



Confidence in Network Meta-Analysis
www.cinema.ispm.ch

Georgia Salanti
University of Bern

The most critical question raised by patients and clinicians at the point of care is

“what is the drug of choice for the given condition?”

Del Fiol G et al. Clinical questions raised by clinicians at the point of care: a systematic review. JAMA Intern Med. 2014

None of the 456 NMAs published until 3/2015 attempted to evaluate the confidence in NMA results!

OPEN  ACCESS Freely available online

 PLOS ONE

BMJ 2014;349:g5

Evaluating the Quality of Evidence from a Network Meta-Analysis

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A GRA quality meta-a

Network me used to exa on how to ra We present NMA estima a published to very low a and likely to

Abstract

Systematic reviews that collate data about the relative effects of multiple interventions via network meta-analysis are highly informative for decision-making purposes. A network meta-analysis provides two types of findings for a specific outcome: the relative treatment effect for all pairwise comparisons, and a ranking of the treatments. It is important to consider the confidence with which these two types of results can enable clinicians, policy makers and patients to make informed decisions. We propose an approach to determining confidence in the output of a network meta-analysis. Our proposed approach is based on methodology developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for pairwise meta-analyses. The suggested framework for evaluating a network meta-analysis acknowledges (i) the key role of indirect comparisons (ii) the contributions of each piece of direct evidence to the network meta-analysis estimates of effect size; (iii) the importance of the transitivity assumption to the validity of network meta-analysis; and (iv) the possibility of disagreement between direct evidence and indirect evidence. We apply our proposed strategy to a systematic review comparing topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. The proposed framework can be used to determine confidence in the results from a

Milo A Puha
Brignardello
Working Group

Methods developed by:

Julian Higgins

Adriani Nikolakopoulou

Anna Chaimani

Matthias Egger

Web developer:

Theodore Papakonstantinou



Welcome to CINeMA!

CINeMA (*Confidence in Network Meta-Analysis*) is a web application that simplifies the evaluation of confidence in the findings from network meta-analysis.

It is based on a framework described in (1) which considers the five **GRADE** domains: **study limitations**, **indirectness**, **inconsistency** and **publication bias**. The framework combines judgments about direct evidence with their statistical contribution to network meta-analysis, enabling evaluation of the credibility of **NMA** treatment effects.

1. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. *PLoS Medicine*. 2014;9(7):e1001682.

To browse your projects or upload a new one go to [My Projects](#)

