How to Conduct High-Quality Systematic Review and Meta-analysis in Radiology and Interventional Radiology

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Abstract

Keywords

► systematic review
► meta-analysis
► pooled estimates
► evidence-based medicine

Systematic reviews and meta-analyses form a secondary research methodology that identifies and critically appraises all the relevant studies that are available in various databases to answer a particular research question in an unbiased and systematic manner. In the pyramid of level of evidence, the systematic review of high-quality studies is placed at the highest hierarchy position. Meta-analysis is the statistical analysis of the systematic review that provides pooled estimates of the effect of individual studies in the systematic review, but sometimes a meta-analysis may not always be possible. This article elaborates the key steps to conduct a high-quality systematic review and meta-analysis in the field of radiology and intervention radiology, which will help the readers to design and conduct them along with to understand and interpret this secondary research.

Introduction

In the era of evidence-based medicine, there is an increase in the requirement of good-quality research to decide upon the most effective intervention/diagnostic tests for patient care. The clinical decisions are generally guided by multiple relevant studies, mainly randomized controlled trials (RCTs), but RCT designs to study subject or intervention imparted might differ from one another even for the same research question. In certain situations, decisions have to be made based on available non-RCT observational studies. Additionally, while a single RCT may not provide enough statistical power to detect a difference, a meta-analysis can combine RCTs to achieve the adequate power. This will ensure that there is no unnecessary research and waste of effort once a state of equipoise has been achieved.

With evolving new interventions, new diagnostic tools, and new laboratory parameters, the results and recommendations of highly cited RCTs can be challenged, or even refuted, thus impacting the decision-making for a particular disease or mode of intervention. Hence, there is a need for a regular and periodic reevaluation of the high-quality studies. These can often be combined to yield a fruitful conclusion. Traditionally, narrative review is a qualitative review of all good-quality primary research but in an unsystematic manner that tries to answer a broad question without employing any method to limit the bias. Systematic reviews differ from narrative reviews because there is rigorous attempt to limit all types of bias in every step of identifying, selecting, and processing of data of primary research studies in systematic reviews. Another difference between systematic and narrative reviews is transparency of

methods, choices, and reproducibility in systematic reviews. A scoping review is a kind of knowledge synthesis that locates and synthesizes an existing or developing body of literature on a particular topic using an organized and iterative process. A scoping review is important to map the literature on evolving or new issues and to identify gaps. It could be a prelude to conducting research or another kind of study, such as a systematic review.[1,2] A meta-analysis is a statistical technique to quantitatively assess the raw data that synthesize the results of multiple primary studies included in a systematic review presented in the form of forest plots and give pooled estimate of individual primary studies. Network meta-analysis (NMA) is a statistical technique that assesses numerous treatments at once by incorporating direct and indirect data from a network of trials. It can be used to compare therapies that have never been directly compared in a single experiment.[3]

Systematic reviews and meta-analyses are the best forms of evidence for answering a research question.[4]

The role of a systemic review and meta-analysis stands tall as it reviews all the relevant studies under one roof in a systemic manner to address a particular research question of interest.[5] This article will give a comprehensive review regarding the methodology to conduct a high-quality systematic review and meta-analysis and guide the readers in interpreting them.

Methods of Conducting Systematic Review

Reviewing Literature

It is proven that knowledge resources help address problems and improve efficiency of clinical decision-making. As we are constantly overwhelmed by the volume of literature, new information keeps popping up in the era of information technology and artificial intelligence. New information travels fast across the globe and thus the doubling time of published knowledge has decreased from 50 years in 1950 to 73 days in 2020. One may find it difficult to analyze all the new information and come to an unbiased conclusion. Hence, there is a need to systematically conduct secondary research that can help lay a foundation of evidence-based medicine. A reliable high-quality systematic review should review, summarize, and critically appraise all the relevant literature pertaining to a particular research question of interest. Systematic reviews use explicit and rigorous methods to identify studies, critically appraise, and synthesize the result of all studies and try to find the whole truth by assembling all the available evidence in the literature. Hence, conducting a literature review to identify and answer a research question is important.

