Systematic Reviews & Meta-Analyses

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Objectives

At the end of this session:

- You will understand the process of conducting a SR&MA
- You will be able to better read and understand journal articles that are reports of SR&MA
- You will have resources for further exploration

What is a systematic review?

A systematic review is a rigorous, systematic literature review focused on a single question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question.

How is it different from a narrative review?

- Clear, explicit objectives with clearly stated inclusion criteria (providing transparency)
- Systematic searching methods (reduces risk of bias)
- Consistent evaluation of studies (reduces risk of bias)
- Gives the readers more information about decisions that were made along the way (increases transparency)
- Potentially greater precision in estimates of effect, especially if meta-analysis (increases accuracy)
- Sets stage for updates as more data is published

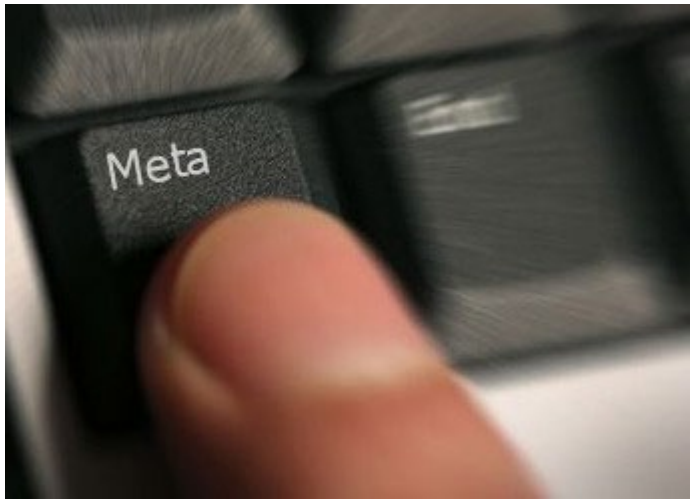
What is a Meta-Analysis?

Analysis of pooled study data

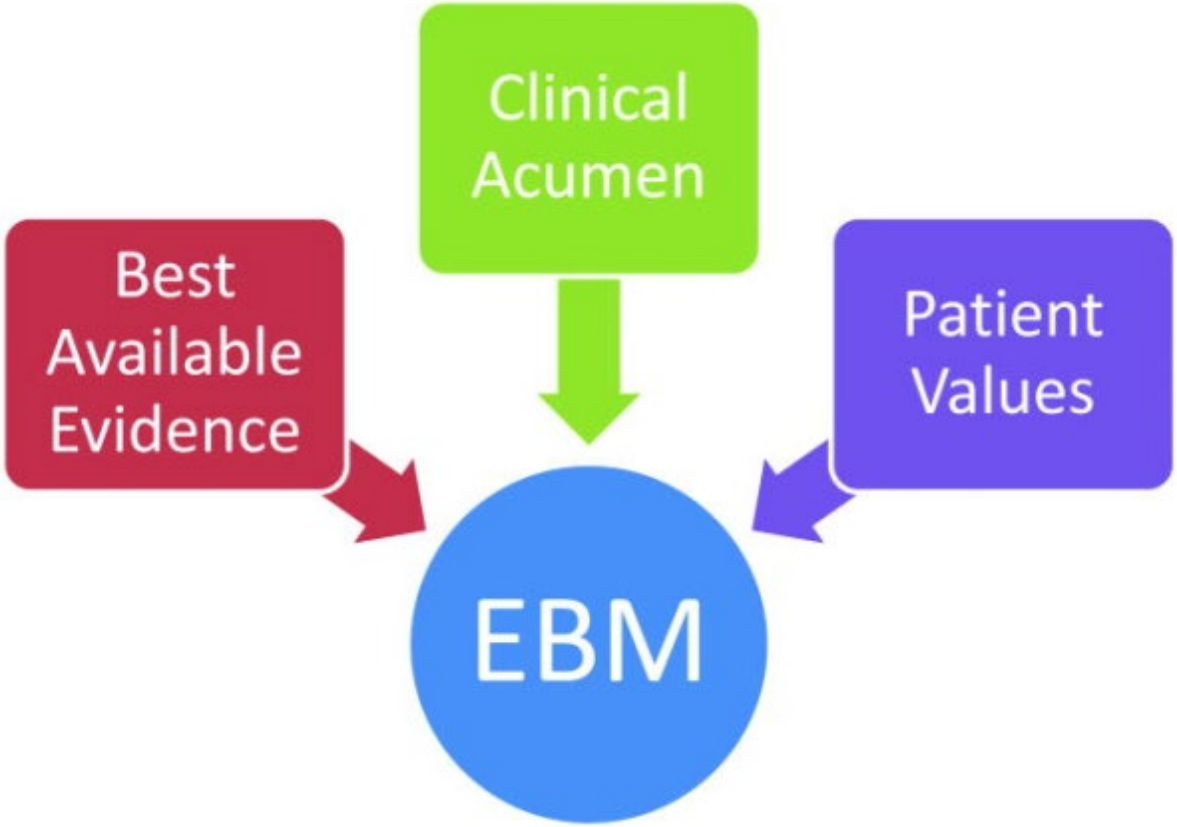
Increases power

Tells you:

- Direction of effect
- Magnitude of effect
- Variation across studies



Evidence-Based Medicine



Sackett, D. L., Rosenberg, W. M., Gray, J. M., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't.

