# CINeMA

Confidence in Network Meta-Analysis

cinema.ispm.unibe.ch

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# Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis

William J Elliott, Peter M Meyer

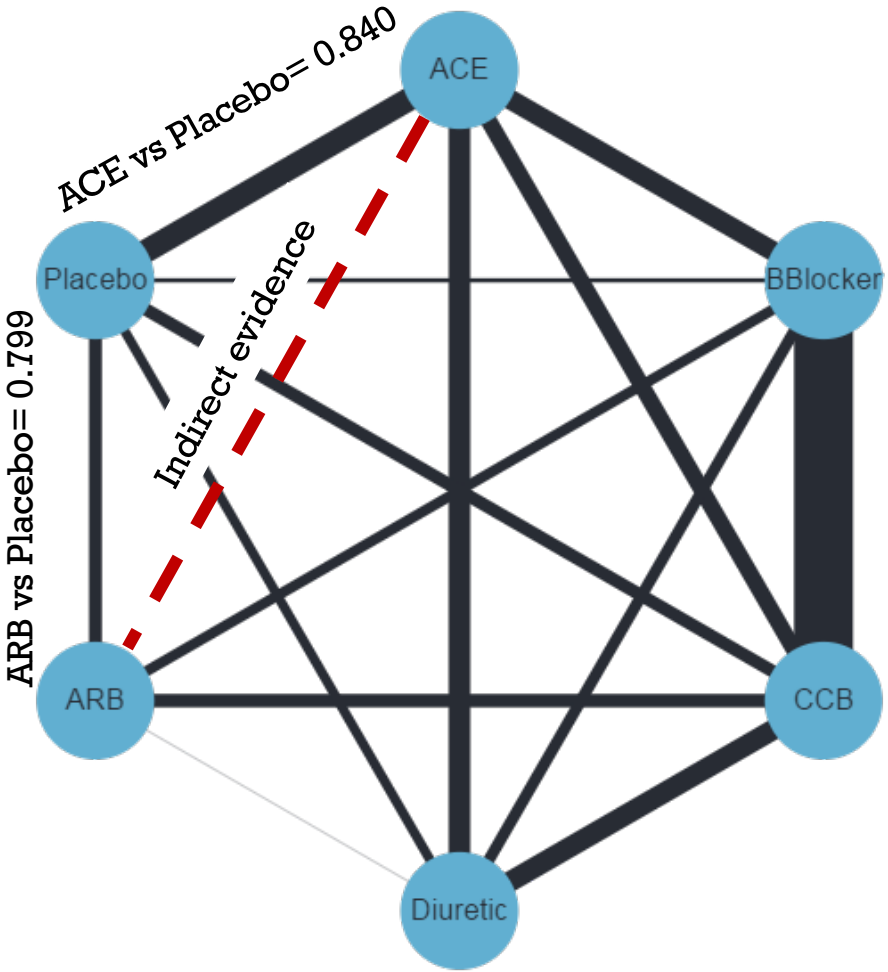

## Summary

**Background** The effect of different classes of antihypertensive drugs on incident diabetes mellitus is controversial because traditional meta-analyses are hindered by heterogeneity across trials and the absence of trials comparing angiotensin-converting-enzyme (ACE) inhibitors with angiotensin-receptor blockers (ARB). We therefore undertook a network meta-analysis, which accounts for both direct and indirect comparisons to assess the effects of antihypertensive agents on incident diabetes.


*Lancet* 2007; 369: 201–07

Department of Preventive Medicine, Rush Medical College of Rush University at Rush University Medical Center, Chicago, IL 60612, USA

| | |
|---|---|
| ***Number of studies*** | 22 |
| ***Number of treatment nodes*** | 6 |
| ***Primary outcome*** | Effect of antihypertensives on incidence diabetes mellitus - proportion of patients who developed diabetes |
| ***Measurement*** | Binary |
| ***Intervention comparison type*** | pharmacological vs placebo |




**Outcome: diabetes cases (Odds Ratio)**

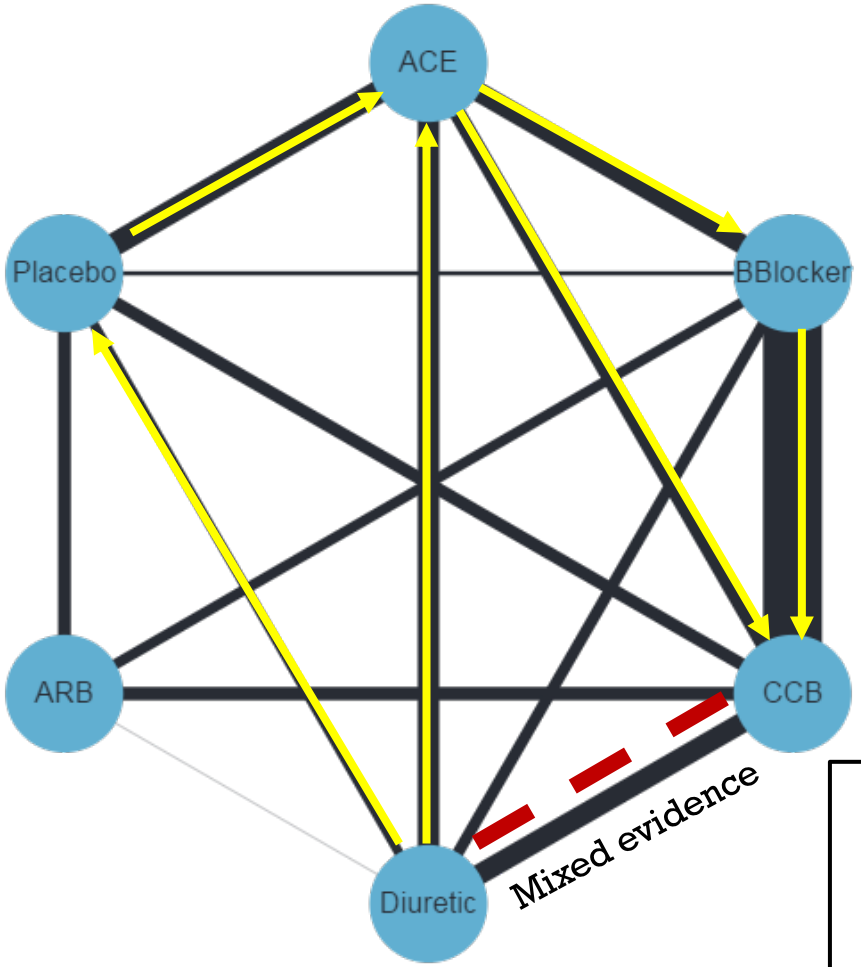
**Direct evidence**

*3 studies* ACE vs Placebo= 0.840 (0.762,0.924)

*2 studies* ARB vs Placebo= 0.799 (0.674,0.947)

$$\text{ACE vs ARB } \textbf{indirect} = \frac{\text{ACE vs Placebo}}{\text{ARB vs Placebo}}$$

ACE vs ARB **indirect**= 1.104 (0.987,1.235)



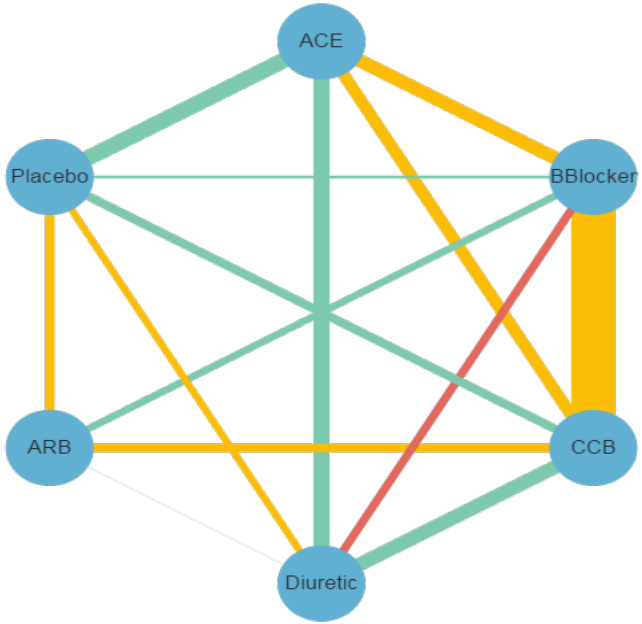

CCB vs Diuretics indirect= 0.731 (0.628,0.852)

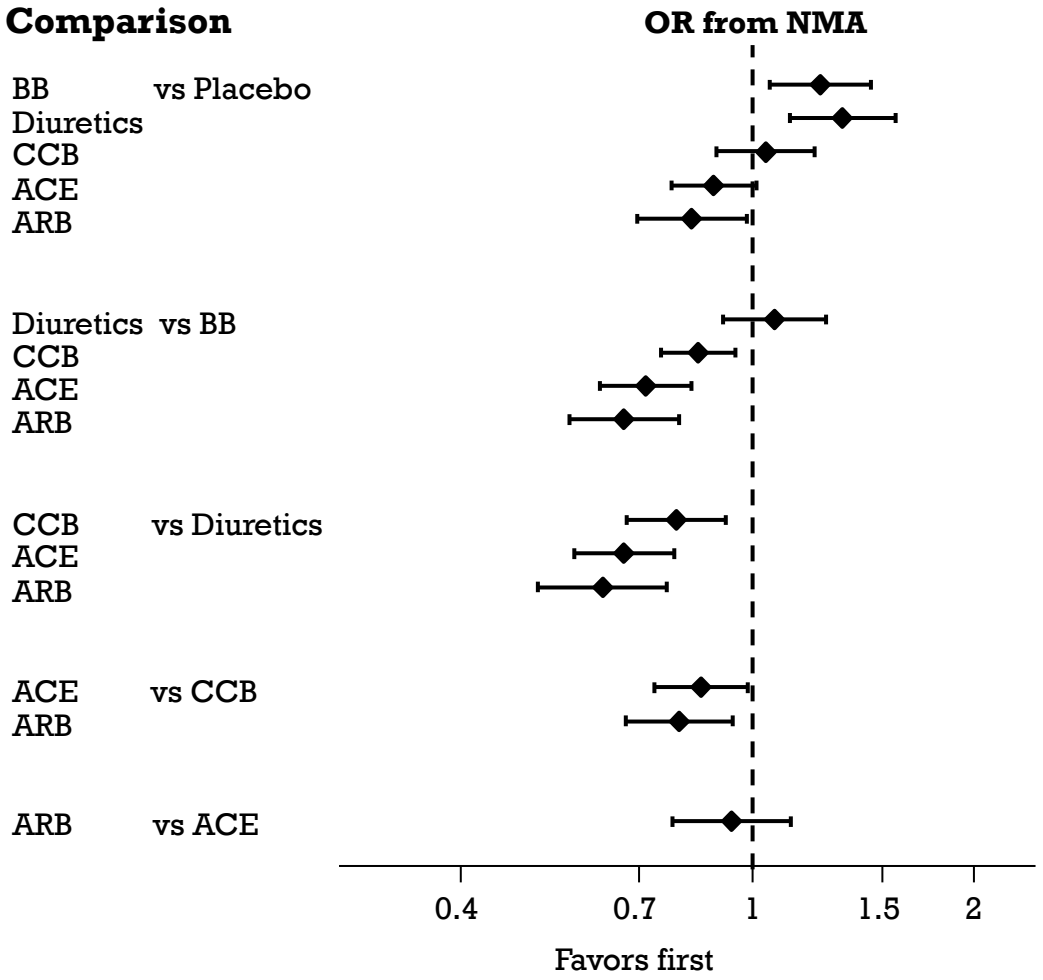
CCB vs Diuretics direct= 0.820 (0.706,0.954)

