Sequential Methods for Meta-Analysis

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Meta-analyses can reduce research ”waste” and improve outcomes for patients

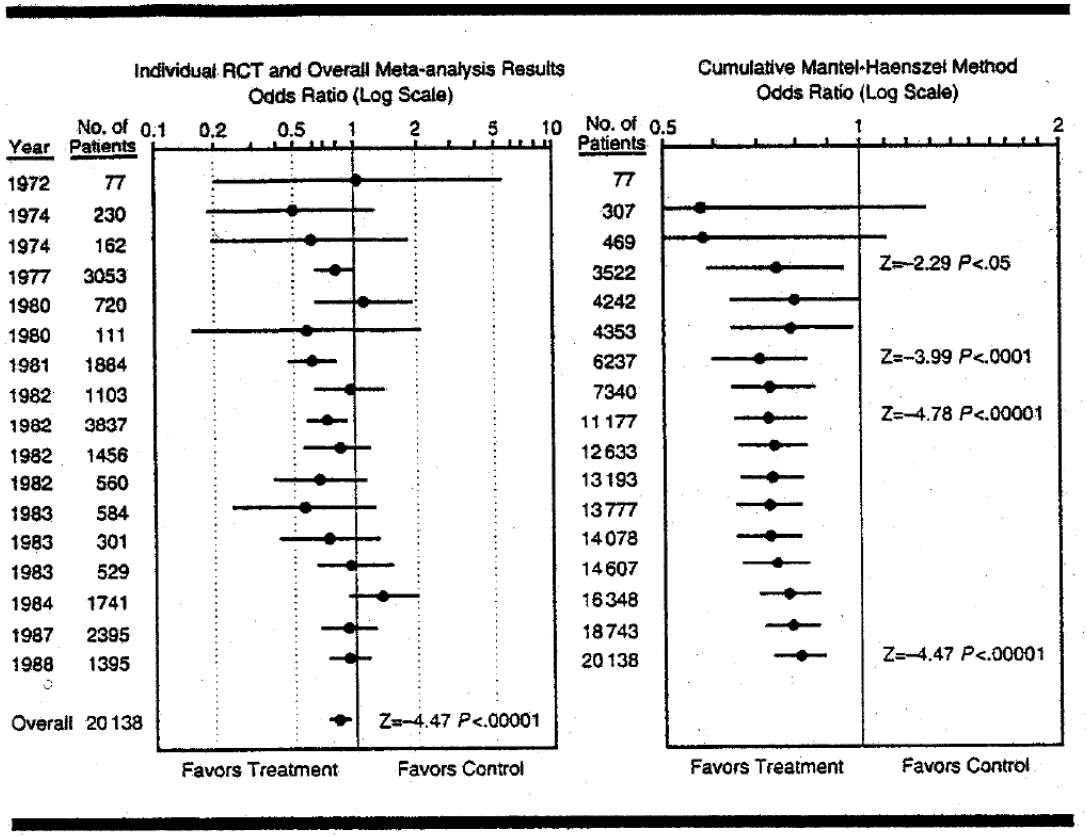


Fig 1.—Results of 17 randomized control trials (RCTs) of the effects of oral β-blockers for secondary prevention of mortality in patients surviving a myocardial infarction presented as two types of meta-analyses. On the left is the traditional one, revealing many trials with nonsignificant results but a highly significant estimate of the pooled results on the bottom of the panel. On the right, the same data are presented as cumulative meta-analyses, illustrating that the updated pooled estimate became statistically significant in 1977 and has remained so up to the present. Note that the scale is changed on the right graph to improve clarity of the confidence intervals.