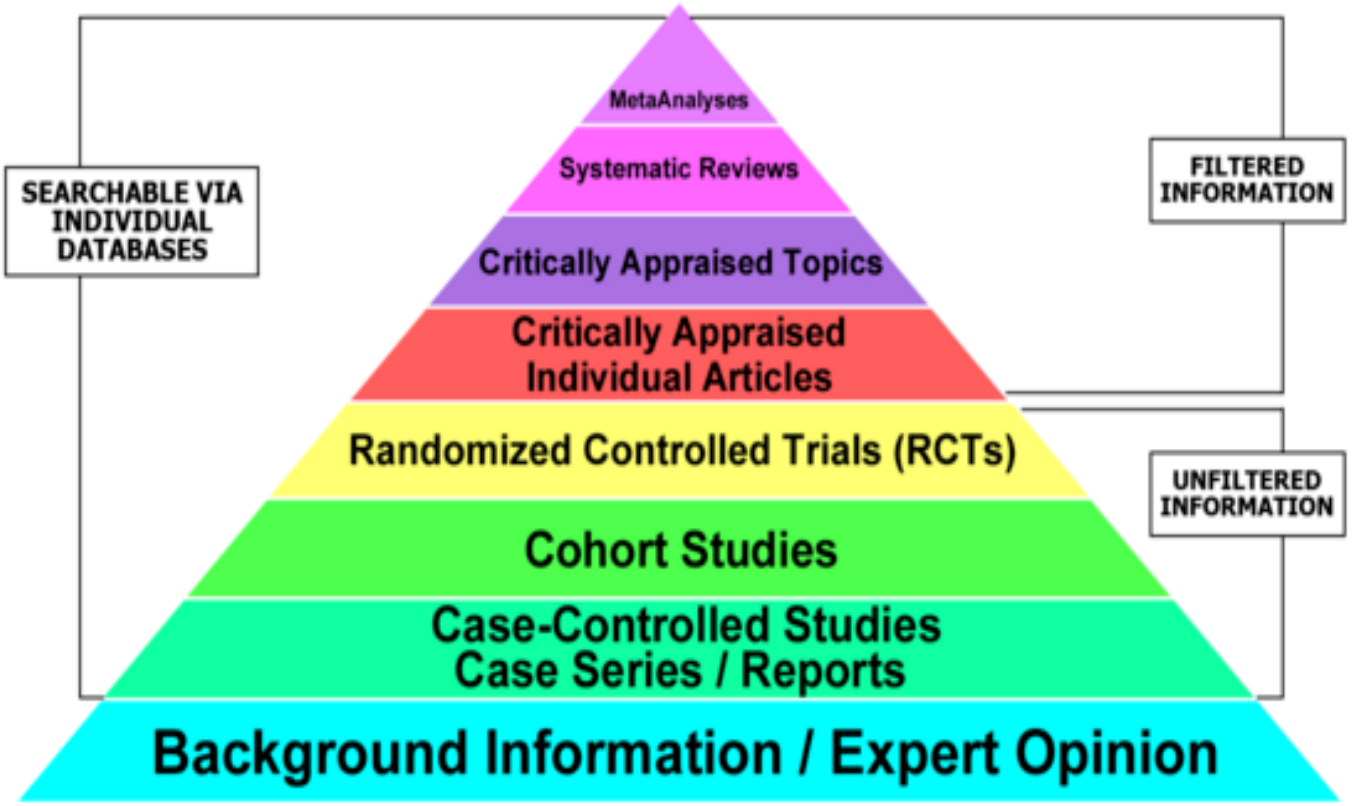
Why do them?

Critically evaluate scope and strength of the evidence and its limitations

Synthesize best evidence on a topic (highest levels of evidence)

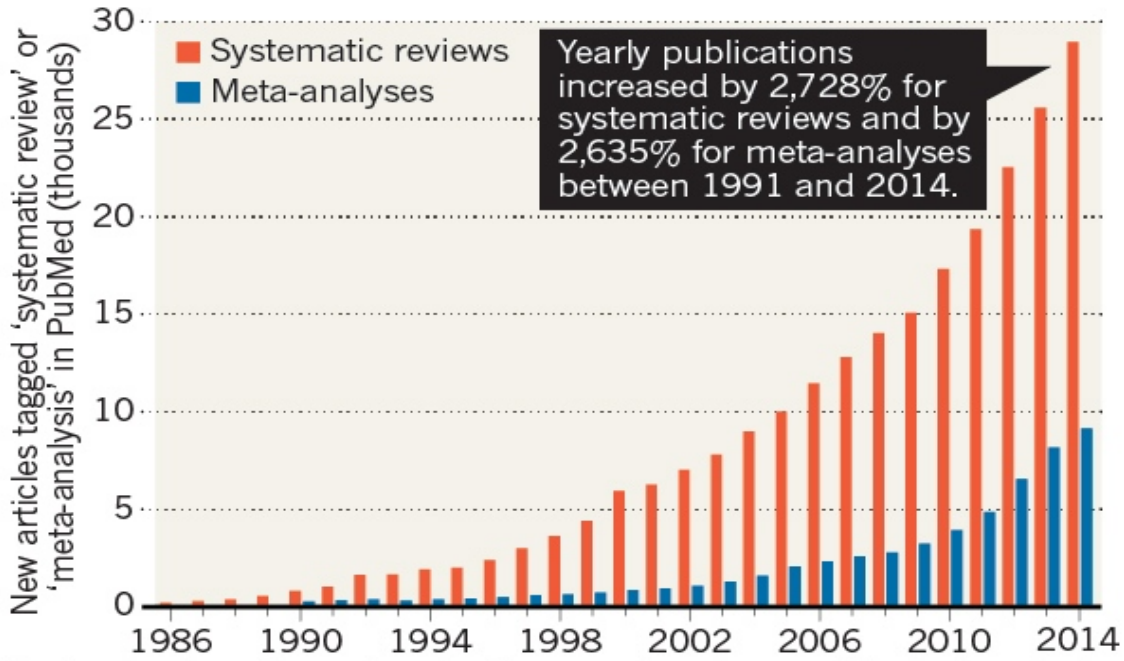
Get timely, relevant results to researchers, clinicians, and the public