Meta-analyse direct and indirect (if they are in broad agreement…)

CCB vs Diuretics mixed= 0.775 (0.696,0.863)

Network meta-analysis is an extension of the idea of putting together direct and indirect evidence for any comparison in the network


ACE
Placebo
BBlocker
ARB
CCB
Diuretic


Comparison
OR from NMA
BB vs Placebo
Diuretics
CCB
ACE
ARB
Diuretics vs BB
CCB
ACE
ARB
CCB vs Diuretics
ACE
ARB
ACE vs CCB
ARB
ARB vs ACE
0.4
0.7
1
1.5
2
Favors first

# CINeMA framework

| Comparison | Number of Studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|---|---|---|---|---|---|---|---|---|
| Mixed evidence | | | | | | | | |
| ACE vs BBlocker | 3 | Some concerns | Undetected | No concerns | No concerns | No concerns | Some concerns | High |
| ACE vs CCB | 3 | No concerns | Undetected | No concerns | No concerns | Some concerns | No concerns | High |
| ACE vs Diuretic | 2 | No concerns | Undetected | No concerns | No concerns | No concerns | No concerns | High |
| ACE vs Placebo | 3 | No | | | | | concerns | High |
| ARB vs BBlocker | 1 | No | | | | | concerns | High |
| ARB vs CCB | 1 | Som | | | | | concerns | High |
| ARB vs Diuretic | 1 | No | | | | | concerns | High |
| ARB vs Placebo | 2 | No | | | | | concerns | High |
| BBlocker vs CCB | 5 | No | | | | | concerns | High |
| BBlocker vs Diuretic | 2 | No | | | | | concerns | High |
| BBlocker vs Placebo | 1 | No concerns | Suspected | No concerns | No concerns | Major concerns | Some concerns | High |
| CCB vs Diuretic | 2 | No concerns | Undetected | No concerns | No concerns | Some concerns | No concerns | High |
| CCB vs Placebo | 1 | No concerns | Suspected | No concerns | Major concerns | Major concerns | No concerns | High |
| Diuretic vs Placebo | 3 | No concerns | Suspected | No concerns | No concerns | Some concerns | No concerns | High |
| Indirect evidence | | | | | | | | |
| ACE vs ARB | -- | No concerns | Undetected | No concerns | Major concerns | Some concerns | No concerns | High |

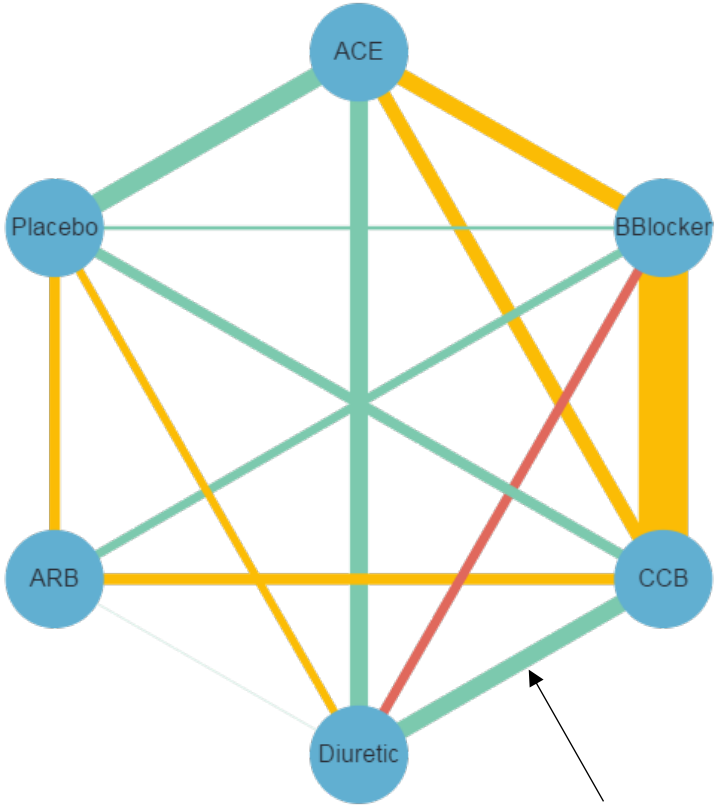
## Process

Explicit rules that classify each network meta-analysis effect for each domain to
No concerns, Some concerns, Major concerns
as described in the documentation

**The rules can be overwritten!**

# WITHIN-STUDY BIAS

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns

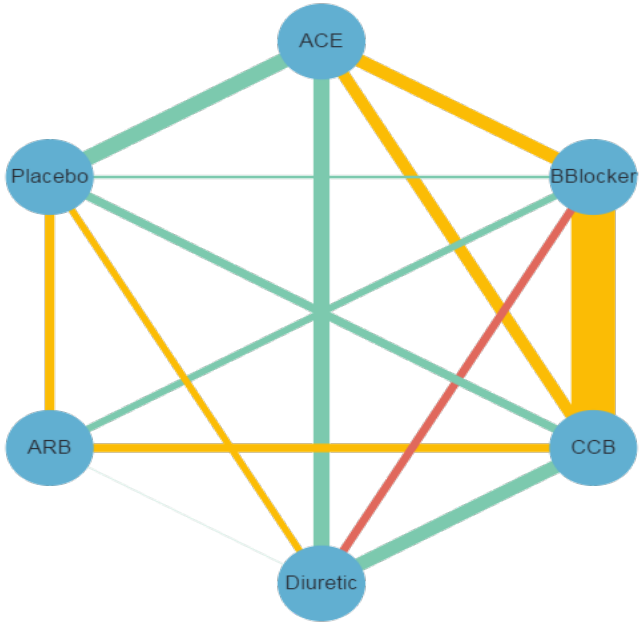



Plot direct comparison in green

**CCB vs Diuretics:** overall low risk of bias

Form risk of bias judgements for each study. Consider selection, performance, attrition, detection and reporting bias