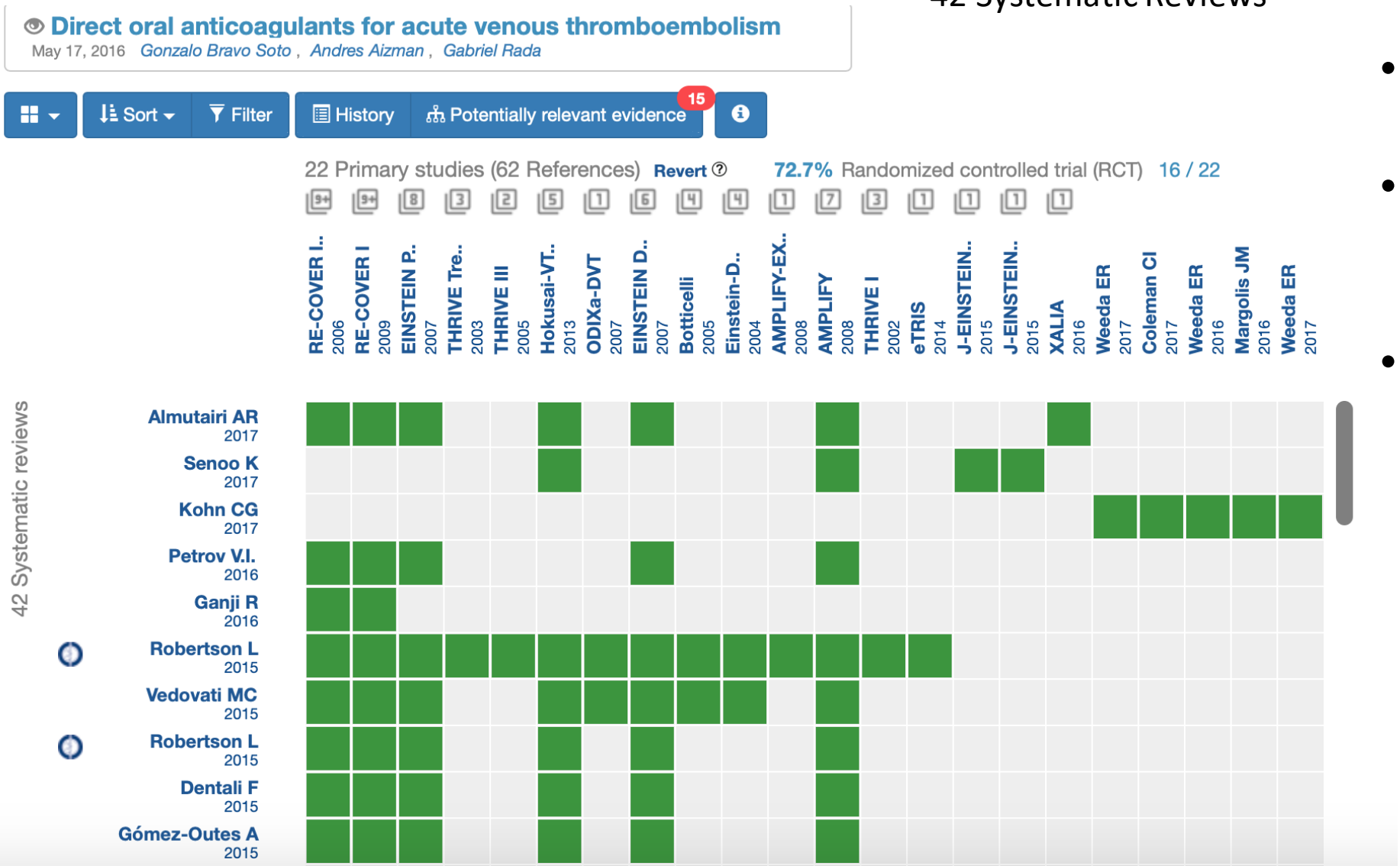
“In some cases effective treatments were not recommended for more than a decade after a meta-analysis of RCTs would have shown them to be effective”

Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: Treatments for myocardial infarction. JAMA. 1992;268:240-8