Highest level of evidence



META MASS PRODUCTION

The number of systematic reviews and meta-analyses published each year has proliferated since 1986.



A systematic review analyses and compiles all papers, and sometimes unpublished work, on a topic. A meta-analysis is a systematic review that combines data from multiple papers.

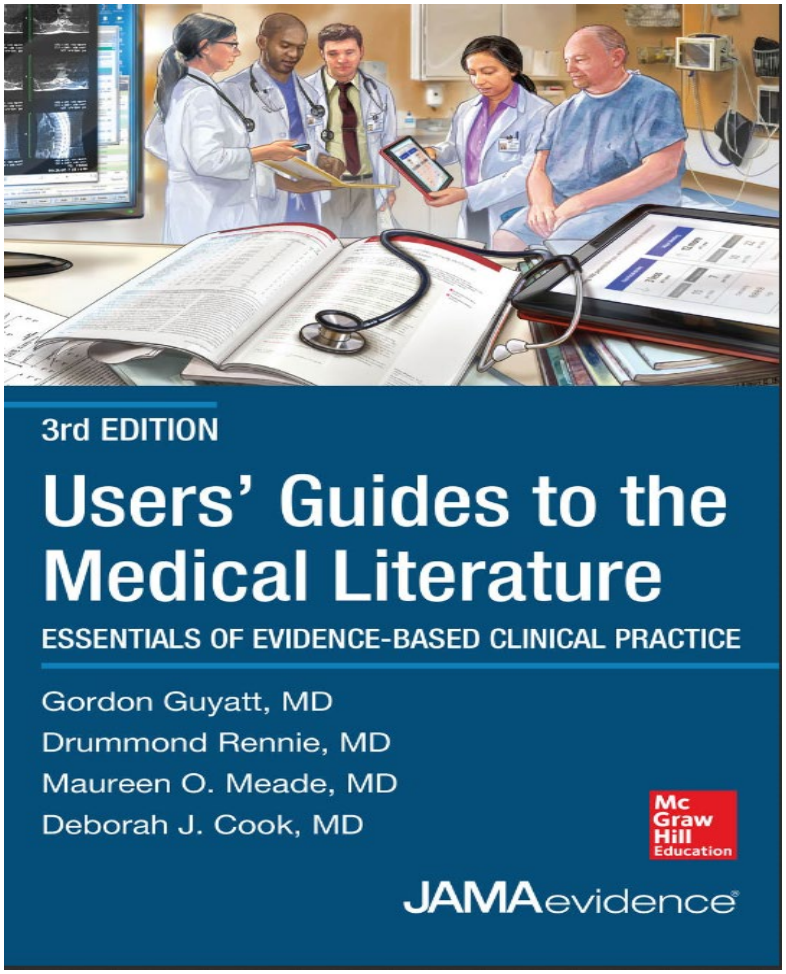
Reader Beware

Have a critical eye—their quality varies!

Use the criteria we will discuss

"Most topics addressed by meta- analyses of randomized trials have overlapping, redundant meta-analyses; same topic meta-analyses may exceed 20 sometimes. Some fields produce massive numbers of meta-analyses; for example, 185 meta-analyses of antidepressants for depression were published between 2007 and 2014. These meta-analyses are often produced either by industry employees or by authors with industry ties and results are aligned with sponsor interests."

Ioannidis, J. (2016). The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *The Milbank Quarterly*, *94*(3), 485-514.



Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, Neumann I, Carrasco-Labra A, Agoritsas T, Hatala R, Meade MO. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. Jama. 2014 Jul 9;312(2):171-9.

Say you encounter this scenario …

CLINICAL SCENARIO

Should Patients Undergoing Noncardiac Surgery Receive β-Blockers?

You receive a request for consultation from a general surgeon regarding the perioperative management of a 66-year-old man undergoing hip replacement surgery in 2 days. The patient has a history of type 2 diabetes and hypertension and is a smoker. He has no history of heart disease. The patient's blood pressure is 135/80 mm Hg. Because the patient has multiple *risk factors* for heart disease, you are considering whether he should be treated perioperatively with β-blockers to reduce the risk of death, nonfatal myocardial infarction, and other vascular complications.

