Critical Appraisal of a Meta-Analysis: Rosiglitazone and CV Death

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Goal

To provide practitioners with a systematic approach to evaluating a meta analysis which can be applied to patient care and practice.
Learning Objectives

By the end of the session participants will:

- Understand how the approach to appraising a meta analysis article differs from an article about therapy, using the JAMA guideline framework.

- Apply the framework for assessing a meta-analysis to the Nissen and Wolski article “Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes”\(^1\).

1. NEJM 2007;356. p2457-2471
The Evidence Pyramid

- RCT-DB
- Cohort Studies
- Case control Studies
- Cross Sectional Surveys
- Case Series
- Case Reports

Meta-analysis/Systematic Reviews

Definitions

Overview: any summary article that attempts to address a focused clinical question.

Systematic Review: any summary article that attempts to address a focused clinical question using methods designed to reduce the likelihood of bias.

Meta Analysis: systematic reviews that use quantitative methods to summarize the results.
User’s Guide Framework for an article about Therapy

1. Are the Results Valid?
   • Were the patients randomized?
   • Were all the patients properly accounted for?
   • Blinding?
   • Were the groups similar at the start of the trial?
   • Were the groups treated equally?

2. What are the Results?
   • How large was the treatment effect? (ARR, RRR)
   • How precise was the estimate of the treatment effect? (CI’s)

3. Will the results help me in caring for my patients?
   • Can the results be applied to my patient(s)?
   • Were all clinically important outcomes considered?
   • Are the likely benefits worth the potential harm? (NNT)
User’s Guide Framework for a Meta-analysis

1. Are the results valid?
2. What are the results?
3. Will the results help me in caring for my patient(s)?
User’s Guide Framework for a Meta-analysis

1. Are the results valid?
   • Did the review explicitly address a focused clinical question?
   • Was the search for relevant studies detailed and exhaustive?
   • Were the primary studies of high methodologic quality?
   • Were the assessments of studies reproducible?

2. What are the results?
   • Were the results similar from study to study?
   • What are the overall results of the review?
   • How precise were the results?

3. Will the results help me in caring for my patients?
   • How can I best interpret the results to apply them to the care of patients in my practice?
   • Were all clinically important outcomes considered?
   • Are the benefits worth the potential harms and costs?
Applying the User’s Guide
Meta Analysis Framework
Did the Review explicitly address a sensible clinical question?²

- Should be apparent from the title or abstract.
  "Effect of Rosiglitazone on the risk of myocardial Infarction and death from cardiovascular causes."¹

- Sensible?
Was the search for relevant studies detailed and exhaustive?²

- Authors should indicate what they did to locate relevant studies that meet the inclusion criteria set out by the authors.
- Search should include databases like Embase, Medline, Cochrane Controlled Trials Register, personal contact with experts in the area, unpublished studies, studies “in press”, etc.
- Publication bias…
  - effect of not including unpublished studies
  - Impact of small number of studies with small sample sizes
Funnel Plots

Precision of estimate of treatment effect

Magnitude of the effect size
Funnel Plots²

Precision of estimate of treatment effect

Magnitude of the effect size

Favour Intervention

Favour Control

Trials missing
Was the search for relevant studies detailed and exhaustive?\(^1,2\)

Inclusion criteria:

1. randomized trials
2. comparing rosiglitazone (rsg) with placebo or active comparators
3. similar duration of treatment in all groups
4. more than 24 weeks of drug exposure, and
5. reported MI or death from CV causes.

- 116 studies were screened and 48 studies met the inclusion
- 6 studies excluded – did not report any MI or CV deaths
- 42 studies included
Were the primary studies of high Methodologic quality?\textsuperscript{1,2}

- Important to determine the validity of the individual trials used in the meta-analysis
- Differences in study design may impact on the results.
- Nissen review
  - 42 trials, all RCT’s (inclusion criteria)
  - None had CV events as the primary endpoint (and were not powered to evaluate this)
  - Initial rosiglitazone trials used surrogate markers of glycemic control as endpoints (not designed)
  - DREAM trial did look at MI or death from CV causes
Were the assessments of studies reproducible?

- Systematic reviews/meta-analysis should have at least 2 individuals assessing...
  - What studies to include
  - Validity of the studies selected
  - What date to extract

- Minimizes bias and errors
Were the results similar from study to study?

- Includes looking at differences in patients, interventions, outcome and research methods
  - Heterogeneity

- Are they similar enough to allow combining them to come up with a single estimate of the treatment effect?
  - “pooling”

- Forest Plots
Forest Plots

Individual Study Results used in Meta Analysis A

- Favours Treatment
- Favours Control
Forest Plots

Individual Study Results in Meta Analysis B

Favours Treatment  Favours Control
Forest Plots\(^4\)

**Individual Study Results used in Meta Analysis C**

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Favours Treatment  Favours Control
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![Diagram of Forest Plots](image)
Were the results similar from study to study?

- Pooled data was not intended to look at CV outcomes
- Limited access to patient level data
- Lack of data shown - no Forest Plot

Heterogeneity “p-values”:
MI = 0.53
Death due to CV causes = 0.68
What are the Overall Results of the Review? And how precise?

• **Summary Odds Ratio for**
  - MI = 1.43 (95% CI, 1.03-1.98; P= 0.03)\(^1\)

• **Summary Odds Ratio for**
  - death from CV causes = 1.64 (95% CI, 0.98-2.74; p=0.06)\(^1\)

**Absolute Numbers\(^1\)**
  - RSG = 86 Mi versus 72 in Control Group
  - RSG = 39 Death from CV cause vs 22 in Control

• **Total number of patients = 27,843!**
How can we interpret the results of this meta-analysis and apply it to practice?

- Interim results of RECORD
  - Non-significant
  - Losing patients due to Nissen article
- BARI – 2D
Homework!😊

• Apply the JAMA framework for Critically Appraising a meta-analysis to:


  ...and compare it how Nissen and Wolski conducted their Meta-Analysis.
References


3. Guyatt, G., Sackett, DL., Cook, DJ. How to use an article about therapy or prevention, B.: What were the results and will they help me in caring for my patients? JAMA January 5, 1994, Vol 271, no.1