u^b



Campbell
Collaboration



Cochrane

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

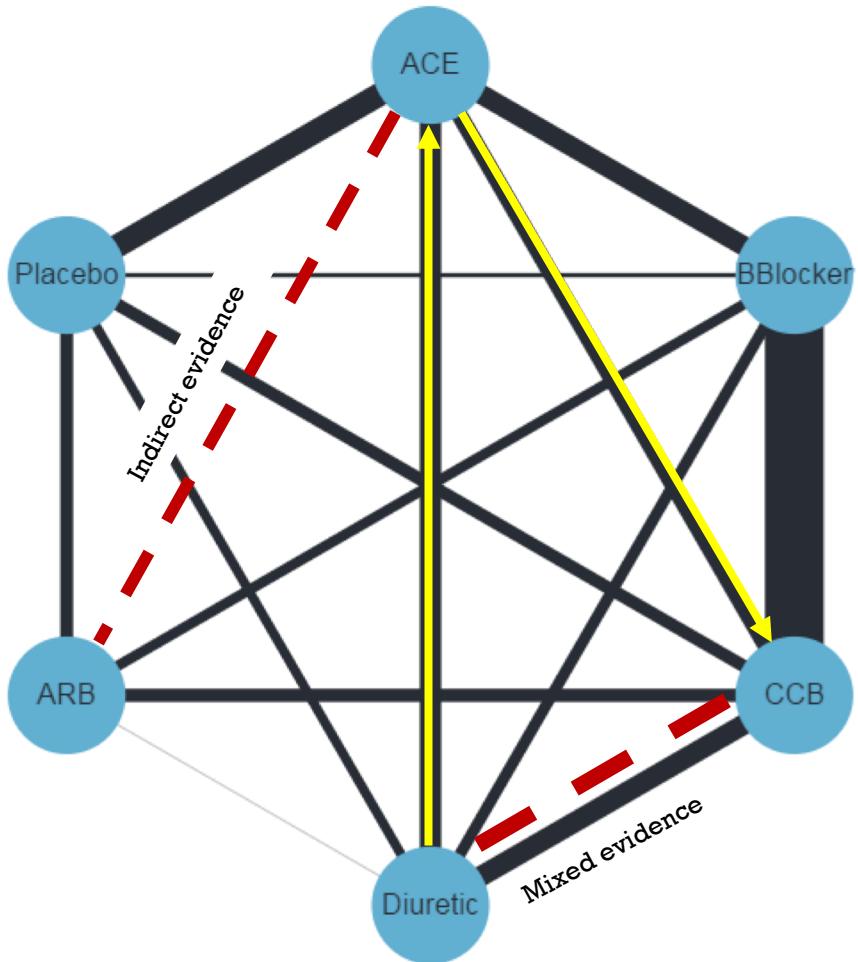
Number of studies 22

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



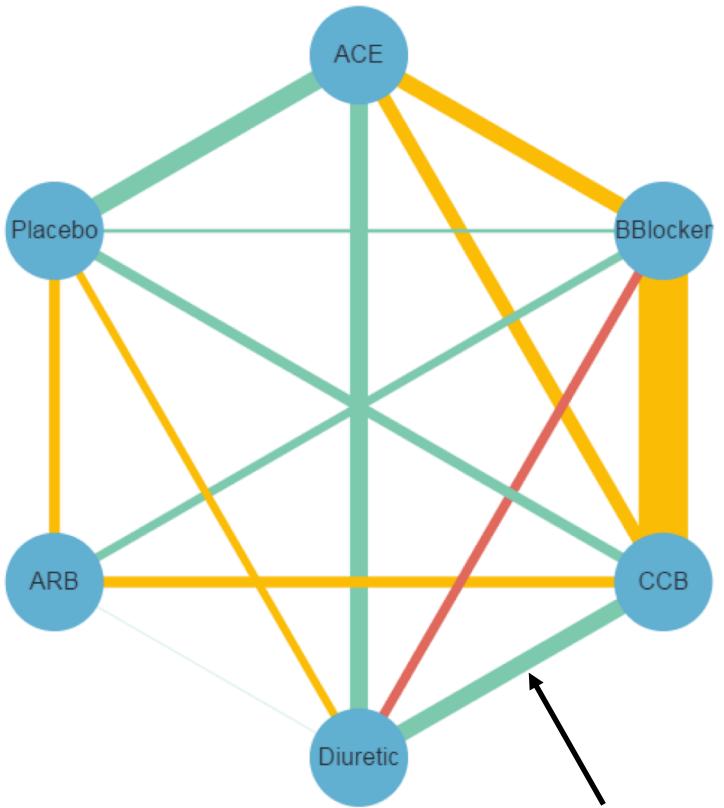
Comparison	Number of Studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
ACE vs BBlocker	3	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	High
ACE vs CCB	3	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	High
ACE vs Diuretic	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ACE vs Placebo	3	No concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	High
ARB vs BBlocker	1	No	Semi-automated 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					
ARB vs CCB	1	Some	The rules can be overwritten!					
ARB vs Diuretic	1	No						
ARB vs Placebo	2	No						
BBlocker vs CCB	5	No						
BBlocker vs Diuretic	2	No						
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	Major concerns	Some concerns	High
CCB vs Placebo	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	High
Diuretic vs Placebo	3	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	High
Indirect evidence								
ACE vs ARB	--	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	High