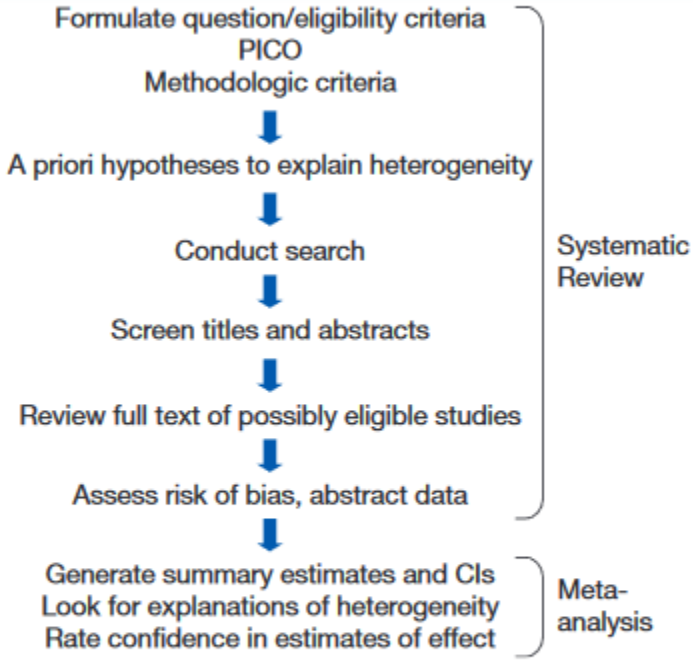
… and you find this meta-analysis

Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery. Heart. 2014 Mar 15;100(6):456-64.

First Judgement: Was the Methodology of the Systematic Review Credible?

FIGURE 14-2

The Process of Conducting a Systematic Review and Meta-analysis



In a systematic review without meta-analysis, the step of generating summary estimates and confidence intervals is not applicable. If the systematic review includes a meta-analysis and presents estimates of effect from individual studies, seeking explanation for heterogeneity and rating confidence in estimates is possible.

Abbreviations: CI, confidence interval; PICO, Patient, Intervention, Comparison, Outcome.

Did they follow established guidelines for designing and reporting their SRMA?

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA): http://www.prisma-statement.org/

Cochrane Handbook for Systematic Reviews of Interventions
http://training.cochrane.org/handbook

Did the review explicitly address a sensible clinical question?

A good SRMA should

- State the focused question they are setting out to answer
- P I C O
  - Patient/Population/ Program
  - Intervention or Exposure
  - Comparison or Control
  - Outcome

PICO Question

We therefore conducted a meta-analysis of the remaining secure intention-to-treat randomised controlled trial (RCT) data on the initiation of a course of β-blockade for the prevention of all-cause mortality and other secondary endpoints in the perioperative period for patients undergoing non-cardiac surgery.

Was the search for relevant studies exhaustive?

A good SRMA should

- State which databases they searched, such as:
  - Ovid Medline (PubMed)
  - SCOPUS
  - CINAHL
  - PsychInfo
  - ERIC
  - Cochrane Controlled Trials Register
- Other sources searched (reference lists, grey literature)
- Provide explicit information on their search strategy so you or I could repeat the search and get the same results.

Search Strategy

- Databases
- Inclusion and Exclusion Criteria
  - Dates
  - Study type
  - Location
  - Population
  - Language
- Search terms—based on PICO question, inclusion and exclusion criteria

Search Strategy

We included published RCTs that compared the initiation of a course of β-blocker therapy in the preoperative period with placebo in adults undergoing non-cardiac surgery. There were no language restrictions. We searched Medline (1966 to 1 April 2013), the Cochrane Central Register of Randomised Controlled Trials, the WHO International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/), Excerpta Medica Database (EMBASE) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) using the search terms available in the online supplement on 23 March 2013 (see online supplementary appendix 1). We also hand-searched previous reviews and meta-analyses for other studies. We excluded non-randomised studies, studies comparing β-blockers with another treatment, studies using a one-off dose preoperatively rather than a course of β-blockers extending into the postoperative period and studies which did not report intention-to-treat data.

Sample Search

APPENDIX 1

Medline Search terms:(“β adrenergic blockers” OR “adrenergic β antagonist” OR “β blockers” OR "beta blockers" OR "adrenergic beta antagonist" OR "beta adrenergic blocker" OR "bisoprolol" OR "metoprolol" OR "atenolol" OR "carvidolol" OR "esmolol") AND (“perioperative" OR “preoperative” OR “intraoperative”) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab] OR "clinical trials as topic"[mesh: noexp] OR "randomly"[tiab] OR "trial"[ti]) NOT ("animals"[mh] NOT"humans"[mh])

Was Selection and Assessment of Studies Reproducible?

A good SRMA should

- State the criteria they used to include and exclude articles
- Describe the process for selecting articles
  - Ideally have two or more reviewers and a measure of agreement

Selection and Assessment of Studies

Data extraction was performed in duplicate by MJS and SB with any disagreements resolved by DPF.