18 years later, we may have more meta-analyses than studies

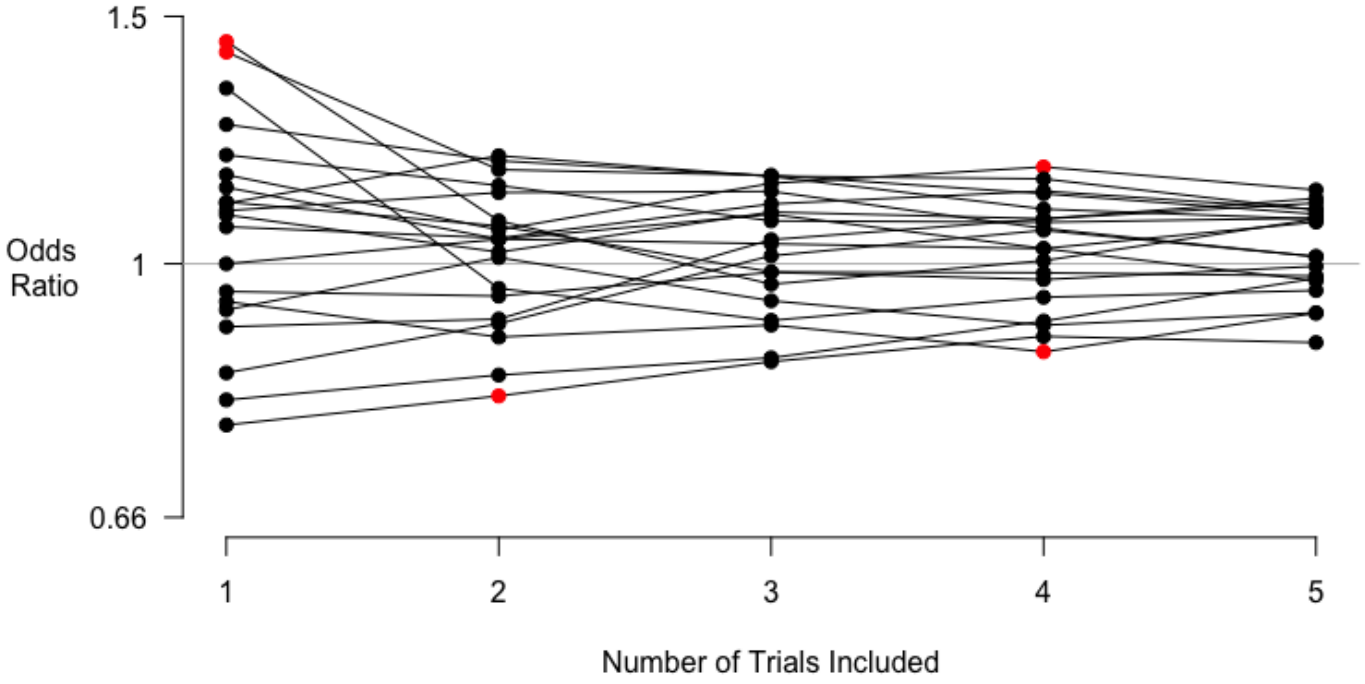
https://www.epistemonikos.org

22 Primary Studies,
42 Systematic Reviews



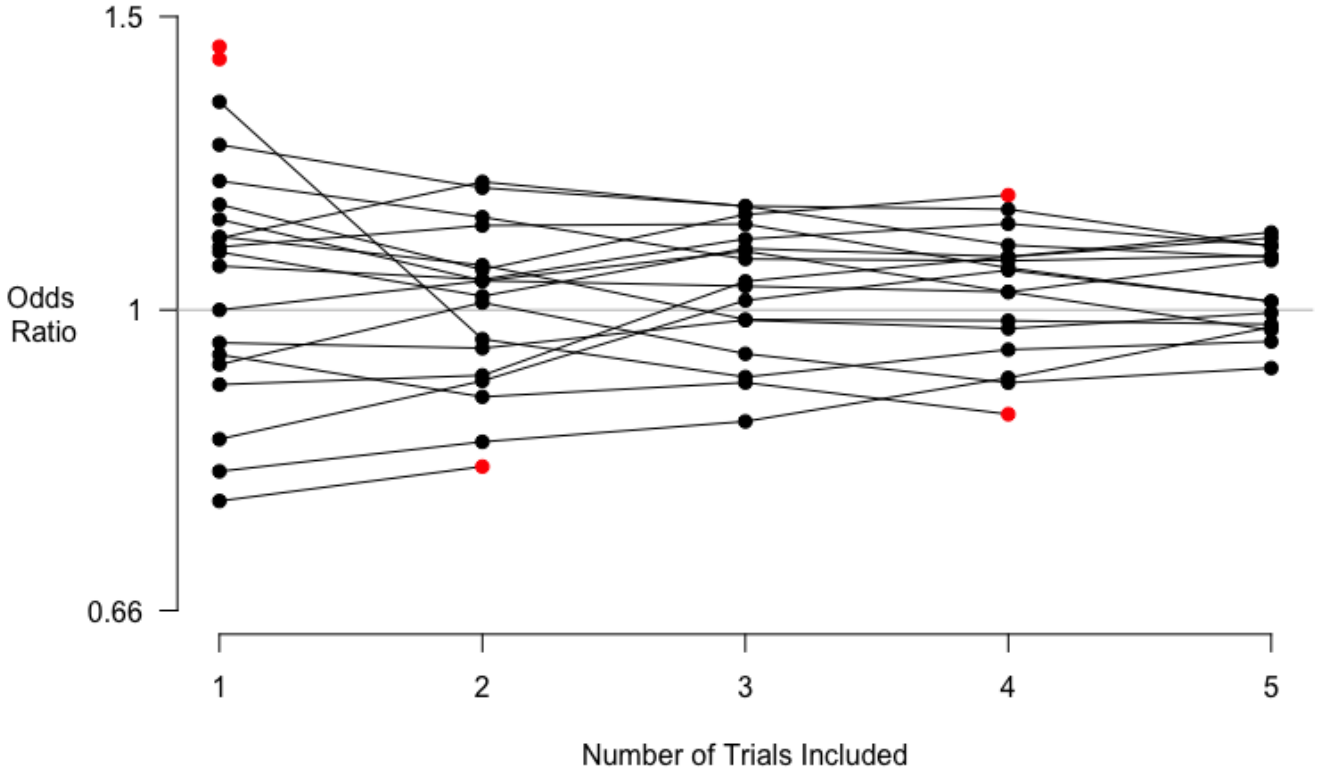
- Meta-analyses are essentially sequential
- Updated as new trials become available
- Living systematic reviews formalize this process
- May also be repeated with different selections of studies and endpoints