Indirect evidence

ACE vs ARB	--	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	High
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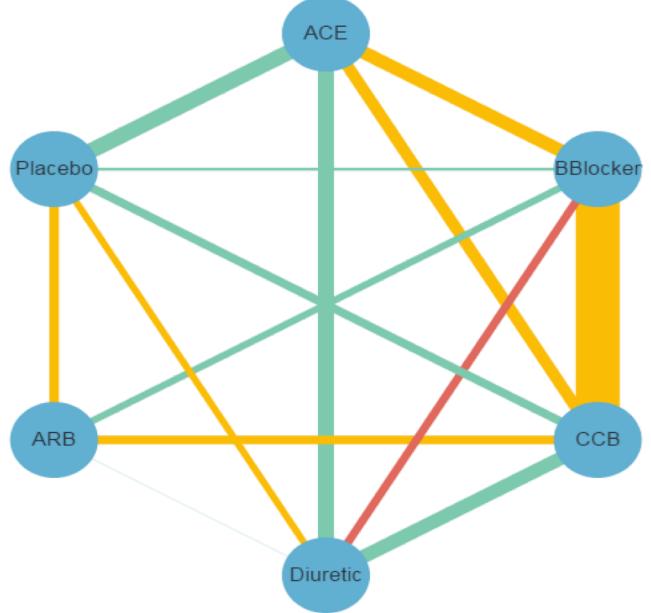
STUDY LIMITATION

- Major concerns
- Some concerns
- No concerns



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

<u>Study name</u>	<u>Risk of Bias</u>
AASK	LOW
ALLHAT	LOW
ALPINE	LOW
ANBP-2	LOW
ASCOT	LOW
CAPP	MODERATE
CHARM	LOW
DREAM	LOW
EWPHE	MODERATE
FEVER	LOW
HAPPY	HIGH
HOPE	LOW
INSIGHT	LOW
INVEST	LOW
LIFE	LOW
MRC	LOW
NORDIL	LOW
PEACE	LOW
SCOPE	MODERATE
SHEP	LOW
STOP-2	MODERATE
VALUE	Moderate