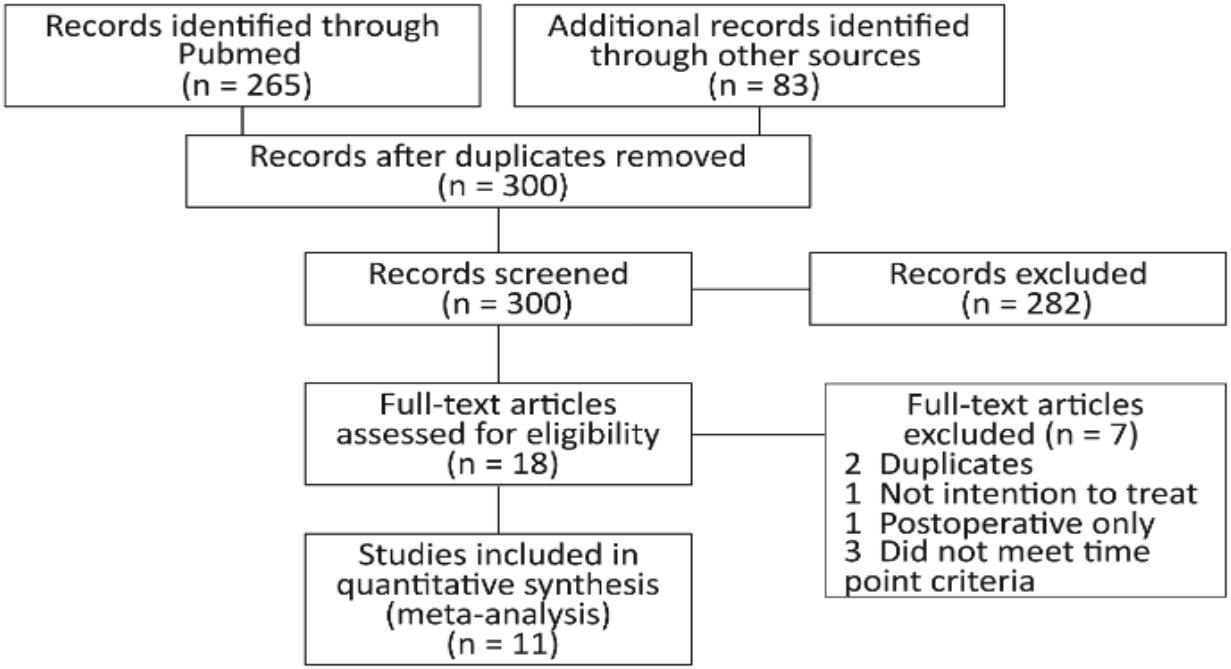
RESULTS

Identification of trials

We identified 300 publications; 265 were initially found on PubMed (see online supplementary appendix 2), 3 from the Cochrane Central Register of Randomised Controlled Trials, 19 from the CINAHL, 1 from EMBASE and 12 via hand searching of references. A total of 282 were excluded after reading the abstract (of which 39 received premedication only) and a further seven were excluded after reading the full text for the following reasons: two were duplicates of other studies,[10 11] one could not be included because 10 patients were excluded after randomisation including one who had pulmonary oedema in the metoprolol arm,[12] three did not meet the time point criteria of 30 days or until discharge,[13–15] and one initiated the β-blockade postoperatively[16] (see online supplementary appendix 2). A total of 11 RCTs met the eligibility criteria (figure 1), of which two were from the DECREASE family (DECREASE I and DECREASE IV[5 17]).