A simulation of repeated (sequential) meta-analyses, updated as new trials become available



- Binary endpoint
- No treatment effect
- Each trial is 100 subjects per arm
- Red points denote false positives ($p<0.05$)

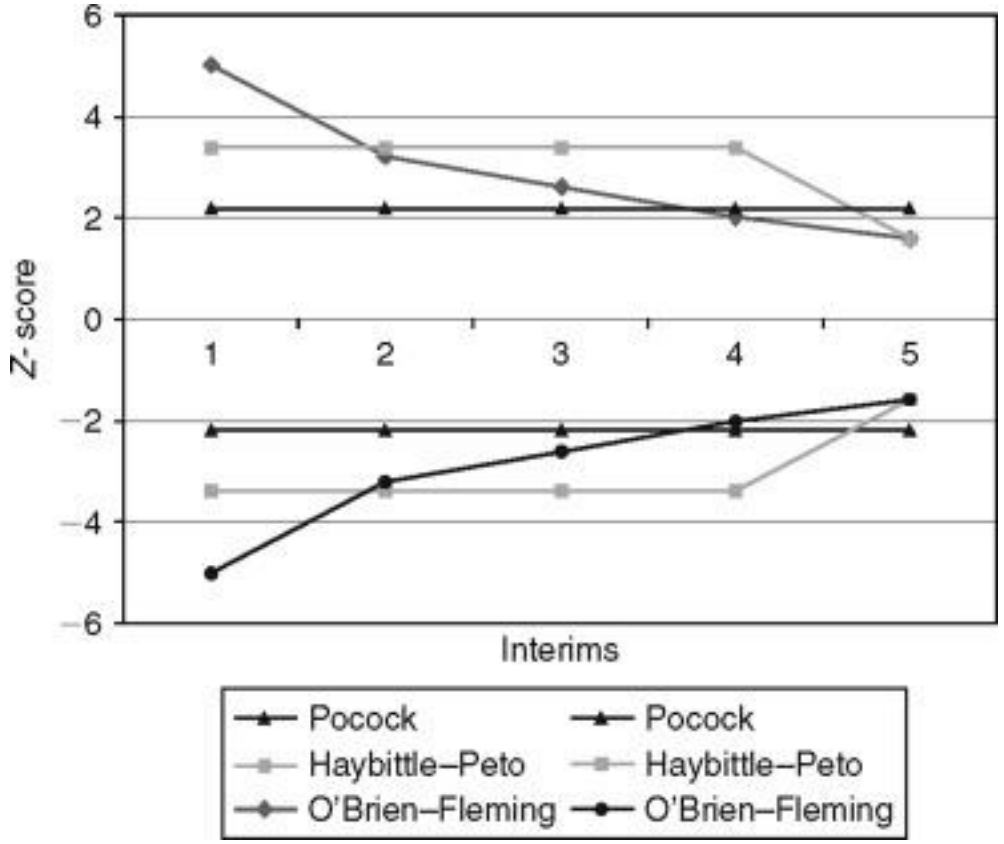
If the results of sequential meta-analyses effect the conduct of future trials…