| Study name | Risk of Bias |
|---|---|
| AASK | LOW |
| ALLHAT | LOW |
| ALPINE | LOW |
| ANBP-2 | LOW |
| ASCOT | LOW |
| CAPPP | MODERATE |
| CHARM | LOW |
| DREAM | LOW |
| EWPHE | MODERATE |
| FEVER | LOW |
| HAPPHY | HIGH |
| HOPE | LOW |
| INSIGHT | LOW |
| INVEST | LOW |
| LIFE | LOW |
| MRC | LOW |
| NORDIL | LOW |
| PEACE | LOW |
| SCOPE | MODERATE |
| SHEP | LOW |
| STOP-2 | MODERATE |
| VALUE | MODERATE |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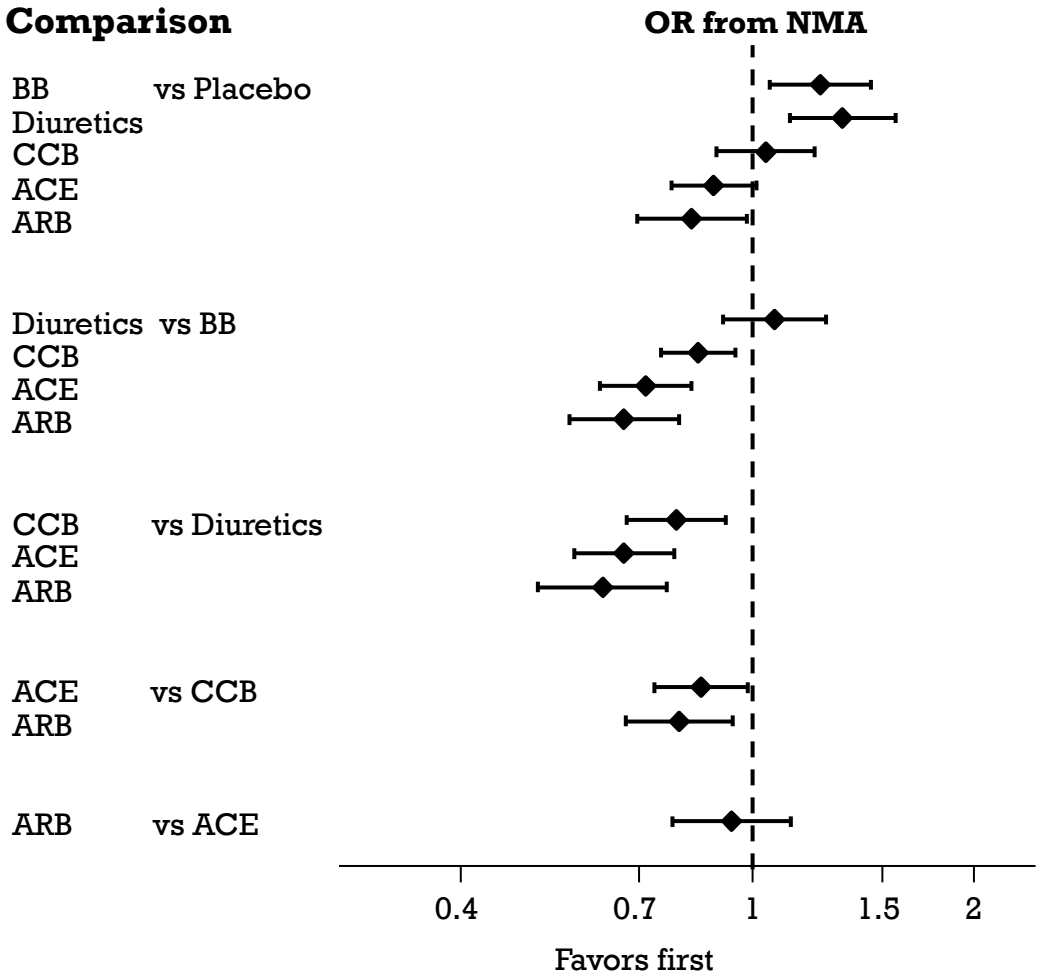
ARB
CCB
Diuretic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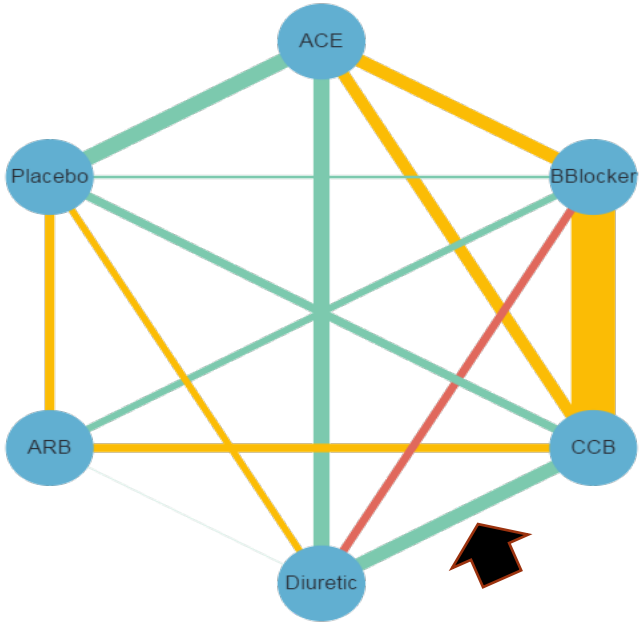
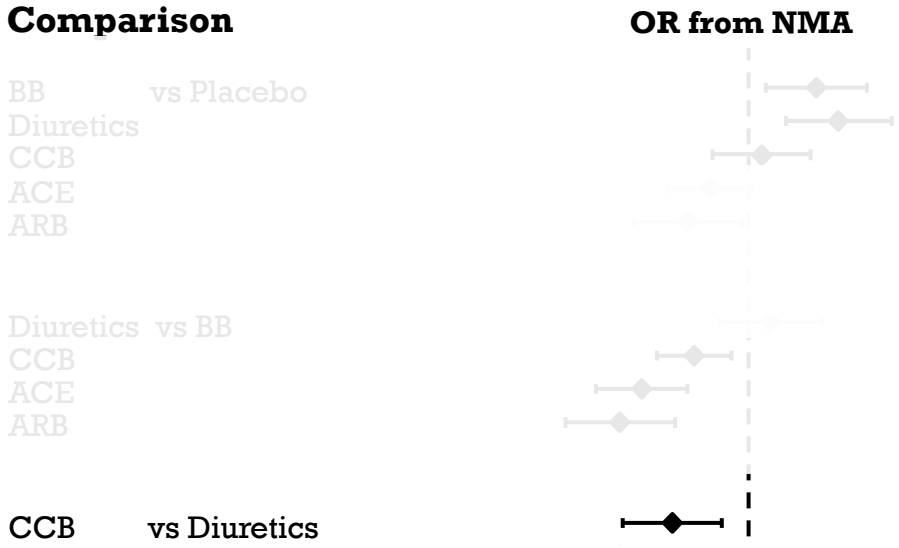
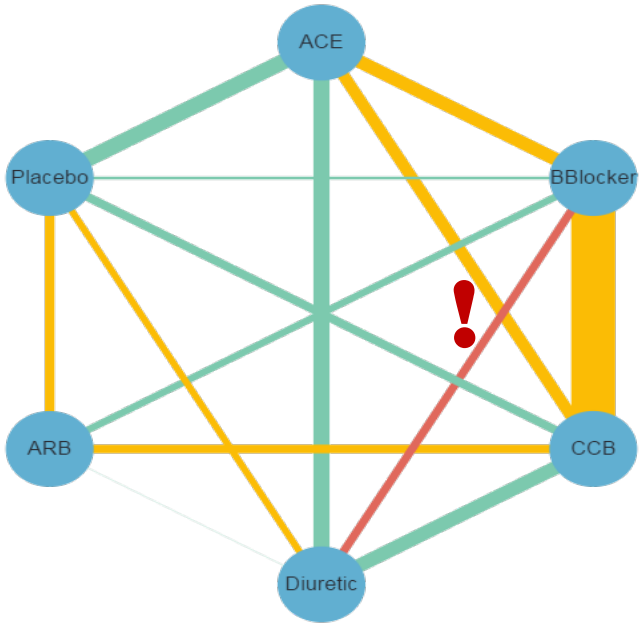


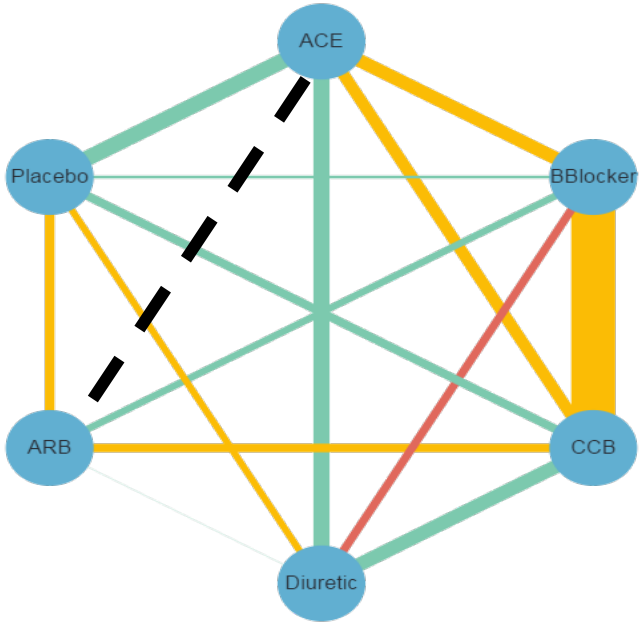




*What is your judgement about within-study bias for this (<u>mixed</u>) OR between CCB vs Diuretics estimated in network meta-analysis?*

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns



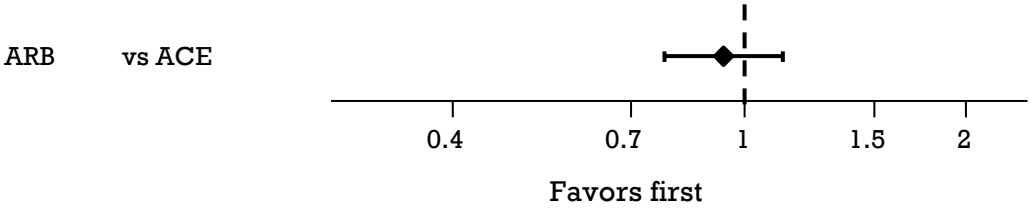

Studies with high risk of bias contribute to the estimation of the OR CCB vs Diuretics!




**Comparison** **OR from NMA**

*What is your judgement about study limitations for this (indirect) OR for ACE vs ARB estimated in NMA?*

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns



An indirect or mixed treatment effect is a combination of the available direct treatment effects

# The contribution matrix

| | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 | Study 7 | Study 8 | Study 9 | Study 10 | Study 11 | Study 12 | Study 13 | ..... |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mixed estimates** | | | | | | | | | | | | | | |
| ACE:BBlocker | 10 | 9 | 0 | 4 | 4 | 25 | 2 | 3 | 0 | 2 | 4 | 2 | 1 | 4 |
| ACE:CCB | 9 | 23 | 0 | 4 | 4 | 8 | 2 | 3 | 0 | 5 | 0 | 2 | 4 | 4 |
| ACE:Diuretic | 3 | 28 | 0 | 21 | 0 | 5 | 0 | 4 | 2 | 1 | 5 | 3 | 5 | 0 |
| ACE:Placebo | 2 | 6 | 0 | 4 | 0 | 3 | 2 | 23 | 1 | 5 | 0 | 15 | 0 | 0 |
| ARB:BBlocker | 2 | 0 | 0 | 0 | 5 | 3 | 6 | 2 | 0 | 1 | 2 | 1 | 0 | 5 |
| ARB:CCB | 1 | 3 | 0 | 0 | 4 | 0 | 7 | 2 | 0 | 5 | 0 | 1 | 2 | 4 |
| ARB:Diuretic | 1 | 12 | 1 | 4 | 0 | 1 | 10 | 2 | 2 | 0 | 6 | 1 | 8 | 0 |
| ARB:Placebo | 1 | 3 | 0 | 0 | 0 | 2 | 29 | 3 | 1 | 5 | 1 | 2 | 1 | 0 |
| BBlocker:CCB | 6 | 5 | 0 | 0 | 19 | 4 | 0 | 0 | 0 | 2 | 3 | 0 | 2 | 19 |
| BBlocker:Diuretic | 3 | 14 | 0 | 7 | 5 | 7 | 1 | 0 | 1 | 1 | 17 | 0 | 8 | 5 |
| BBlocker:Placebo | 4 | 3 | 0 | 0 | 4 | 8 | 5 | 7 | 2 | 8 | 4 | 4 | 1 | 4 |
| CCB:Diuretic | 2 | 30 | 0 | 6 | 3 | 1 | 1 | 0 | 1 | 4 | 6 | 0 | 20 | 3 |
| CCB:Placebo | 3 | 9 | 0 | 0 | 3 | 2 | 5 | 6 | 2 | 20 | 1 | 4 | 4 | 3 |
| Diuretic:Placebo | 0 | 12 | 0 | 7 | 0 | 1 | 2 | 6 | 7 | 6 | 3 | 4 | 5 | 0 |
| **Indirect estimates** | | | | | | | | | | | | | | |
| ACE:ARB | 4 | 8 | 0 | 3 | 0 | 7 | 11 | 7 | 0 | 0 | 1 | 5 | 1 | 0 |

Papakonstantinou T, Nikolakopoulou A, Rücker G *et al.* Estimating the contribution of studies in network meta-analysis: paths, flows and streams [version 1]. *F1000Research* 2018, 7:610

An indirect or mixed treatment effect is a combination of the available direct treatment effects

## The contribution matrix

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| ARB:CCB | 1 | 3 | 0 | 0 | 4 | 0 | 7 | 2 | 0 | 5 | 0 | 1 | 2 | 4 |
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| ARB:Placebo | 1 | 3 | 0 | 0 | 0 | 2 | 29 | 3 | 1 | 5 | 1 | 2 | 1 | 0 |
| BBlocker:CCB | 6 | 5 | 0 | 0 | 19 | 4 | 0 | 0 | 0 | 2 | 3 | 0 | 2 | 19 |
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| Diuretic:Placebo | 0 | 12 | 0 | 7 | 0 | 1 | 2 | 6 | 7 | 6 | 3 | 4 | 5 | 0 |
| **Indirect estimates** | | | | | | | | | | | | | | |
| ACE:ARB | 4 | 8 | 3 | | | | | | | | | | | |