Systematic Review versus Meta-Analysis

Systematic reviews give a transparent and impartial survey of the literature, provide an appraisal of the existing literature, and recognize the limitations as well as inconsistencies of all individual studies together. Meta-analysis refers to a portion of the systematic review that involves the statistical analysis.[6] It is a statistical process of analyzing and combining the results of several high-quality similar studies. Hence, it can be said that the systematic review is a qualitative review of a particular research question, whereas a meta-analysis is the quantitative analysis of that particular resource question that was summarized in the systematic review (►Table 1). The heart of the meta-analysis is the forest plot, which provides pooled effect of studies in the form of a graph (described later). It can be stipulated as a clinical policy and provides future directions for further forthcoming research. Systematic review and meta-analysis are placed in the highest position of the pyramid of quality of evidence when compared with other types of research like case controls or cohort studies.

The Systematic Review Team

The work of systematic review and meta-analysis is not an individual job. There is the need for a team that meet to discuss interests and decide on individual roles and responsibilities. Sometimes, the team can seek funding, which can be obtained via internal/intramural grant (from own institute) or extramural grant from recognized and available governmental or nongovernmental funding agencies. Ideally, there should be a minimum of three content experts (2 reviewers and 1 tie breaker), one statistician for meta-analysis, and one information technology (IT) professional who could also be a librarian who is trained in systematic reviews.

Steps in Conducting a Systematic Review

One should follow the steps of a systematic review for progressive and systematic research as given in ►Table 2. The first step is to formulate an appropriate research question followed by developing the protocol for a systematic review. The inclusion and exclusion criteria of identifying relevant studies are then formulated for a literature search in various databases. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the final included studies are narrowed down based on predefined inclusion and exclusion criteria. Further, data extraction and data analysis are done by identifying and addressing the bias with critical appraisal. Finally, a conclusion is made, which tries to objectively answer the research questions. The quality

Table 1 Comparison between narrative reviews, systematic reviews, and meta-analyses

Narrative review	Summary of various research studies without any explicit method to limit bias and are focused on broad-based question
Systematic review	It is a qualitative review of a clearly formulated question that uses systematic methods to identify, select, and critically appraise relevant research and to collect and analyze data by identifying and limiting bias from the studies that are included in the review
Meta-analysis	It is a quantitative pooling of raw data by using statistical techniques to synthesize results of multiple primary studies that are included in systematic review

Table 2 Steps in conducting a systematic review

Sl. no.	Steps of conducting of systematic review
1	Formulating research question (PICOTS)
2	Protocol and registration
3	Defining inclusion and exclusion criteria
4	Literature search
5	PRISMA flowchart: final study selection
6	Quality of evidence
7	Data extraction
8	Analysis of data
9	Assessment of level of evidence
10	Results and conclusion

Abbreviations: PICOTS, patient, intervention, comparison, outcome, time, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of review depends on the extent to which the systematic review methods try to minimize error and bias.

Formulating Research Question

The first and often the critical step is to formulate a good research question. It defines the objective of the review and formulates a focused clinical question. It should not be too broad to limit feasibility and risk of heterogeneity, or too narrow to limit the clinical relevance and generalizability of the result. It is essential to check whether a similar review has been recently published or registered (i.e., ongoing project). The review question should adhere to the PICOT format (►**Table 3**), where "P" stands for patient problem/population (i.e., who does the question relate to), "I" stands for intervention (i.e., it can be intervention or therapy or diagnostic test or prognostic factor), "C" stands for comparison (i.e., another intervention/diagnostic test/placebo, or standard of care), "O" stands for outcomes (i.e., interested outcome points like decrease in pain score, decrease in major adverse cardiovascular event [MACE], and decrease in leg amputation rate), and, finally, "T" stands for time frame in which the outcomes are recorded (e.g., 3-year patency rate,