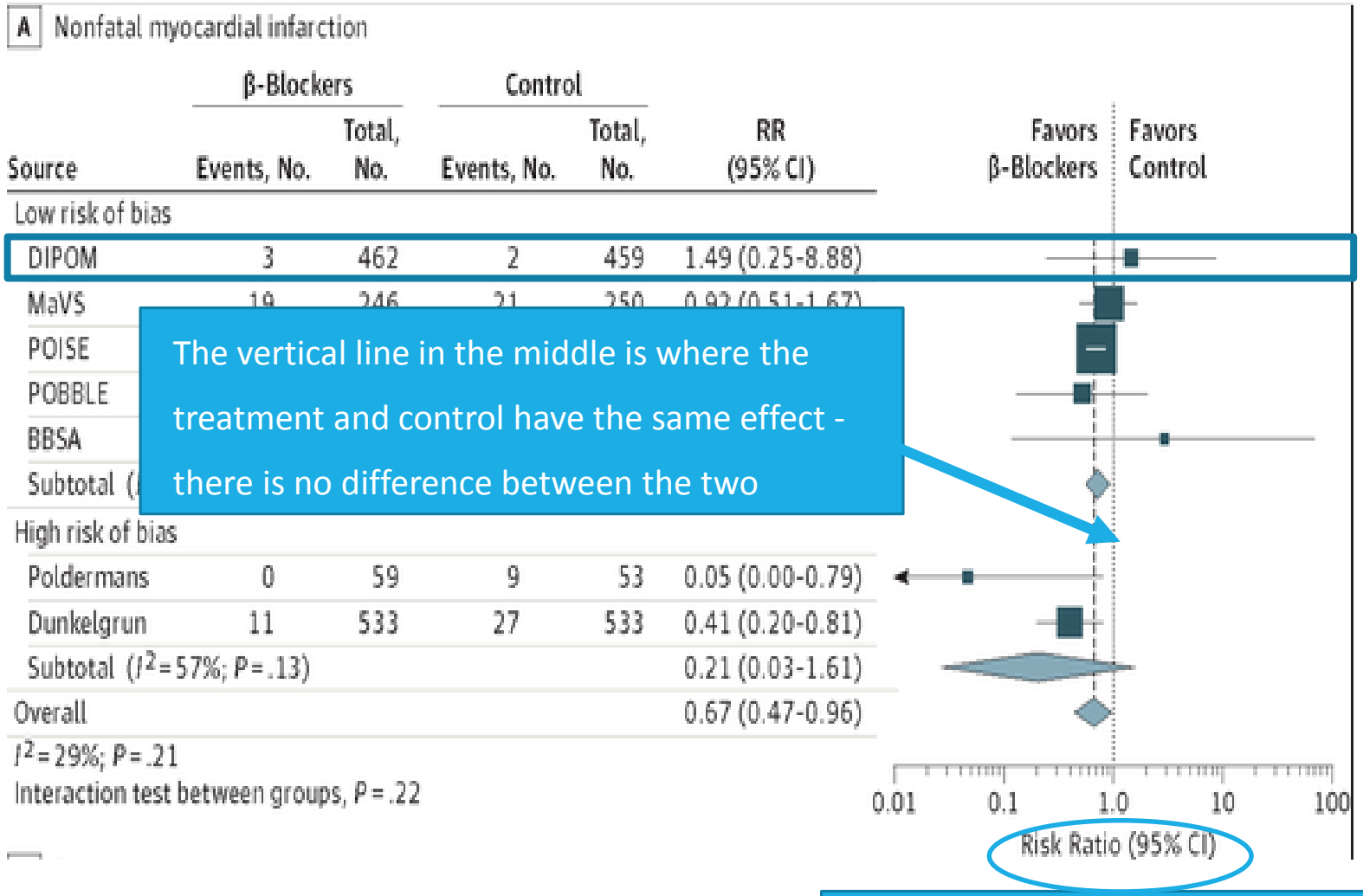
PRISMA Diagram

A good SRMA should describe the process of getting to the final selected articles in a PRISMA diagram



Did the Review Present Results that are Ready for Clinical Application?

- Meta-analyses provide estimates in terms of effect size (relative risk, odds ratio, differences in risk, hazard ratios, weighted mean differences, standardized mean differences)
- Presented in a Forest plot



The vertical line in the middle is where the treatment and control have the same effect - there is no difference between the two

The label tells you what statistic has been used

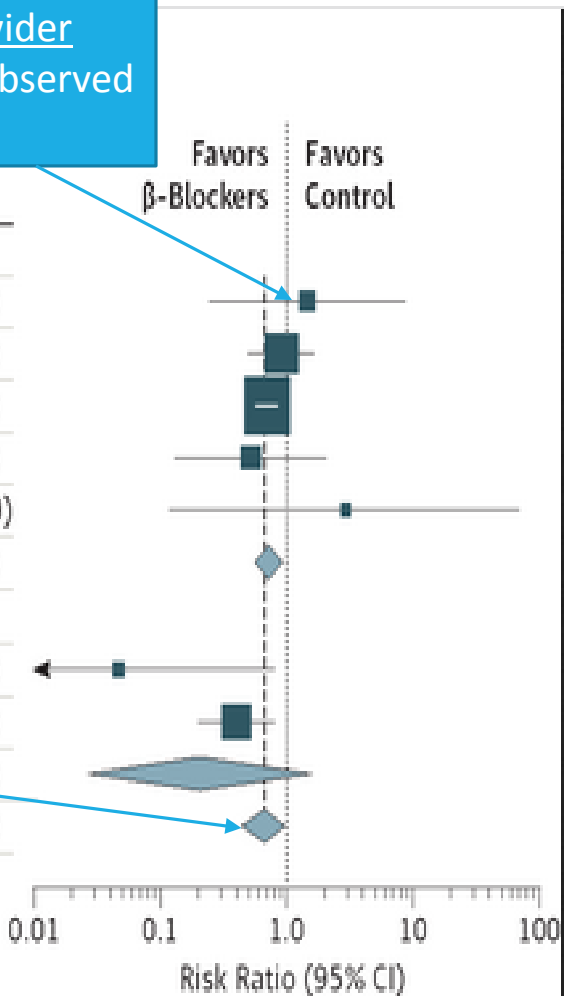
- Each study is given a symbol, placed where the data measure the effect.
- The size of the symbol is proportional to the % weight
- The horizontal line is called a confidence interval-he wider the horizontal line is, the less confident we are of the observed effect.

Source	Events, No.	No.	Events, No.	No.	(95% CI)
Low risk of bias					
DIPOM	3	462	2	459	1.49 (0.25-8.88)
MaVS	19	246	21	250	0.92 (0.51-1.67)
POISE	152	4174	215	4177	0.71 (0.58-0.87)
[illegible]	3	55	5	48	0.52 (0.13-2.08)
				109	2.97 (0.12-72.19)
					0.73 (0.61-0.88)
				53	0.05 (0.00-0.79)
				533	0.41 (0.20-0.81)
					0.21 (0.03-1.61)
Overall					0.67 (0.47-0.96)

$I^2 = 29\%$; $P = .21$

Interaction test between groups, $P = .22$

The pooled analysis is given a diamond shape where the widest bit in the middle is located at the calculated best guess (point estimate), and the horizontal width is the confidence interval