An indirect or mixed treatment effect is a combination of the available direct treatment effects

# The contribution matrix

| | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 | Study 7 | Study 8 | Study 9 | Study 10 | Study 11 | Study 12 | Study 13 | ..... |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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| ACE:BBlocker | 10 | 9 | 0 | 4 | 4 | 25 | 2 | 3 | 0 | 2 | 4 | 2 | 1 | 4 |
| ACE:CCB | 9 | 23 | 0 | 4 | 4 | 8 | 2 | 3 | 0 | 5 | 0 | 2 | 4 | 4 |
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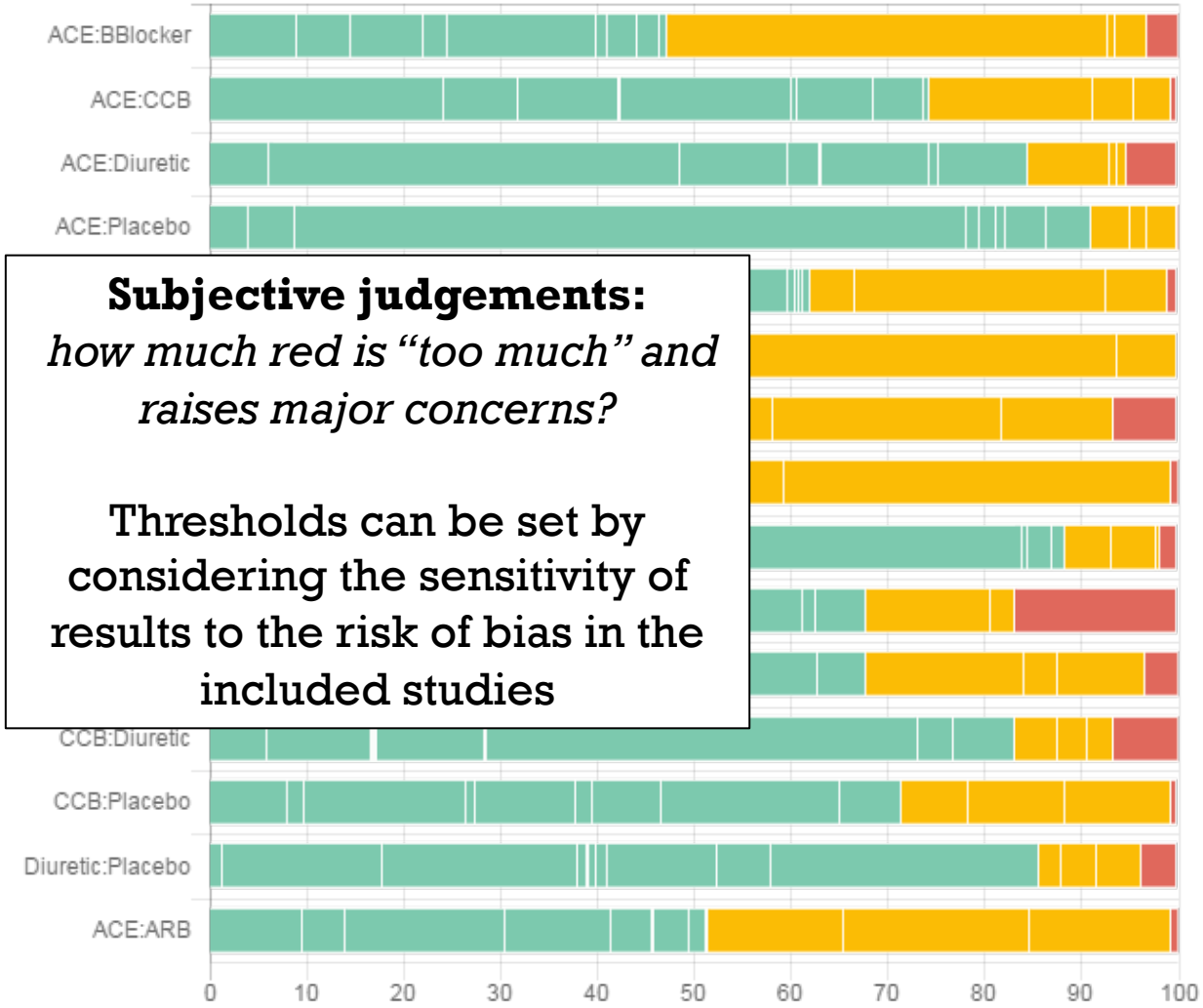
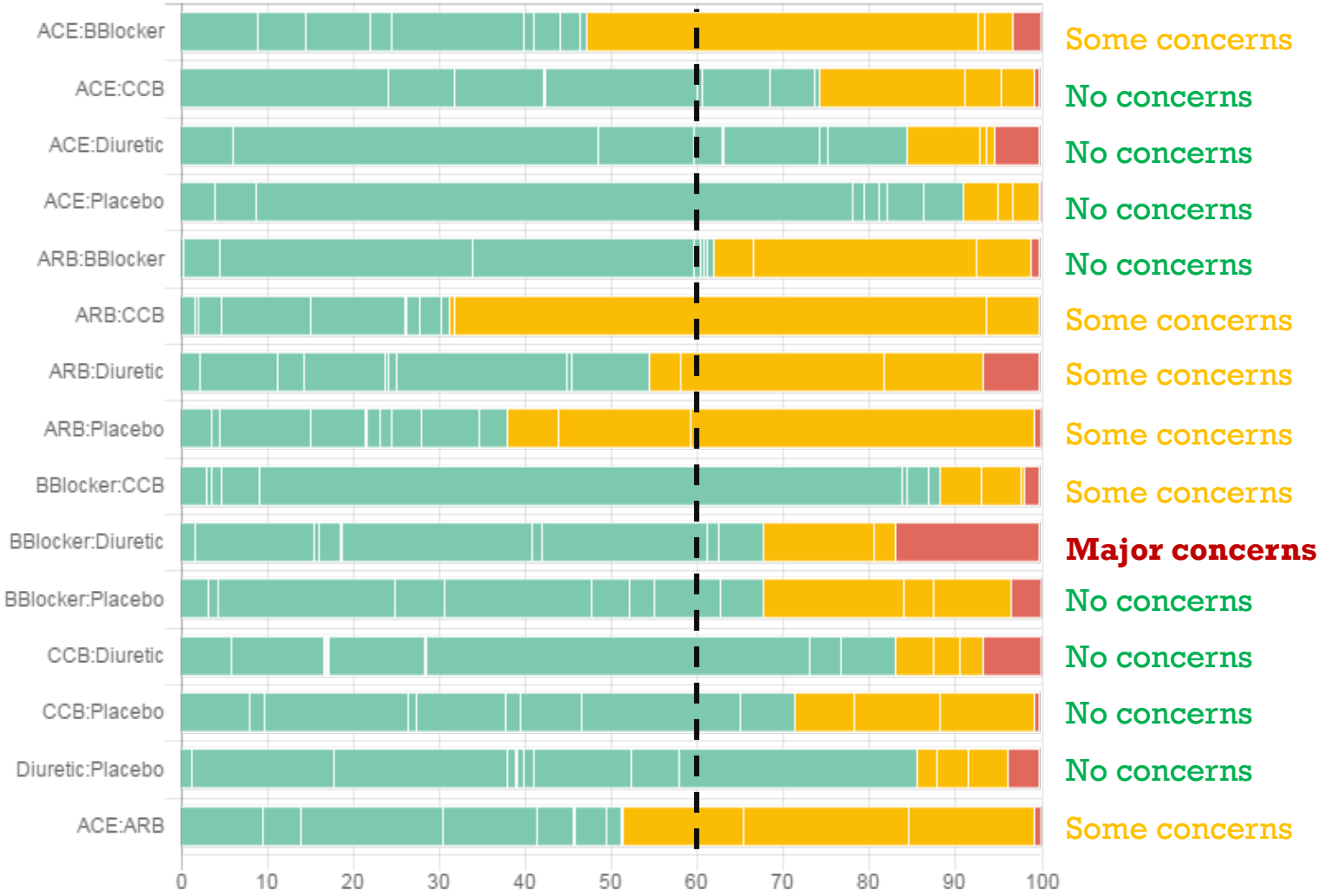
| **Indirect estimates** | | | | | | | | | | | | | | |
| ACE:ARB |  | | | | | | | | | | | | | |




**Subjective judgements:**
*how much red is "too much" and raises major concerns?*

Thresholds can be set by considering the sensitivity of results to the risk of bias in the included studies


ACE:BBlocker
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BBlocker:Diuretic
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CCB:Placebo
Diuretic:Placebo
ACE:ARB
0
10
20
30
40
50
60
70
80
90
100
Some concerns
No concerns
No concerns
No concerns
No concerns
Some concerns
Some concerns
Some concerns
Some concerns
Major concerns
No concerns
No concerns
No concerns
No concerns
Some concerns

# INDIRECTNESS

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns

*The idea is to evaluate the confidence intervals and the prediction intervals against the spectrum of values relevant to decision-making.*

# INDIRECTNESS

- Considerations similar to those in a pairwise meta-analysis
- **How relevant is the study PICO and setting to the research question?**
- **Score each study at 3 levels**
  - Low indirectness to the research question
  - Moderate indirectness to the research question
  - High indirectness to the research question
- Then study-level judgements are summarized within pairwise comparisons and across the network using the contribution matrix exactly as with the Risk of Bias.
- This also addresses the condition of transitivity!
  - If the studies across comparisons have differences in important characteristics (e.g. effect modifiers) compared to the target population, then the transitivity assumption is challenged

Now it is time for….