Comparison

BB vs Placebo

Diuretics

CCB

ACE

ARB

Diuretics vs BB

CCB

ACE

ARB

CCB vs Diuretics

ACE

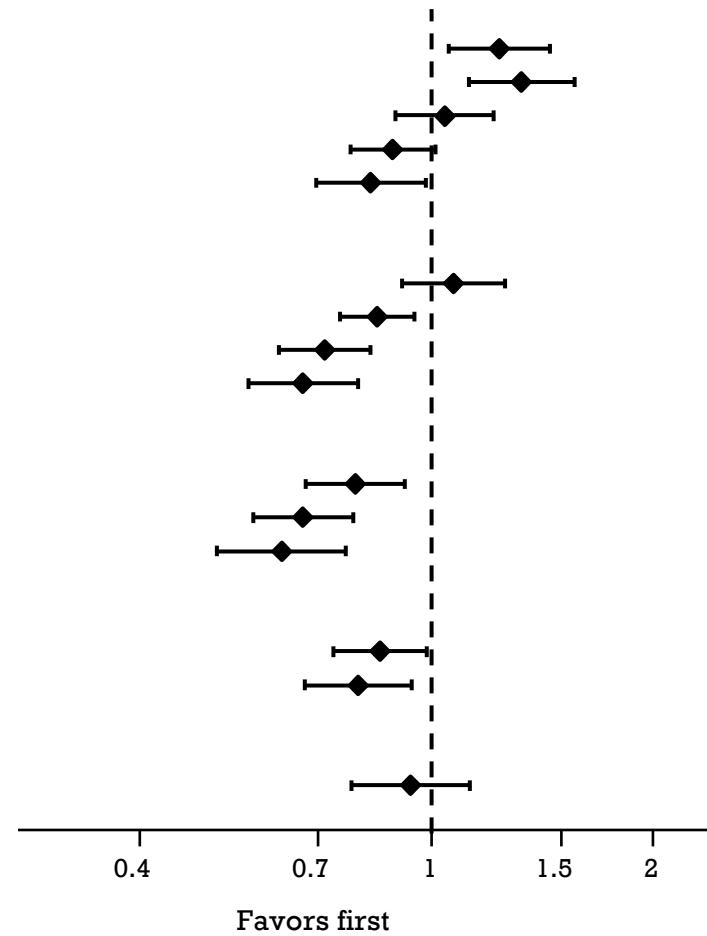
ARB

ACE vs CCB

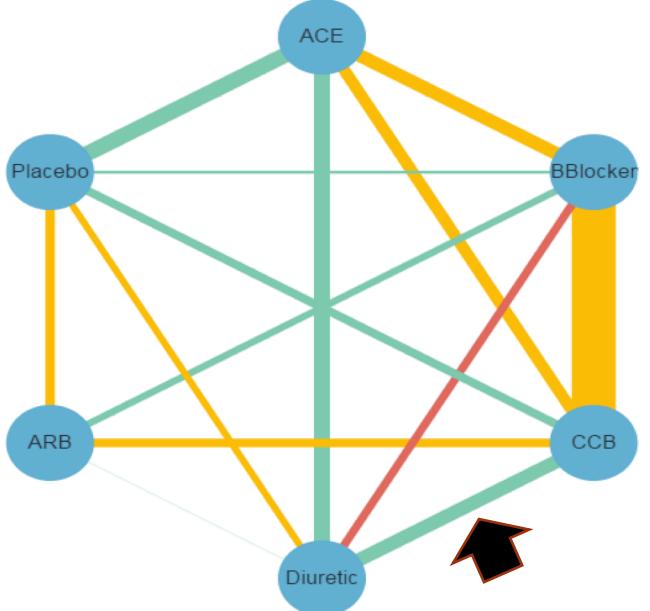
ARB

ARB vs ACE