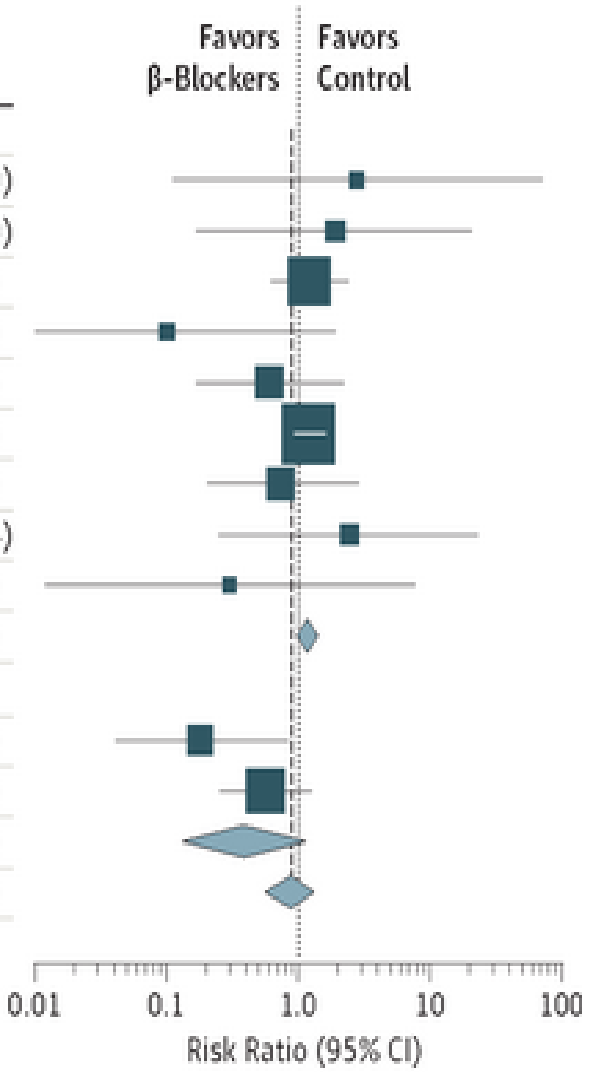


B Death

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
BBSA	1	110	0	109	2.97 (0.12-72.19)
Bayliff	2	49	1	50	2.04 (0.19-21.79)
DIPOM	20	462	15	459	1.32 (0.69-2.55)
MaVS	0	246	4	250	0.11 (0.01-2.09)
Neary	3	18	5	20	0.67 (0.19-2.40)
POISE	129	4174	97	4177	1.33 (1.03-1.73)
Mangano	4	99	5	101	0.82 (0.23-2.95)
POBBLE	3	55	1	48	2.62 (0.28-24.34)
Yang	0	51	1	51	0.33 (0.01-8.00)
Subtotal (I^2 = 0%; P = .68)					1.27 (1.01-1.60)
High risk of bias					
Poldermans	2	59	9	53	0.20 (0.05-0.88)
Dunkelgrun	10	533	16	533	0.63 (0.29-1.36)
Subtotal (I^2 = 44%; P = .18)					0.42 (0.15-1.23)
Overall					0.94 (0.63-1.40)

I^2 = 30%; P = .16

Interaction test between groups, P = .04



C Nonfatal stroke

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
POBBLE	1	53	0	44	2.50 (0.10-59.88)
DIPOM	2	462	0	459	4.97 (0.24-103.19)
MaVS	5	246	4	250	1.27 (0.35-4.67)
Yang	0	51	2	51	0.20 (0.01-4.07)
POISE	27	4174	14	4177	1.93 (1.01-3.68)
Subtotal (I^2 = 0%; P = .60)					1.73 (1.00-2.99)
High risk of bias					
Dunkelgrun	4	533	3	533	1.33 (0.30-5.93)
Overall					1.67 (1.00-2.80)

I^2 = 0%; P = .71

Interaction test between groups, P = .75

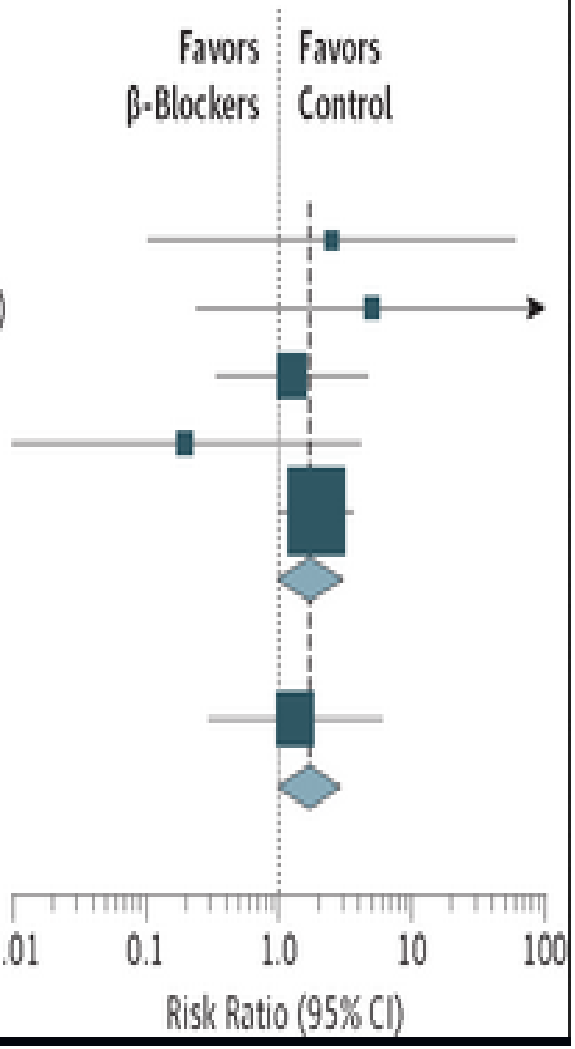


Table. Evidence Summary of the Perioperative β-Blockers Question

Outcome	No. of Participants (Trials)	Confidence	Relative Effect (95% CI)	Risk Difference per 1000 Patients[a]
Nonfatal myocardial infarction	10 189 (5)	High	0.73 (0.61-0.88)	14 fewer (6 fewer to 20 fewer)
Stroke	10 186 (5)	Moderate	1.73 (1.00- 2.99)	2 more (0 more to 6 more)
Death	10 529 (9)	Moderate	1.27 (1.01-1.60)	6 more (0 more to 13 more)