If no further trials are conducted after statistically significant ($p<0.05$) meta-analysis

- False positive rate for final meta-analysis ($p<0.05$): 0.14
- Proportion of 95% confidence intervals for final meta-analysis including true value: 0.14

Individual trial analyses are carefully adjusted to take account of repeated efficacy analysis



- P-Values/confidence intervals are adjusted to take account of the effects of multiple 'looks' at the data

Corresponding approaches have been developed for meta-analyses…

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Apparently conclusive meta-analyses may be inconclusive—Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses

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Background Random error may cause misleading evidence in meta-analyses. The required number of participants in a meta-analysis (i.e. information size) should be at least as large as an adequately powered single trial. Trial sequential analysis (TSA) may reduce risk of random errors due to repetitive testing of accumulating data by evaluating meta-analyses not reaching the information size with monitoring boundaries. This is analogous to sequential monitoring boundaries in a single trial.

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Sequential methods for random-effects meta-analysis

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Although meta-analyses are typically viewed as retrospective activities, they are increasingly being applied prospectively to provide up-to-date evidence on specific research questions. When meta-analyses are updated account should be taken of the possibility of false-positive findings due to repeated significance tests. We discuss the use of sequential methods for meta-analyses that incorporate random effects to allow for heterogeneity across studies. We propose a method that uses an approximate semi-Bayes procedure to update evidence on the among-study variance, starting with an informative prior distribution that might be based on findings from previous meta-analyses. We compare our methods with other approaches, including the traditional method of cumulative meta-analysis, in a simulation study and observe that it has Type I and Type II error rates close to the nominal level. We illustrate the method using an example in the treatment of bleeding peptic ulcers.

Keywords: meta-analysis; sequential methods; cumulative meta-analysis; prospective meta-analysis; prior distributions

…and analytic solutions proposed

Arguments for adjusting meta-analyses to account for multiple looks

- If we do not adjust and the result of meta-analyses influence the conduct of future trials
  - Uncertainty in effect estimates of effects will be underestimated
  - Treatment effects will be over-estimated
- There may be multiple meta-analyses conducted as evidence develops
  - Not all by the same author (not all conducted by Cochrane)
- Cochrane guidance influences how others conduct their review
- Increasing emphasis on the evaluation of existing evidence before investing in new clinical trials
  - Can indicate whether further trials are ‘futile’

Arguments against adjusting meta-analyses to account for multiple looks: we don't need to do it

- Meta-analyses are not updated frequently enough for this to be a problem
- Meta-analyses should stand on their own, summarising current evidence. Decisions should not be influenced by previous meta-analyses or plans for future updates.
- Focus should be estimation of effect and its uncertainty (e.g. confidence interval), rather than rejection of the null hypothesis
- Recommendations (that a meta-analysis is no longer updated) are only made when the result is convincing for benefit (or harm) and when further data are likely to change conclusions. Ensuring conclusions are not based on "small amounts of evidence" will avoid "early stopping issues" which sequential methods are address
- It will increase the false negative rate

https://methods.cochrane.org/sites/default/files/public/uploads/tsa_expert_panel_guidance_and_recommendation_final.pdf

Arguments against adjusting meta-analyses to account for multiple looks: we cannot do it

- Meta-analyst has no control over designing of trials, therefore impossible to construct a set of workable stopping rules and design a retrospective sequential program that would maintain desirable properties as new studies appeared erratically.
- Meta-analyses do relate to a single decision or decision-maker, sequential adjustment will not capture the complexity of the decision-making process.
- 'Sequential methods have methodological limitations in the presence of heterogeneity'
- More complex than necessary?

https://methods.cochrane.org/sites/default/files/public/uploads/tsa_expert_panel_guidance_and_recommendation_final.pdf

Discussion

- Do we believe that there is a problem with estimates obtained from ‘repeated’ meta-analysis?
- What does this mean for ’living Systematic Reviews’
- Do the methods need to be ‘perfect’ to be useful?
  - Are they a useful ‘second best’ approach