1-year mortality rate).[7,8] Additionally, "S" can be added in PICOTS, where "S" stands for study design (e.g., RCT for intervention studies and diagnostic test study for diagnostic accuracy assessment).[8] The PICOTS format is applicable for all types of resource questions in systematic reviews. But sometimes, the PICOT format may not be possible, for example, in single-arm studies or prevalence meta-analyses. The research question is usually specified in the introduction section of a systematic review and ideally should be framed in the PICOTS format. If the research question is not clearly defined, it may give rise to bias and thus undermine the whole purpose of a systematic review .

Developing and Registering a Systematic Review Protocol

After the research question is formulated, there is a need to clearly delineate the inclusion and exclusion criteria. It is important to employ reproducible search strategies, which needs detailing the search terms and the databases that are included in the search if needed. A priory plan hypothesis with subgroup and sensitivity analysis can be defined to identify potential sources of heterogeneity. It is a good practice to describe the data abstraction element and approach to risk-of-bias assessment and statistical methods that will be employed. Additionally, the outcomes and methods should be established in advance to ensure transparency, and any deemed changes should be notified. Finally, all the authors should read the protocol and give their approval. The protocol should be registered in an open access platform, such as PROSPERO, Inplasy, Open Science Framework registries, Campbell Collaboration, Cochrane Database of Systematic Reviews (CDSR), Research Registry, JBI Systematic Review Register, and protocols. io.[9,10] The inclusion and exclusion criteria should be explicitly designed or defined so that the boundaries of systematic review are objectively defined. For the study characteristics, the topic and scope of research should be defined. The characteristics of study population such as the age and clinical condition should be defined; regarding publication characteristics, time frames, publication status, and research language should be included, and any additional types of publication included in the research should be defined. Some journals make it mandatory to publish systematic review protocols like Cochrane Review before

Table 3 Explanation of various components of PICOTS with appropriate examples

P	Patient, problem, or population, corresponding to who does the research question relate to, e.g., critical limb ischemia, patients who are having TASC I and II aortoiliac disease
I	Intervention; can be a therapy, diagnostic test, prognostic factor, exposure, or issue, e.g., covered stent
C	Comparison; can be another intervention, therapy, diagnostic test, prognostic factor, no exposure, placebo, or standard of care, e.g., bare stent
O	Outcome(s); objective outcomes/measurement should be stated like decrease in pain score, increase in primary patency rate
T	Time frame; outcomes are more meaningful when they are recorded in a specified time frame, e.g., within 90 d of treatment, 1-y primary patency rate
S (Optional)	Study designs that are to be included can be mentioned; e.g., only RCT or mixed study like RCT and non-RCTs/cohort study

Notes: Other formats of research questions are SPICE (Setting, Population, Intervention, Comparison, and Evaluation); SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, and Research type); ECLIPSE (Expectation, Client, Location, Impact, Professionals, and Service); and TASC (Trans-Atlantic Inter-Society Consensus).

starting the systematic review work and others expect them to be available online that can be assessed by anyone. It is very difficult to publish systematic reviews in good journals without prior registration of the protocol. It is important to ensure that appropriate methodology is used and disclosed beforehand without modification after the data of the results are available, and the whole process should be systematic, objective, reproducible, and transparent.[8]

Literature Search

The literature search step is designed to identify all relevant primary researches that have the potential to answer the formulated research questions (►**Table 4**). The search and inclusion of studies should be systematic, objective, reproducible, and transparent. It is a good practice to follow the PICOTS format. For the inclusion of a particular study, the study should fulfil all the components of PICOTS that the authors have listed in the research question formulation. For the participants included in the study, we need to elaborate the participant characteristics in the primary studies like age group, gender, disease duration, and severity/classification. We should ensure that the inclusion criteria are broad, but try to objectively diagnose disease or its severity, like stage 4 or 5 Rutherford classification for peripheral arterial disease (PAD) patient as inclusion criteria. The I segment of PICOTS should be detailed in the methodology section, for example, the intervention drug (s), doses, frequency, duration, and administration route should be mentioned; for intervention techniques or material, it is essential to specify the access route, exact material or specification of the drug used for transarterial embolization, or range of concentration of drug in drug-coated balloon with duration