# IMPRECISION

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns

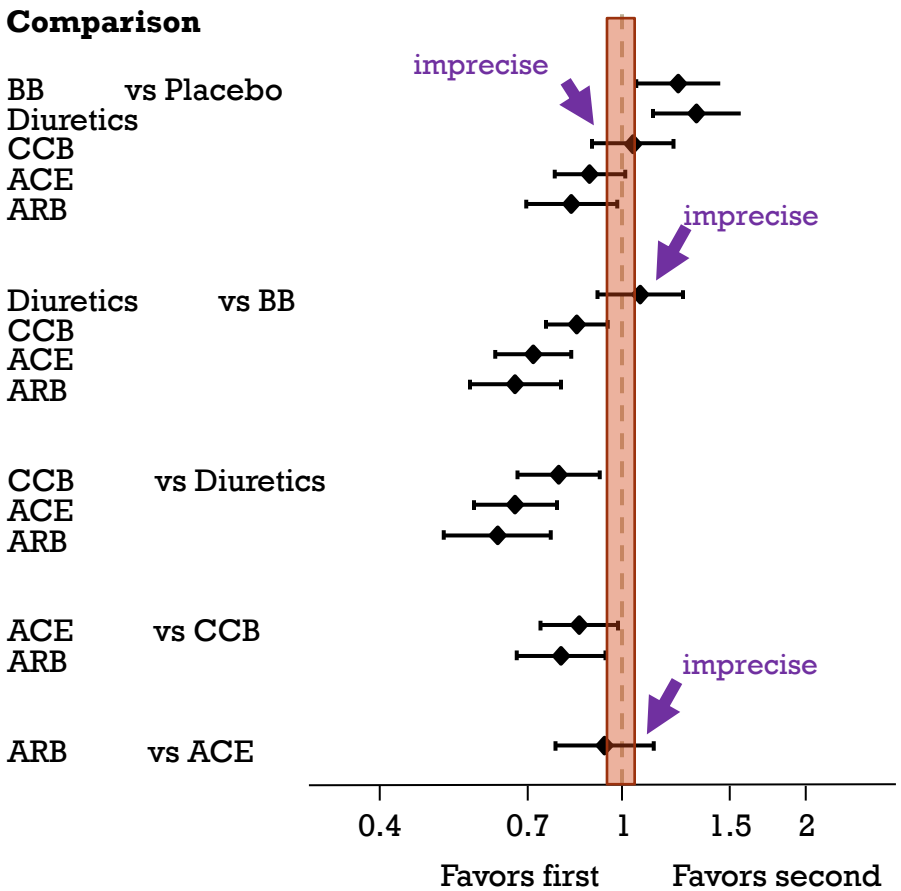
# IMPRECISION

- Traditional GRADE considers, among others, the total sample size available and compares it with the Optimal Information Size
- The sample size in a NMA relative effect makes little sense (as studies in the network contribute direct and indirect information!)
- Imprecision relates to the width of the 95% confidence interval:

**Does the 95% CI include values that lead to different clinical decisions?**

- Set a ”margin of equivalence”
  - the range of relative treatment effect around the no-effect line that do not signify important differences between the interventions

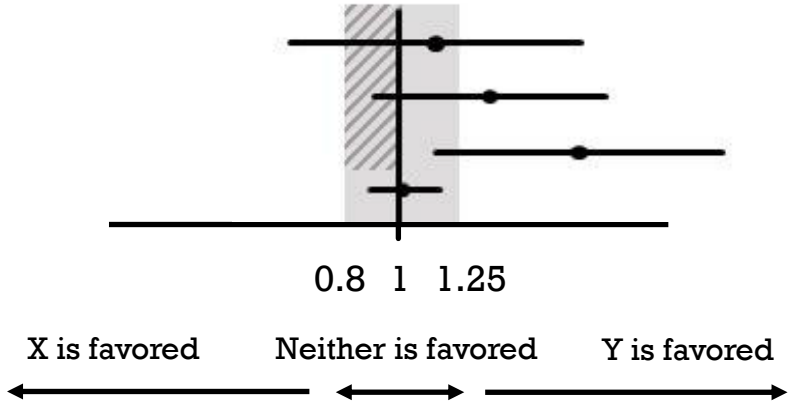
# NMA estimated odds ratios for diabetes




**Imprecision:**
Confidence intervals include values that lead into different clinical decisions

Margin of equivalence:
OR=1.05 in either direction
Imprecision when the confidence interval **crosses both 0.95 and 1.05**

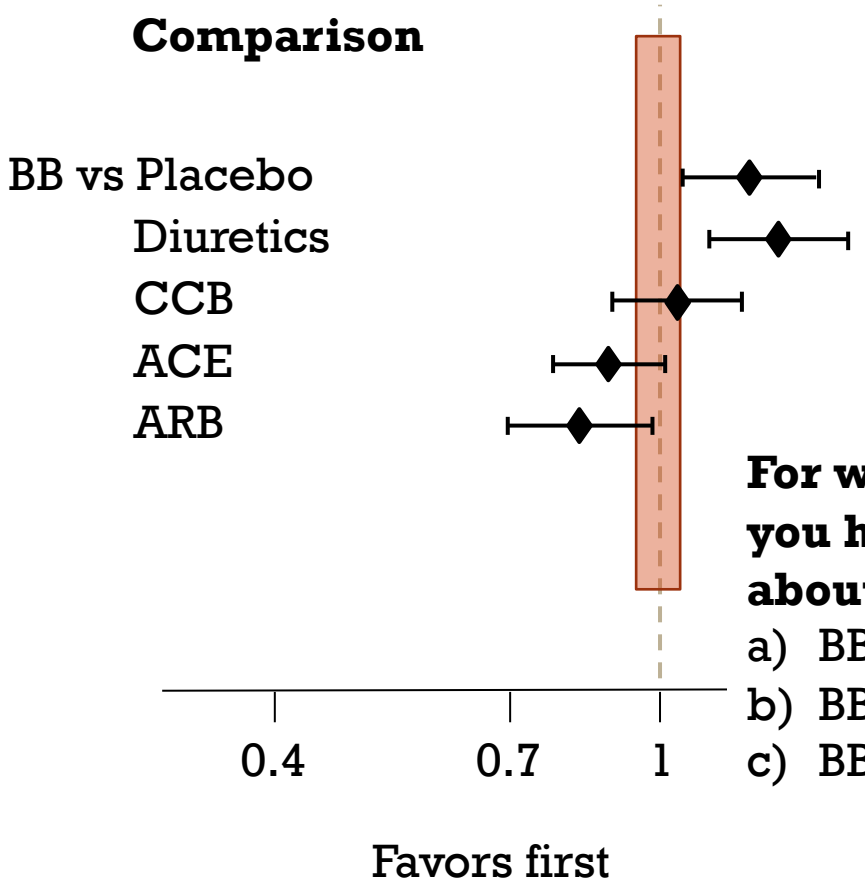
# IMPRECISION




1 **Major concerns**
2 Some concerns
3 No concerns
4 No concerns

Compare the 95% confidence interval with a **subset of the range of equivalence,** the range between the no effect line and the edge of the range of equivalence that is in the direction opposite to the observed point estimate.

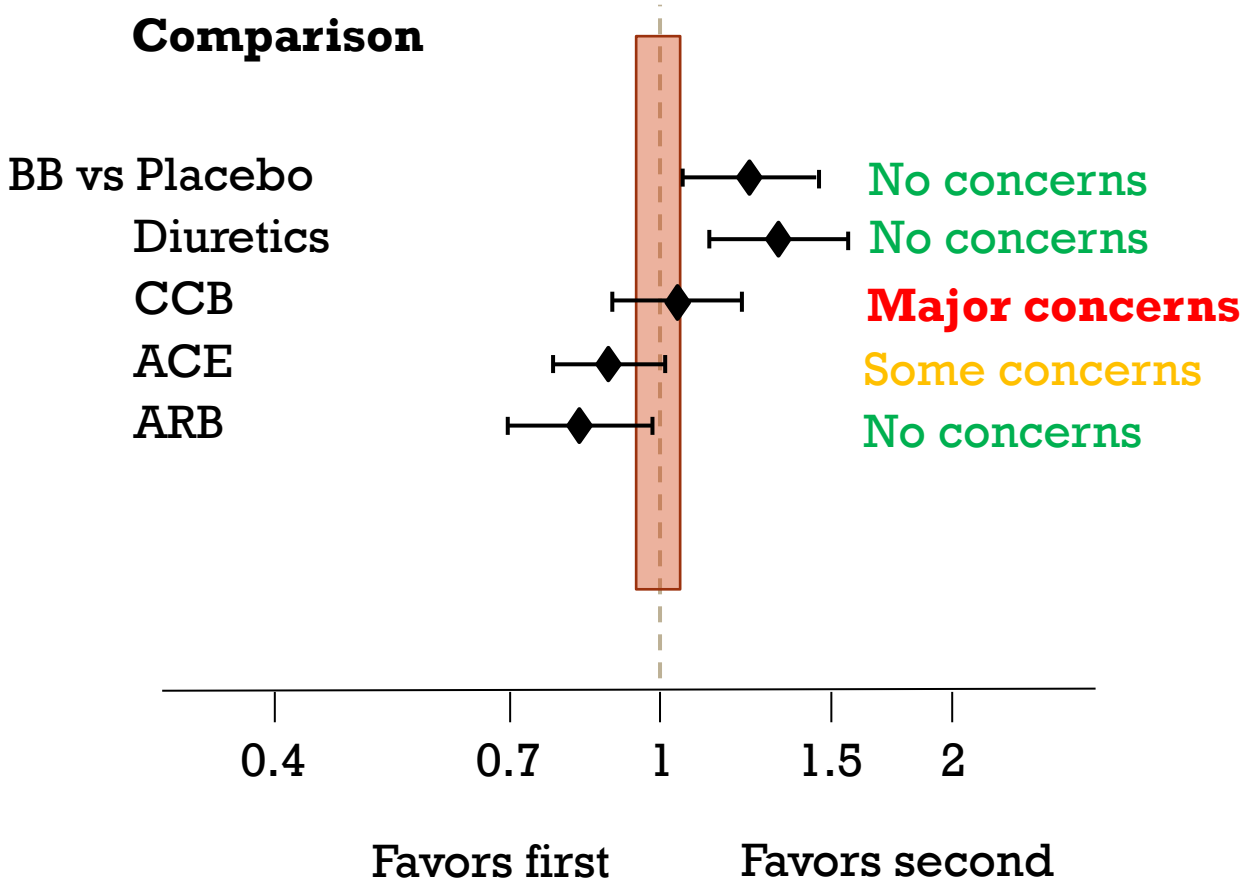
# NMA estimated odds ratios for diabetes




**For which comparison do you have major concerns about imprecision?**

a) BB vs CCB
b) BB vs ACE
c) BB vs ARB

# NMA estimated odds ratios for diabetes



Now it is time for….

