studies interpreted the results in favor of transcatheter closure of patent foramen ovale

Results

Case Study Cont.

- After careful review, differences in results could have been due to:
 - Different definitions of the primary trial endpoints
 - Utilization of different software for analysis
 - Variability in the models used for analysis (such as fixed vs random effects)
 - Different choices for the measures of effect, as well as different interpretation of similar results

Issues

- Lack of quality among many reviews
 - For Ex. Often when describing results there was inappropriate interpretation and account of heterogeneity, as well as a lack of subsequent analyses based on prior analyses
- Most analyses did not use the already established Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the quality of included studies
- The first 16 MA's did not note that there is substantial bias when the MA involved a small number of studies
 - Thus, it is pertinent to note that 16 SR's were performed before a network MA was performed that compared different devices and included data from 4 trials.

Findings in Context

- Quality of published SR's should be tightly regulated
 - Characteristics such as trial selection, primary and secondary outcome selection, adequacy of their characterization, and analytic methods examined more carefully to identify sources of bias or difference in reported results
- Report outcomes compared with protocols
 - For Ex.
 - Bolland and Grey examined 7 published MA's looking at the effects of vitamin D supplementation on bone fractures and found that 4 studies did not include all the potentially eligible studies, and 2 studies included trials that clearly did not meet their eligibility criteria.
 - A study inspected 288 SR's with their protocols and found that every fourth SR had at least 1 discrepant outcome in the completed review

Upside?

- Redundant MA's can improve the reliability of a given finding by pointing out the occasional errors, such as incorrect inclusion or exclusion of a study and errors in data extraction

More Cost than Benefit?

- Most reviewers work unpaid and are taking time out from their own work to perform peer review
- Adverse effect on a journal's impact factor, because the various journals that have published similar MA's will be competing for the citations on the same topic
- When the redundant MA is published, editors might have to reject excellent-quality work from other investigators because of space constraints

Reasons for the Redundant and Disorganized Systematic Review Publications

- Lack of registration of SR's
 - An evaluation of 300 SR's demonstrated that none of them had been registered into a central source
- Journals that have a long lag time between receiving a manuscript and publishing the article
- Publication of updated versions of previously published SR's
 - 20% of new MA's belong to this category

The Way Forward and Formulation of Recommendations: Registration of Systematic Reviews and Meta-analyses

- Mandatory registration, such as PROSPERO
 - Promote transparency
 - Reduce bias
 - Avoid selective reporting biases as well as duplication and meta-analyses by maintaining a public record
- Enable authors who are planning to undertake new reviews to check whether there are any similar reviews “in the pipeline,” thereby ensuring that global research funding would be invested astutely

What is PROSPERO?

- An open public access and user-friendly registry with no charges for registering a study protocol
- Required nominated named contact, such as the corresponding author, to ensure that the submitted information is valid and updated when necessary
- Required submission of a minimum dataset so that protocols can only be registered once for a SR
- After acceptance of the protocol, unique number is assigned
- Records are permanent
- Allows amendments to the protocols when deemed necessary by the authors, changes are visible to ensure that bias has not been introduced due to changes
- Complete process requires approx. 30 minutes

The Way Forward and Formulation of Recommendations: Reporting of Systematic Reviews

- PRISMA checklist should be updated to support registration of SR's
 - Prompt and dynamic as a better understanding of methodology and conduct of SR's emerges
 - Edited to indicate the type of MA, number of previous MA's and how the current MA is different from previous MA's in terms of study selection, statistical analyses, and conclusions
 - Including ROB and the summary of findings tables in PRISMA to endorse GRADE recommendations
 - Clear reason documented when a MA of a small number of studies is performed
 - When analyses such as I^2 is appropriate, the synthesis of results must include confidence intervals around I^2

The Way Forward and Formulation of Recommendations: The Role of Living Systematic Reviews

- Living SR's are up to date online summary evidence created from millions of published studies
- Help to make an evidence ecosystem guiding clinical decision making
- Reduce publication of many redundant SR's of low quality

The Way Forward and Formulation of Recommendations: Guidelines for Updating Systematic Reviews

- Updating too frequently can result in bias as well as a waste of resources
- However, failure to update meta-analyses in a timely manner can result in physicians and researchers using outdated evidence
 - No consensus to when updating should occur
- Takwoingi et al created a multicomponent decision tool for prioritizing the updating of SR's and MA's in 3 steps:
 - Whether a clinical question is either no longer relevant or has been already been answered
 - Whether there are new factors to be considered relevant to the existing review
 - Whether information from new studies is available

Conclusions

- Better communication between trialists
- Specific quality control at the level of editors and reviewers
- Promoting living systematic reviews
- Prospective registration of protocols for systematic reviews
- Updating of the PRISMA checklist to address redundancy and selective reporting bias