Table 4 Various databases/registers and gray literature that should be searched for coverage of all records and reports for doing a systematic review for a particular research question

Electronic databases	Medline
	Embase
	Scopus
	Cochrane Register of Trials
Additional literature databases	Hand searching: reference lists of included studies
	Clinical trials registry
	Conference abstract
	Database of nonindexed journals
	Local/regional sources
Other sources/gray literature	IndMED
	Wanfang Data (Chinese literature)
	LILACS (Latin American and Caribbean literature)
	Open Gray
	WorldCat
	Google Scholar
	OpenDOAR

of inflation or technical details, if pertinent. For diagnostic and prognostic test, the intervention is usually an exposure or specific imaging sequence or biochemical/pathological investigation. The C component in the PICOTS format should be identified and explained in the methodology section. The comparison can be placebo or other interventional drug/material or best medical therapy. If the primary studies do not have a comparison group, the systematic review can still be done, but inference derived from these studies should be read with caution as the extracted information is inferior to the studies that have a comparison group. Usually there is one primary outcome that may be broad like efficacy or narrow like mortality rate and quality-of-life measurement in an objective manner. The outcome measurement should be elaborated in detail so that the objective is clear and the method to objectively measure the outcome is defined in the protocol. The safety outcome can also be an outcome and the method to identify/categorize the adverse effect should be mentioned beforehand, namely the Society of Interventional Radiology (SIR) adverse event. Hard outcomes like death, limb loss, and MACE are preferred as compared with soft outcome marker. Also, the time frame of recording of this outcome should be mentioned like limb loss at 1 year after initiation of treatment.

Finally, systematic reviews may include high-quality RCT as the primary research in the RCT design as it eliminates bias due to its inherent design, but non-RCT/moderate-quality design study can also be included if deemed necessary. The authors should try to conduct a separate analysis of high- and low-quality studies and explore the difference between them.

For a comprehensive review, multiple relevant electronic reference databases should be searched, such as PubMed (Medline), Embase, and Cochrane Review. Additional literature search of relevant articles related to the research topic should be searched in the Scopus or Web of Science, among others. Additionally, efforts should be made to identify published abstracts and ongoing trials. Gray literature should be searched in databases such as Open Grey, OpenDOAR, World Cat, Google Scholar, regional sources, and conference proceedings or abstracts.[5,8] Researchers can make use of Boolean operators' synonyms and filters to restrict the result or broaden the survey. Publication bias is a reality where publishers tend to publish studies that show statistically significant values (or results) or are positive studies. Hence, nonsignificant results often are not submitted or get rejected by the reviewers. This is not good for evidence-based medicine, because a cutoff of $p < 0.05$ is arbitrary and p value combines information about effect size and sample size. Thus, a significant p value can be a large effect size or a small effect size in a large sample. Hence, if we include only published literature or statistically significant results, it can lead to overestimation of effect size and thus inappropriate conclusions. Hence, optimal literature search should include both published and unpublished researches that fulfil the predefined inclusion and exclusion criteria.

Study Selection (Importance of Inclusion/Exclusion Criteria)

Once a comprehensive list of references has been retrieved from the various searched literatures, duplicate versions

should be recognized and deleted. Then the title and abstract of the remaining articles should be screened to identify potential studies that match the eligibility criteria. Once the relevant studies are finalized, the full-text version should be assessed and studies fulfilling all eligibility criteria should finally be retained in the systematic review analysis. The reason for exclusion of a particular primary study should be mentioned to ensure transparency. More than one author should do this sorting and a tiebreaker to include/exclude should be done by a referee (senior researcher) or by consensus. Usually, a citation manager such as EndNote, RefWorks, or Mendeley can help and potentially save time as well. One should make a PRISMA flowchart (►**Fig. 1**) for the study selection and documentation of the number of studies retrieved, rejected, and evaluated at the final stage.[11]