Second Judgement: What Is the Confidence in the Estimates of Effect?

How Serious is the Risk of Bias in the Body of Evidence?

Cochrane Risk of Bias Tool: 9 studies low-risk, 2 high

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding participants and researchers to the intervention a participant receives)
- Detection bias (blinding of outcome assessment from knowledge of what intervention a participant received)
- Attrition bias
- Reporting bias
- Other bias

Funnel plot: Used to assess publication bias; no evidence

Funding sources: Who funded the included studies, and might that contribute to bias?

Are the Results Consistent Across Studies? How Precise are the Results?

- Examine Forest Plot
- Calculate $I^{2:}$
  - Interpretation involves judgement, but as a general rule
    - 25% indicates low heterogeneity
    - 50% indicates moderate heterogeneity
    - 75% indicates high heterogeneity
- Perform subgroup analyses
- Perform test of interaction (low p-value means differences in subgroups less likely to be due to chance)

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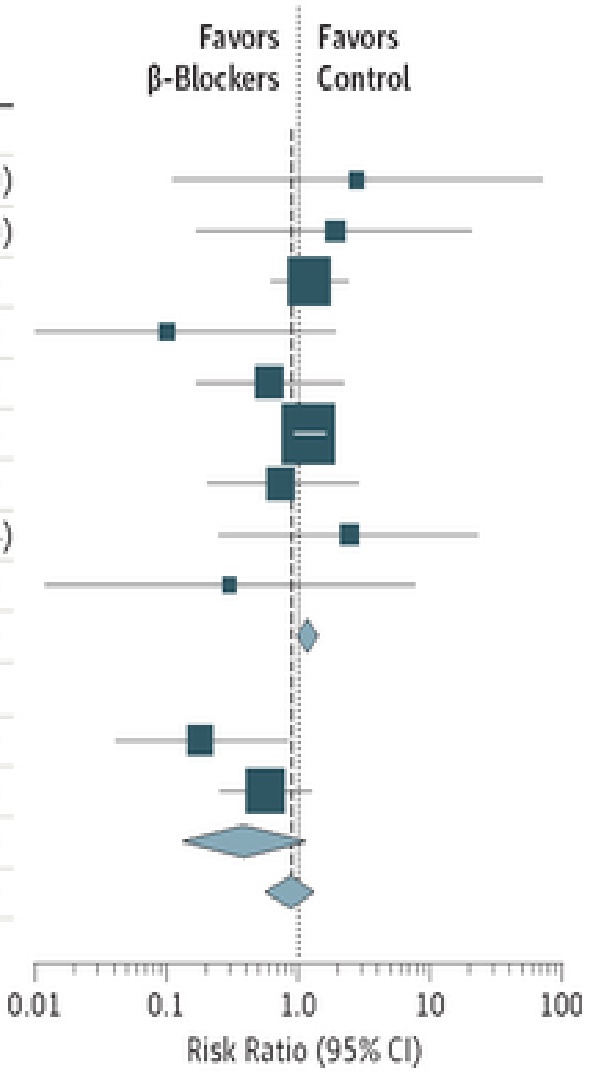

Do the Results Apply Directly to My Patient?

Look at the population, intervention and outcomes:

Population: What are the demographics of the participants in the included studies?

Interventions: Are the interventions compared with usual care, or head-to-head comparisons?

Outcomes: Are the outcomes examined in the meta-analysis the most relevant ones for you and your patient?

Conclusions

Was the Methodology of the Systematic Review Credible?

YES

What Is the Confidence in the Estimates of Effect?

Confidence in the Estimates

Overall, evidence warranting high confidence suggests that individuals with risk factors for heart disease can expect a reduction in risk of a perioperative nonfatal infarction of 14 in 1000 (from approximately 20 per 1000 to 6 per 1000). Unfortunately, they can also expect an increase in their risk of dying or having a nonfatal stroke. Because most people are highly averse to stroke and death, it is likely that the majority of patients faced with this evidence would decline β-blockers as part of their perioperative regimen. Indeed, that is what this patient decides when informed about the evidence.

Additional Resources

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA): http://www.prisma-statement.org/

Cochrane Handbook for Systematic Reviews of Interventions: http://training.cochrane.org/handbook

Scott Memorial Library: http://jefferson.libguides.com/systematicreviews

Recent DFCM meta-analysis: Cunningham AT, Crittendon DR, White N, Mills GD, Diaz V, LaNoue MD. The effect of diabetes self-management education on HbA1c and quality of life in African-Americans: a systematic review and meta-analysis. BMC health services research. 2018 Dec;18(1):367.