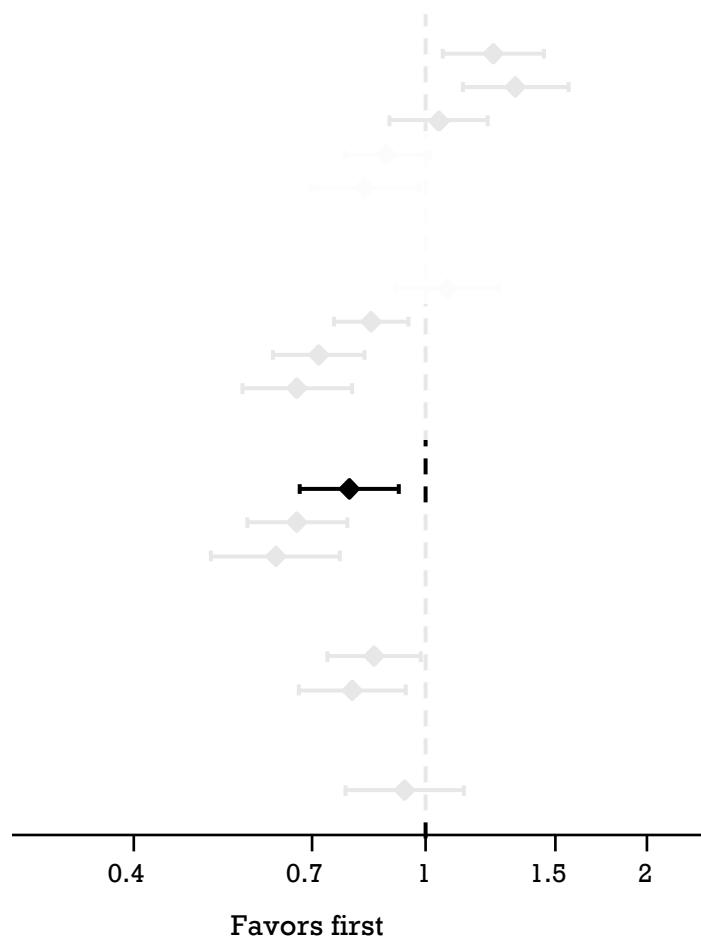
OR from NMA



Comparison

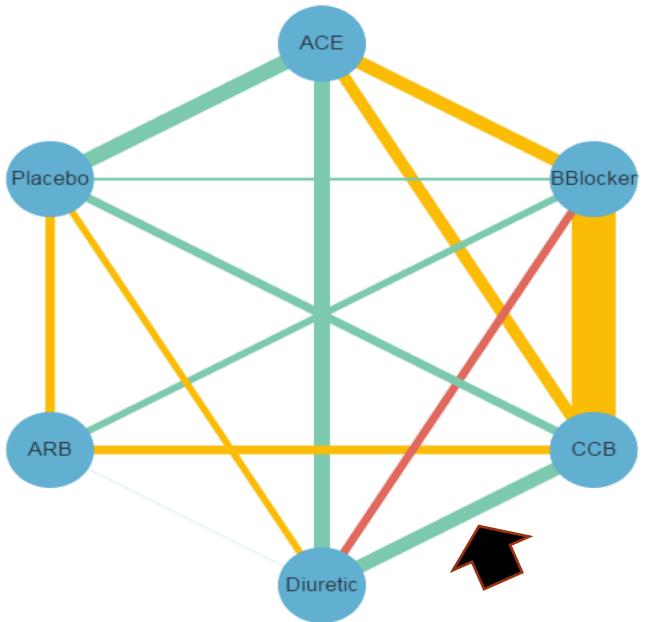


OR from NMA





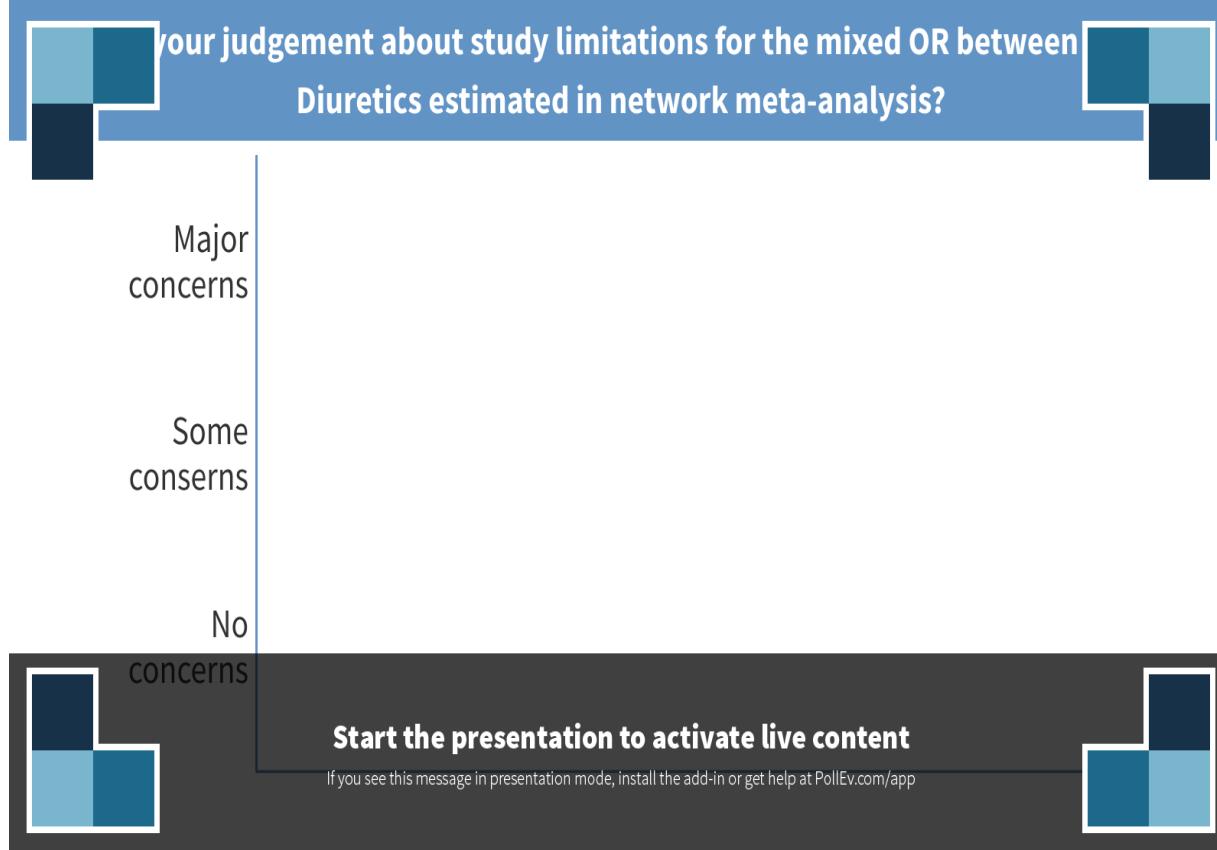
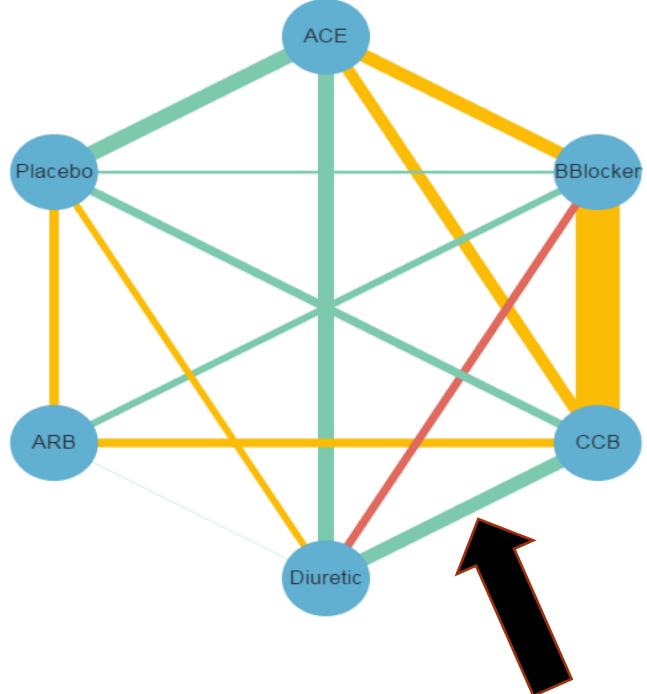