Critical Appraisal

The authors of a systematic review have the responsibility to do critical appraisal of all individual studies and assess the efforts of primary investigator's efforts in reducing the bias during the conduct of respective studies. Bias can be due to inappropriate study designs or methodology, and appraisal is generally restricted only to these issues. Sources of bias and various tool for assessment of bias are presented in ►**Table 5**.

For an RCT, the Cochrane risk-of-bias tool is a standard tool and assesses design elements like random sequence generation, allocation concealment, blinding, and incomplete or selective reporting of outcomes. For assessment of non-RCTs, the Newcastle–Ottawa Scale (NOS) or Non-Randomized Studies of Interventions tool (ROBINS-1) are often used.

Data Extraction/Analysis

The meaning of data extraction is to extract relevant data cautiously and methodically for inclusion from the individual studies in the final research analysis. One should extract the included article characteristics (source, year, author), study characteristics (PICOTS information), appraisal for bias, and outcome data for statistical computations, which will ultimately yield the effect size. It is possible that the desired data may not be reported by all the individual studies that are included in the research. In such cases, a sincere effort should be made to contact the corresponding author to acquire the pertinent data and, if available, it should be included in an appropriate analysis. Study quality can be characterized differently across various research designs and disciplines, and for that, various assessment tools exist and these should be used so that the estimates/data derived from all primary research are of a similar format and conducive for doing a pooled estimate. Sometimes, there might be a need for raw data from primary studies to resolve these issues if all data needed for interpretation are not available in the published article. The study limitations are evaluated using the risk-of-bias method, which assesses the quality of evidence based on the processes, highlighted in ►**Table 5**.[5,12]
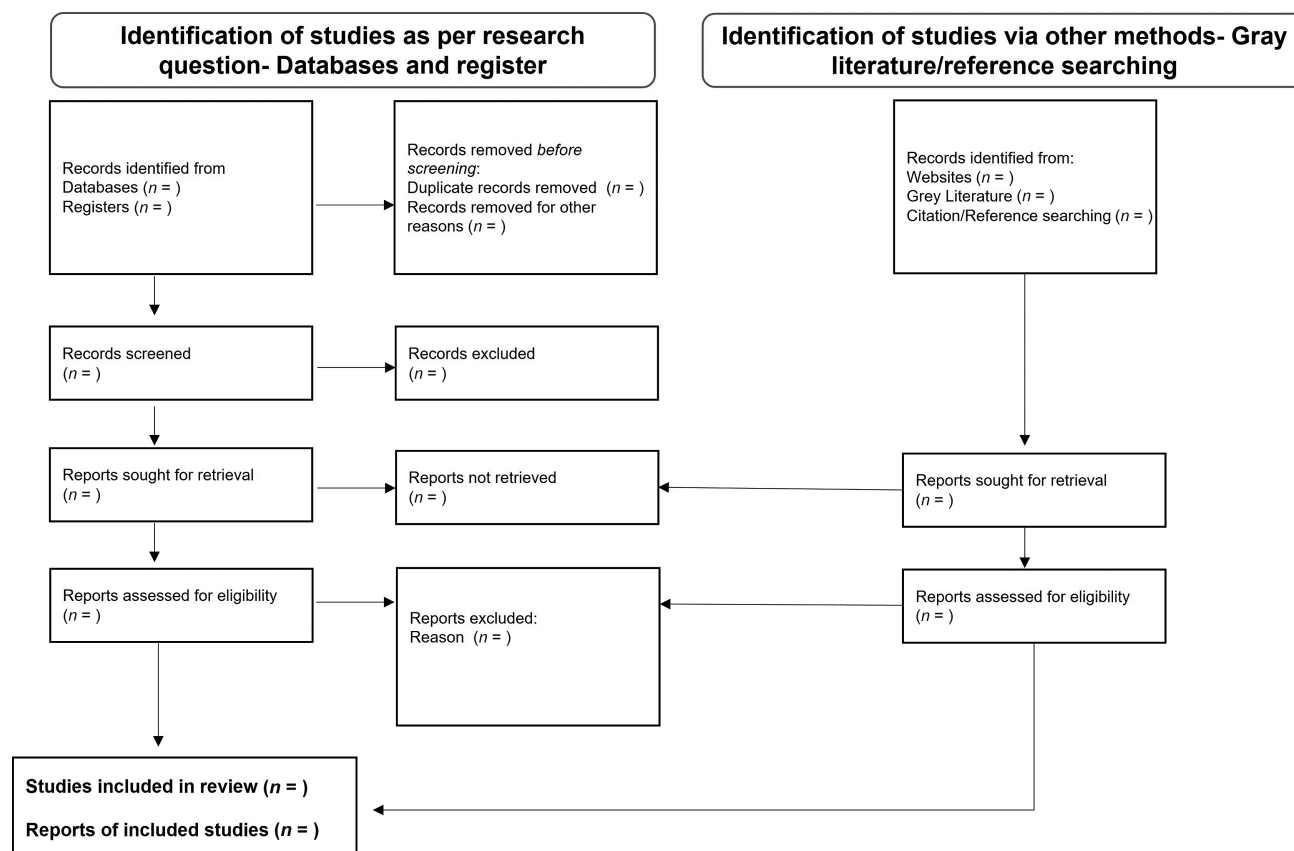