# VARIABILITY BEYOND CHANCE

**Heterogeneity**

between-study variance within a comparison

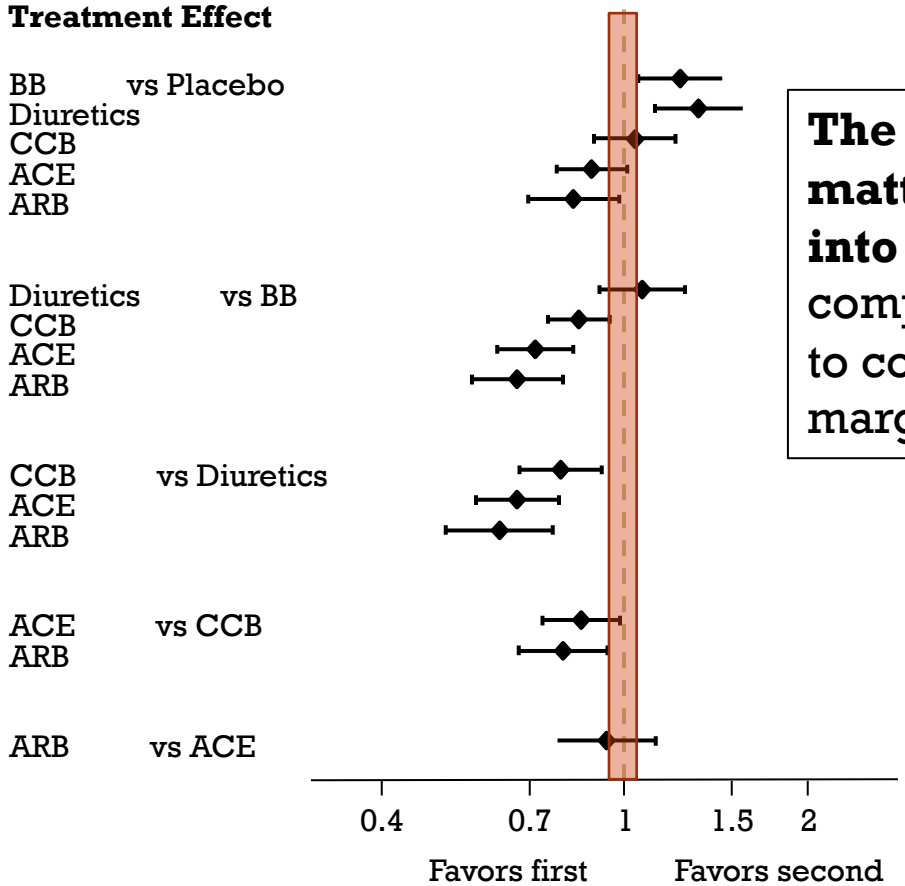
- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns

# HETEROGENEITY

- The major driver in judging heterogeneity is whether it impacts on clinical decisions
- Heterogeneity is represented by the **predictive intervals**: the intervals within which we expect to find the true effect size of a new study
- They are extensions of the confidence intervals

# HETEROGENEITY




**The amount of heterogeneity matters only when it leads into different conclusions:** compare prediction intervals to confidence intervals and the margin of equivalence.

# HETEROGENEITY

**Prediction interval:**
Where is the true effect in a new study?

Heterogeneity changes conclusions!

**Treatment Effect**

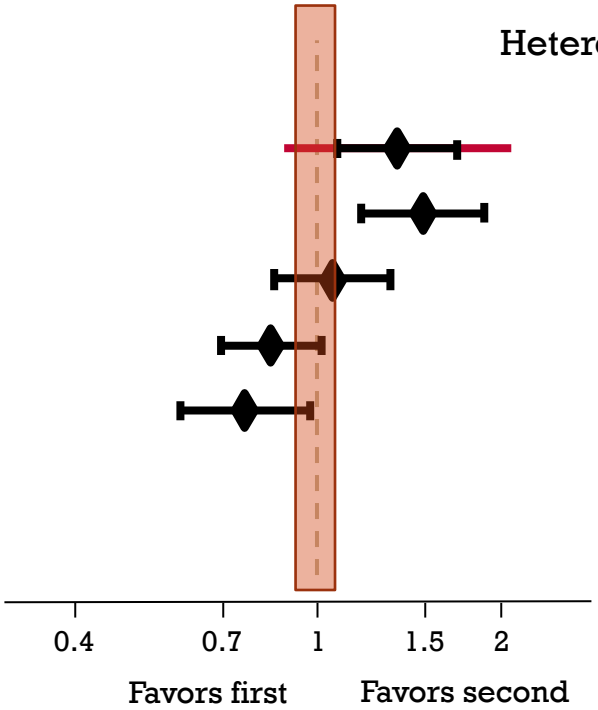
BB vs Placebo

Diuretics

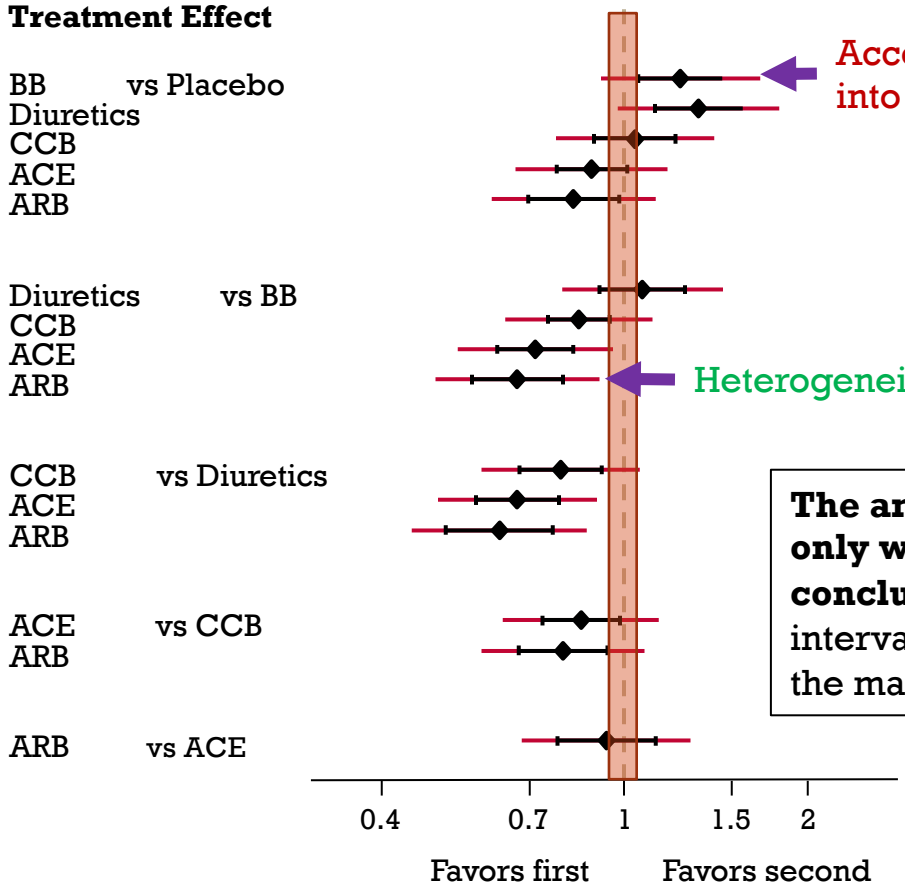
CCB

ACE

ARB



# HETEROGENEITY



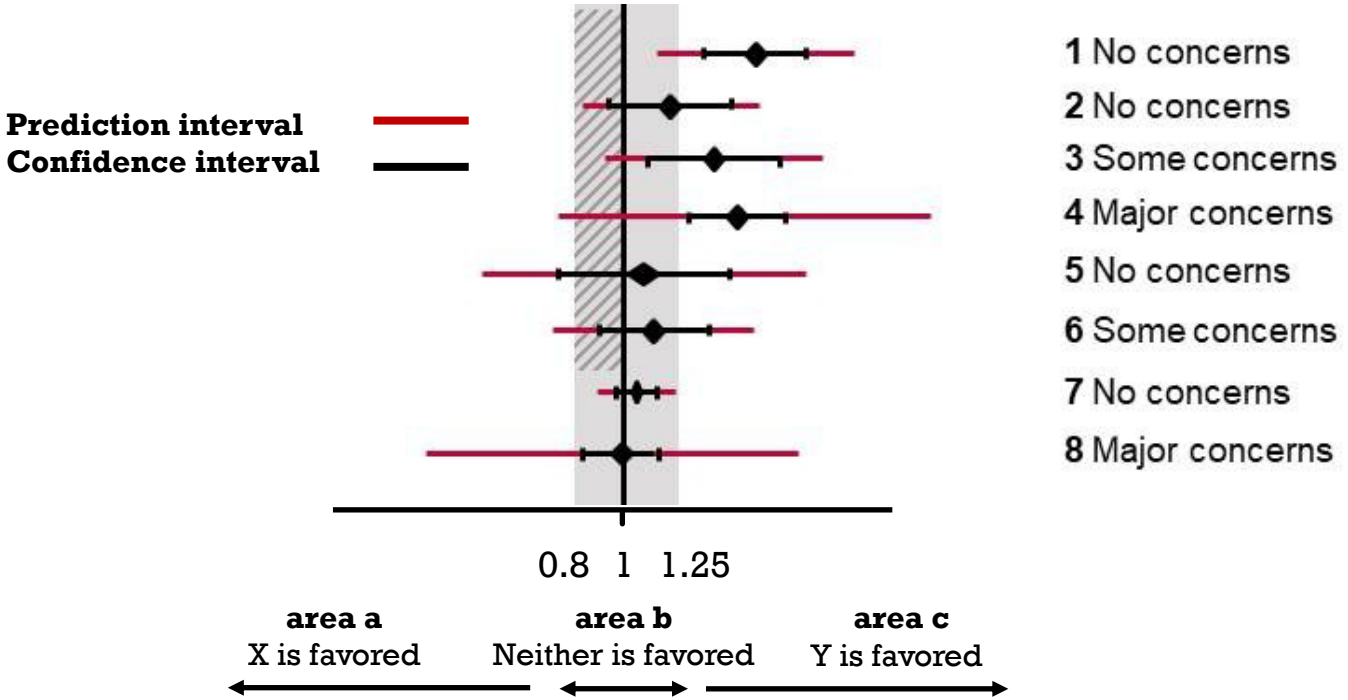

Accounting for heterogeneity leads into different clinical decisions!

Heterogeneity does not changes conclusions!

**The amount of heterogeneity matters only when it leads into different conclusions:** compare prediction intervals to confidence intervals and the margin of equivalence.