Fig. 1 Various steps in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart for identification, screening, and inclusion of various studies for systematic review.

Table 5 Various types of bias in RCT and tools for risk-of-bias assessment

Types of bias in RCT	Questions to be searched and answered
Selection bias	Random sequence generation done or not?
	Allocation concealment done or not?
Performance bias	Blinding of participants/personnel done or not?
Detection bias	Blinding of outcome assessment done or not?
Attrition bias	Incomplete outcome data are there?
Reporting bias	Selective reporting done or not?
Other bias	Any other bias like publication bias and sponsorship bias?
Various tools available for assessment of bias according to the study types included in systematic review/methodology employed in primary studies	
Study types	**Tools for assessment of bias**
RCT	Cochrane risk-of-bias tool
Non-RCT	Newcastle-Ottawa Scale
	Risk of bias in nonrandomized studies of interventions tool
Diagnostic accuracy test	QUADAS (includes patient selection, index test, reference standard/gold standard, and timing)

Abbreviation: RCT, randomized controlled trail; QUADAS, quality assessment of diagnostic accuracy studies.

Meta-Analysis

A meta-analysis is a statistical method to calculate a pooled estimate of the effect of individual studies/primary researches included in the systematic review. The studies with a narrow confidence interval and larger sample size have greatest weightage. The geographical representation of all these data is presented in the form of a forest plot graph (►**Fig. 2**). For calculating the effect size, a forest plot is an effective way of reporting the effect size.[8,13] The location of the square indicates the effect size. The area of the square indicates the weight reflected in the meta-analysis. The line represents the confidence interval.

The diamond represents the odds ratio calculated across all included studies. The bold vertical line (in the center) represents the line of no effect, that is, a lack of therapeutic effect (odds ratio = 1). If the confidence interval includes an odds ratio equal to 1, it indicates that no significant difference was found between the treatment and control groups. The robustness of the analysis can be assessed by observing the change in effect size when excluding one study at a time. If the effect size shows no substantial change upon exclusion of any individual study, it indicates the strength of the results. After calculating the overall effect size, it is important to assess the presence or absence and the level of heterogeneity across the studies. Heterogeneity refers to a variation in the effect due to random chance if all studies were conducted in the same fashion, but in real-world scenarios, there are additional factors that can lead to heterogeneity as studies differ in their methodology from one another. One statistical technique for quantifying the variation in results between studies in a meta-analysis is heterogeneity analysis. In meta-analyses, heterogeneity must be evaluated because it can affect the results and make them more difficult to understand. It is calculated using the Cochrane's Q test and Higgins I^2 statistics.[14] A significant Q value indicates significant heterogeneity across studies. I^2 statistics estimates the pro- portion of observed variants that reflect absolute difference in effect sizes, with values greater than 75% indicating a strong heterogeneity. Moderators are factors assumed to affect the effect sizes within the studies in which these factors are present. For moderator analysis, we have to decipher the factor that can explain the fact that some studies report differences, while others do not. When the feature of interest is a categorical variable, a subgroup analysis is performed (e.g., design of the trial as an RCT or clinical controlled trial). When the characteristic of interest is a metric variable, such as the sample size of the trials, a meta-regression analysis is performed.

Regression analysis is a statistical technique called meta-regression, which is used to aggregate study results from several studies. This method is an expansion of the conventional meta-analysis and has the following applications: examine how study characteristics influence intervention effects, analyze variations among the categorical explanatory variables, and examine the effects of several variables at once.[15]

Presenting the Results

Results can be presented in the form of PRISMA that is preferred for reporting items for systematic reviews and meta-analysis, meta-analysis reporting standards (MARs), or meta-analysis of observational studies in epidemiology (MOOSE). However, the MOOSE guidelines are old, so it is better to use the PRISMA guidelines for systematic reviews. According to the type of studies and trials included in our systematic review, we have to present the result. The quality of the level of evidence can be graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool by using study limitations (study design and risk of bias), inconsistency in evidence, indirectness of evidence, volume of data, imprecision of effect estimates, and publication bias. For each key outcomes, a Summary of

Comparison of Option 1 (POBA) vs. Option 2 (DCB) in PAD with below-knee lesion for efficacy; primary outcome is amputation-free survival at 1 year
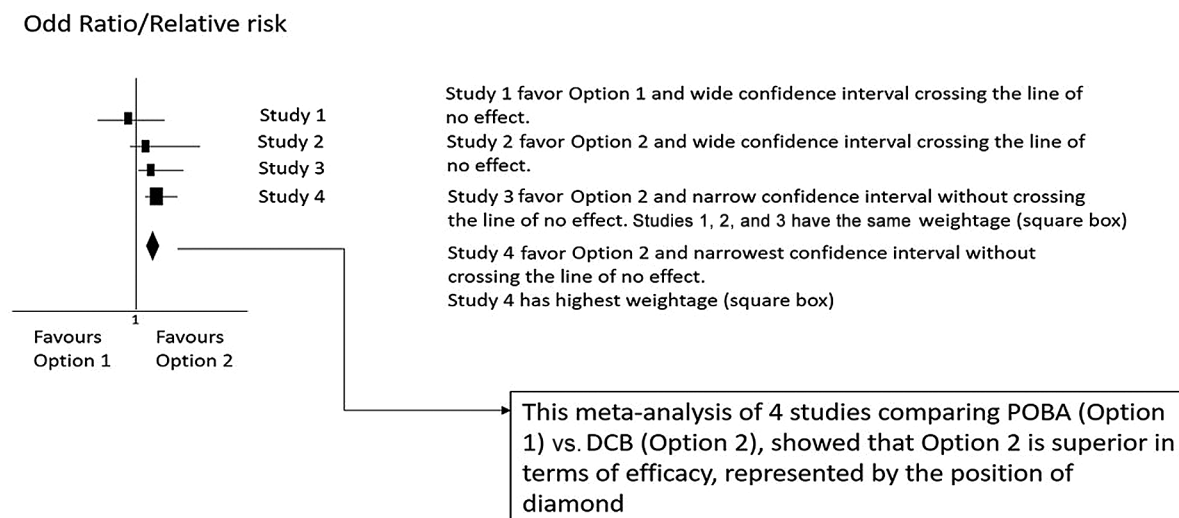
Odd Ratio/Relative risk