# HETEROGENEITY

Rules implemented in the software



# HETEROGENEITY

- The major driver or our decisions is whether the heterogeneity impacts on clinical decisions
- Heterogeneity is represented by the **predictive intervals**: the intervals within which we expect to find the true effect size of a new study
- They are extensions of the confidence intervals
- Pairwise meta-analysis heterogeneity variances $\tau^2$ can be estimated
  - But their estimation makes sense when you have enough studies
  - The observed values of $\tau^2$ can be compared with the expected values from empirical evidence *(Turner et al Int J Epidemiol. 2012, Rhodes et al. J Clin Epidemiol. 2015)*
  - The expected values depend on the nature of the outcome and the treatments being compared

# VARIABILITY BEYOND CHANCE

**Heterogeneity**
between-study variance within a comparison

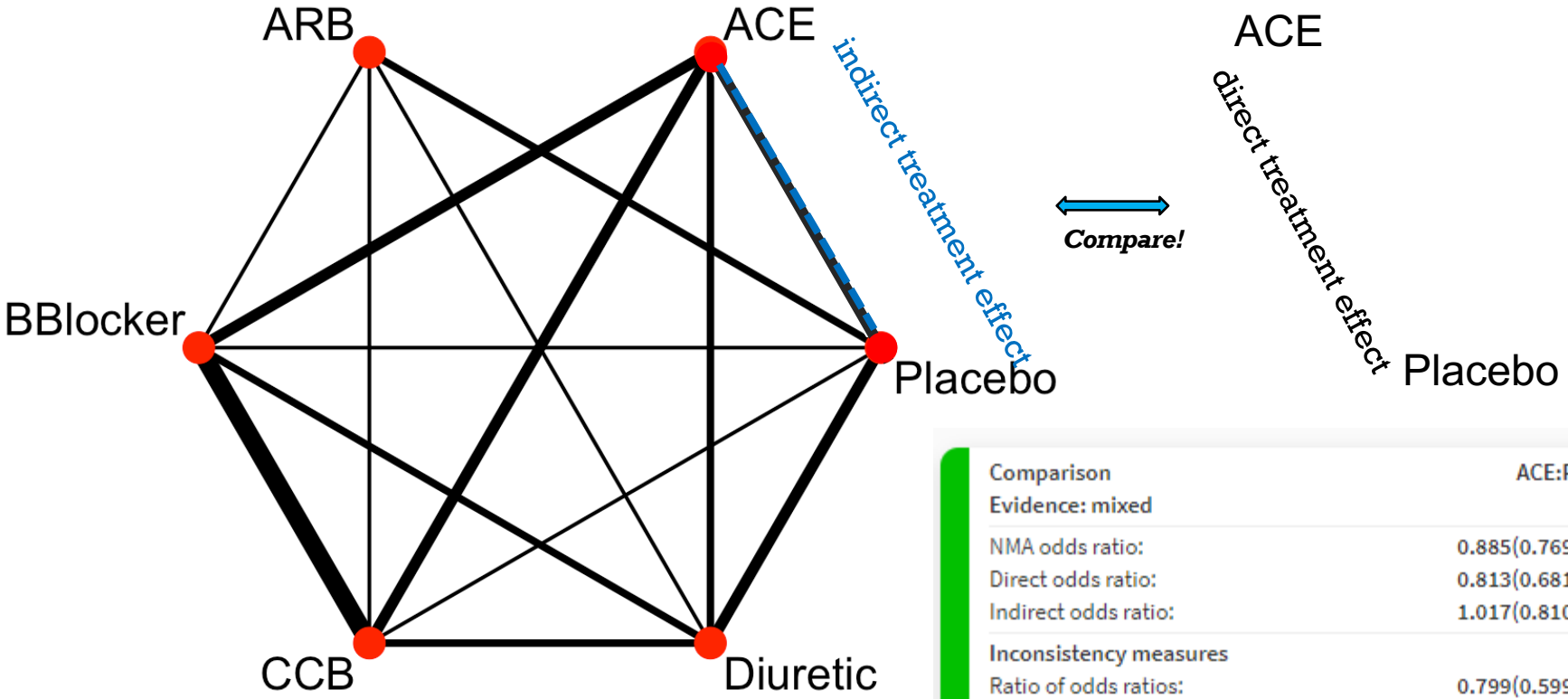
We consider prediction intervals for the **impact of heterogeneity** in clinical decision making

**Incoherence**
disagreement between different sources of evidence

We consider **how serious is the disagreement** between direct and indirect evidence with respect to clinical decision making

# INCOHERENCE

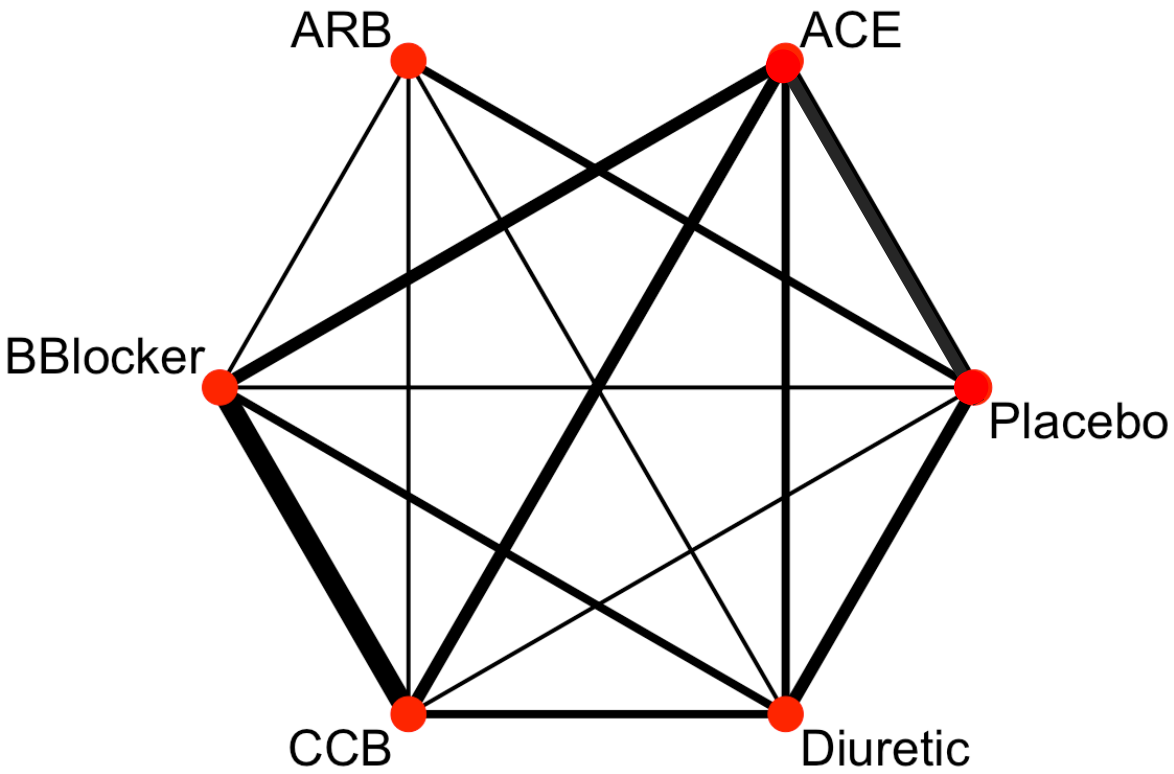
Separate Indirect from Direct Evidence test




| Comparison | ACE:Placebo |
|---|---|
| Evidence: mixed | |
| NMA odds ratio: | 0.885(0.769,1.017) |
| Direct odds ratio: | 0.813(0.681,0.971) |
| Indirect odds ratio: | 1.017(0.810,1.277) |
| Inconsistency measures | |
| Ratio of odds ratios: | 0.799(0.599,1.067) |
| P value: | 0.128 |

*Dias et al. Checking consistency in mixed treatment comparison meta-analysis Stat Med 2010*

# INCOHERENCE



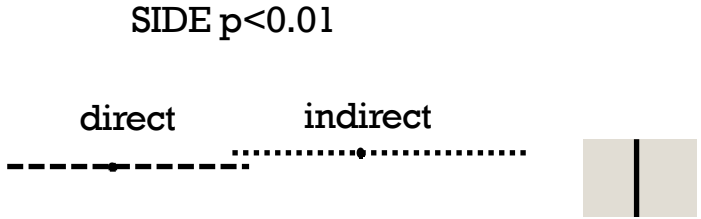

**Design-by-treatment $X^2$ test**

**Does the assumption of coherence hold for the entire network?**

$\chi^2$ =19.325 (13 df)
P-value=0.113

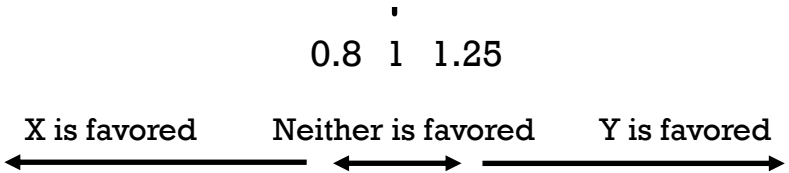
*White et al. Consistency and inconsistency in network meta-analysis. Res Synth Meth 2012*

# INCOHERENCE

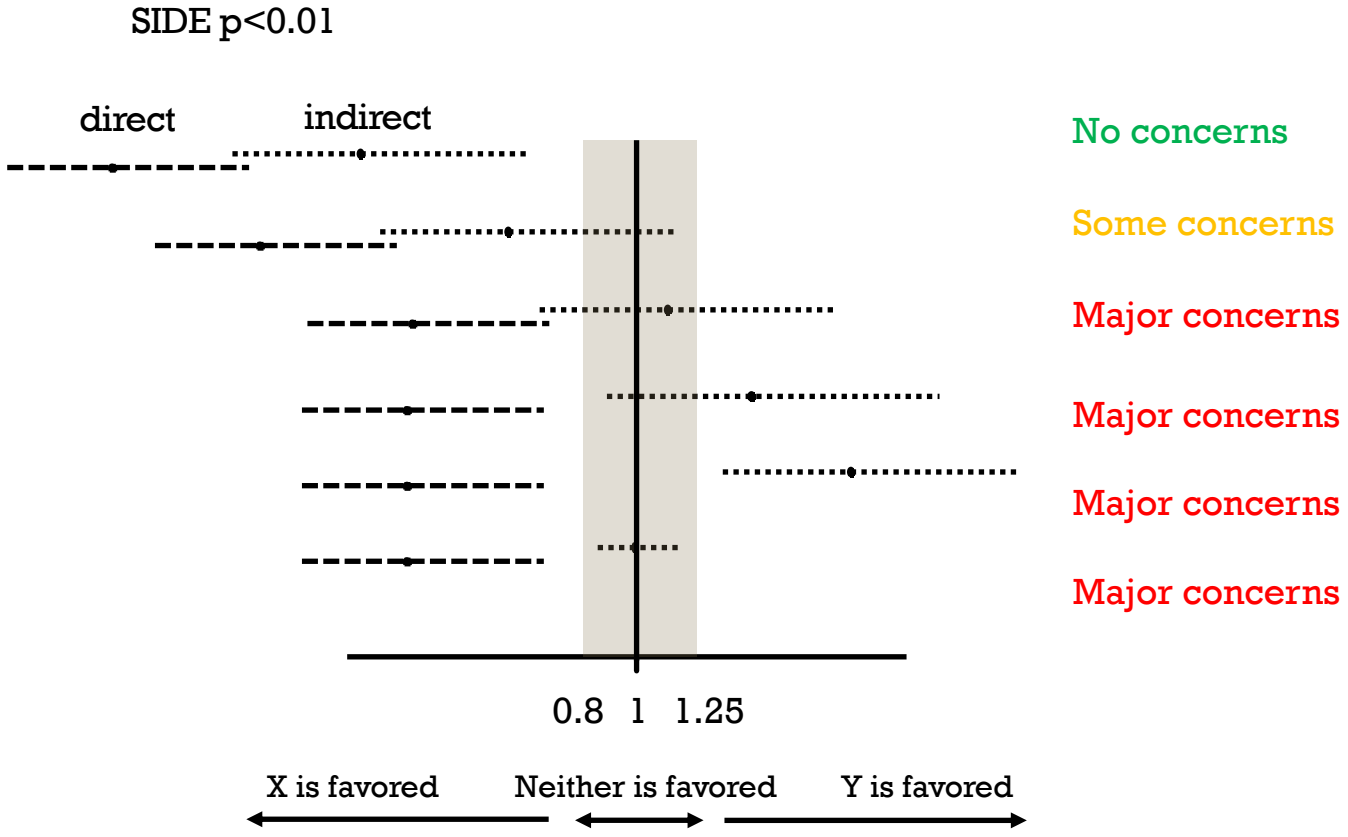



*What is your judgement about incoherence for this estimate (SIDE test p-value <0.01)?*

- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns



# INCOHERENCE



# INCOHERENCE

**Comparisons with both direct and indirect evidence:**
SIDE test p-value

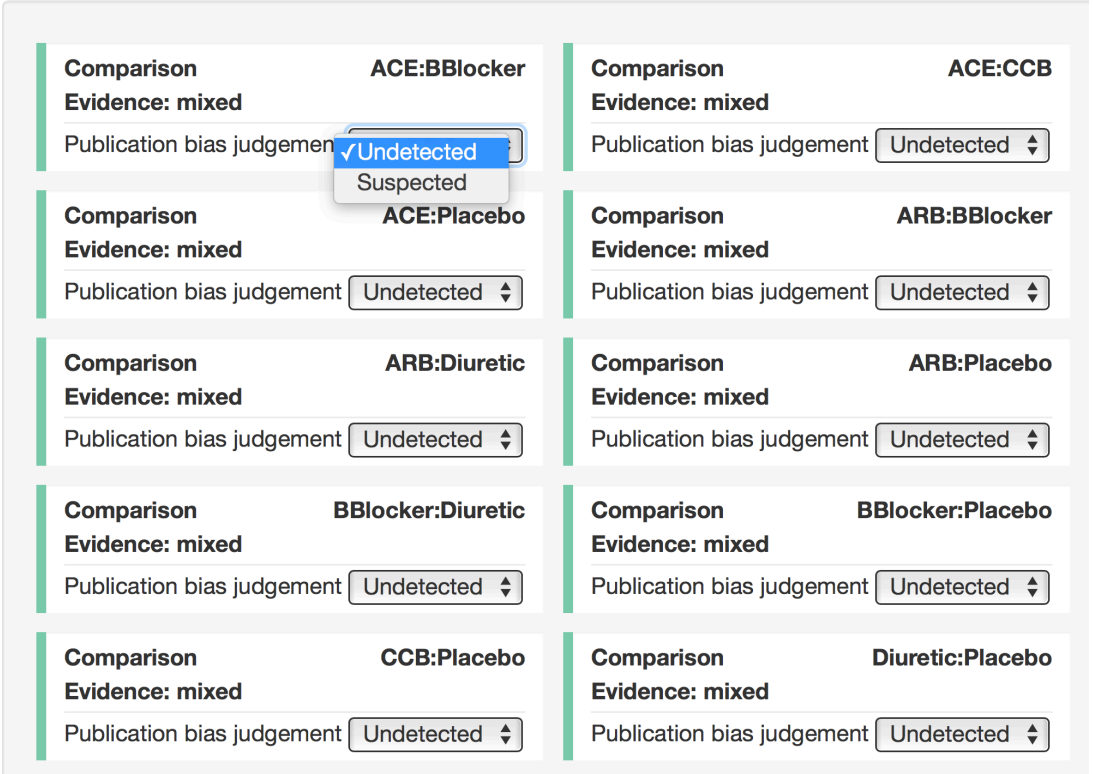
1. '*No concerns*' if p-value>0.10.
2. if p-value<0.10, check confidence interval overlaps and boundaries crossed.

**Comparisons with only direct or indirect evidence:**
design-by-treatment interaction test

1. '*Major concerns*' if p-value<0.05 or test is not estimable
2. '*Some concerns*' if 0.05<p-value<0.10
3. '*No concerns*' otherwise

# REPORTING BIAS

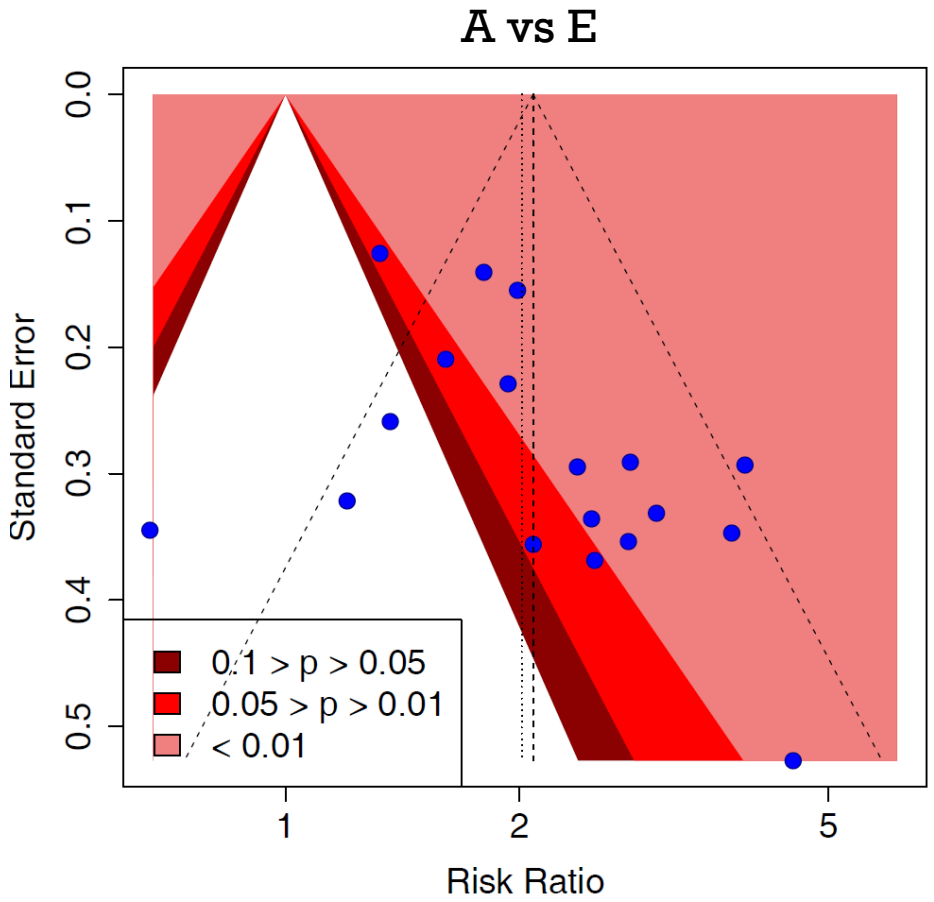
- ❑ Suspected
- ❑ Undetected



# REPORTING BIAS

## WORK IN PROGRESS

| comparison | slope | p-value | interpretation |
|---|---|---|---|
| A vs E | 0.21 | 0.05 | "Small studies give smaller effect for 1st intervention" |
| A vs C | 0.02 | 0 | "Small studies give smaller effect for 1st intervention" |
| A vs D | 0.19 | 0 | "Small studies give smaller effect for 1st intervention" |
| A vs F | 0.14 | 0.05 | "Small studies give smaller effect for 1st intervention" |
| A vs G | -0.35 | 0.01 | "Small studies give larger effect for 1st intervention" |



# REPORTING BIAS

## WORK IN PROGRESS

**Framework for assessing risk of bias due to missing results in a synthesis (Cochrane Handbook)**

1. Select syntheses to assess for risk of bias due to missing results.
2. Define which results are eligible for inclusion in each synthesis.
3. Record whether any of the studies identified are missing from each synthesis because results known (or presumed) to have been generated by study investigators are unavailable: the '*known unknowns*'.
4. Consider whether each synthesis is likely to be biased because of the missing results in the studies identified.
5. Consider whether results from additional studies are likely to be missing from each synthesis: the '*unknown unknowns*'.
6. Reach an overall judgement about risk of bias due to missing results in each.

Now it is time for….

# New updates funded by Cochrane

## Reporting bias functionalities already mentioned

Already implemented

| | |
|---|---|
| Update rules in judging imprecision, heterogeneity incoherence | Previous "rules" were too strict, we now consider one boundary and the null, effect when judging results. |
| Improve help with importing data | Prompting questions about nature of data |
| Facilitate scale up | Use ISPM's servers already provided |
| Sensitivity analysis for low RoB | User has to choose to exclude high or high and unclear studies and league table will be produced. If networks are disconnected the feature will be disabled |
| Presentations of results | League table and forest plot |
| Full report | Generate a PDF document for the entire process, including all graphs and tables and the final table and judgements |
| Final judgement | Choose the domains to downgrade by, and link them to the final confidence judgement (Each interim judgement is currently is marked as 'no concerns', 'some concerns' or 'major concerns', and these should be clickable to choose whether you want to downgrade by one or two levels) |
| Question mark buttons | To link the process steps with the documentation |
| Save past projects | Import export project |
| Technical testing | The system needs technical testing e.g. use weird data and see what it gives, testing with very large or disconnected networks etc. We will come up with |