Study 1   Study 1 favor Option 1 and wide confidence interval crossing the line of no effect.
Study 2   Study 2 favor Option 2 and wide confidence interval crossing the line of no effect.
Study 3   Study 3 favor Option 2 and narrow confidence interval without crossing the line of no effect. Studies 1, 2, and 3 have the same weightage (square box)
Study 4   Study 4 favor Option 2 and narrowest confidence interval without crossing the line of no effect.
Study 4 has highest weightage (square box)

1
Favours   Favours
Option 1   Option 2

This meta-analysis of 4 studies comparing POBA (Option 1) vs. DCB (Option 2), showed that Option 2 is superior in terms of efficacy, represented by the position of diamond

Fig. 2 Illustration of forest plot graph showing comparison of plain balloon angioplasty (POBA) versus drug-coated balloon (DCB) in peripheral arterial disease (PAD) patients with various self-explanatory parts of the forest plot graph.

Findings Table (SoFT) can be made that shows absolute and relative effect of the intervention.[8,16] Zotero can be used as a free reference manager.

Level of Evidence Assessment and Drawing a Conclusion

The quality of conclusions drawn from a systematic review reflect the level of evidence extracted by individual studies included in the review. Therefore, it is crucial to clinically apply this conclusion only after assessing the advantages and disadvantages of each individual study and after vigorously interpreting the result. There are various factors like research design, risk of bias, volume of evidence, inconsistency and indirectness of evidence, precision of effect estimates, and the risk of publication bias that should be considered to determine the strength of the overall evidence as discussed earlier. For the critical appraisal of systematic review, the Assessment of Multiple Systematic Reviews (AMSTAR) or AMSTAR 2 measurement tool can be used.[5,17] Definitions of terminology used in a meta-analysis and this article with examples are presented in ►Table 6.

Table 6 Definition of some parts of meta-analysis

Pooled effect	Weighted average of the effect sizes from multiple studies
Degree of heterogeneity	It is a measure of how much a study deviates from being perfectly uniform when multiple primary studied are compared/analyzed
Forest plot	It is a graph that summarizes the results of multiple studies that are part of a meta-analysis
Critical appraisal	It is a process of carefully and systematically assessing the reliability, value, and relevance of scientific research of a research question
Level of confidence/ confidence interval	A probability that a parameter/estimate will fall between a set of values, e.g., if we construct a 95% confidence level, we are confident that 95 out of 100 times the estimate will fall between the upper and lower values, which are specified by the confidence interval
A priori	Detailed methodology is disclosed before collection of data
Post hoc	Methodology is modified after obtaining the data
Bias	Systematic error that leads away from the truth
Random error	Error that occurs by chance
Risk of bias	It is the possibility of systematic error in the results of a systematic review
Odds ratio	It is the ratio of the odds of the event occurring in an exposure (intervention) group as compared with the nonexposed (comparison) group

Limitations

There are some limitations of systematic reviews and meta-analyses. Among them, the final summary and conclusion are only as reliable as the methods employed in each of the primary studies included. It does not correct bias as a result of selective publication.

As more than three-quarters of meta-analyses did not report any empirical assessment of publication bias, the true frequency of this form of bias is unknown. Interpretation of results, particularly when the results of discordant studies are included in a meta-analysis, should be made cautiously. Combining studies of poor quality with those that were more rigorously conducted may not be useful and can lead to worse estimates. A false sense of precision can occur when various subgroups of patients differ in their observed responses, which may mislead us to an aggregated pooled effect. Finally, mere labeling of a manuscript as a systematic review or meta-analysis does not guarantee that the review was conducted or reported with due rigor. It requires a systematic approach to answer a research question by analyzing previous high-quality studies, reducing bias, and reaching a meaningful conclusion that can guide clinical decision-making.

Conflict of Interest
None declared.

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