What is your judgement about study limitations for this (mixed) OR between CCB vs Diuretics estimated in network meta-analysis?

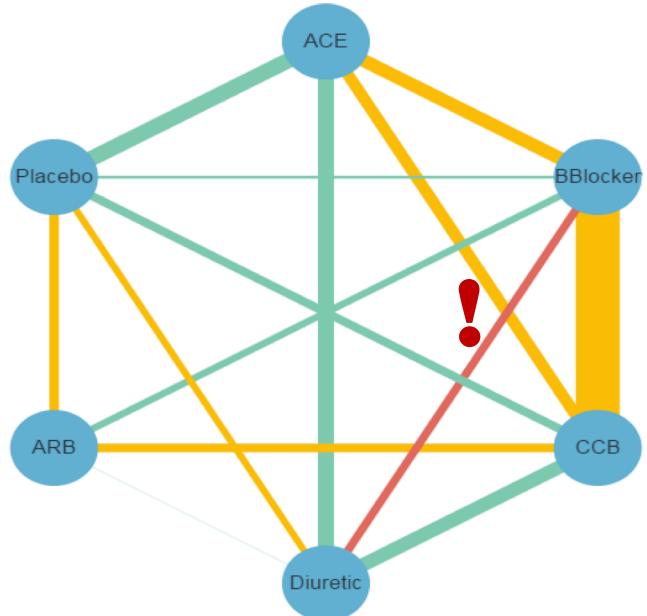


- Major concerns
- Some concerns
- No concerns

Go to:

pollev.com/gmhbe



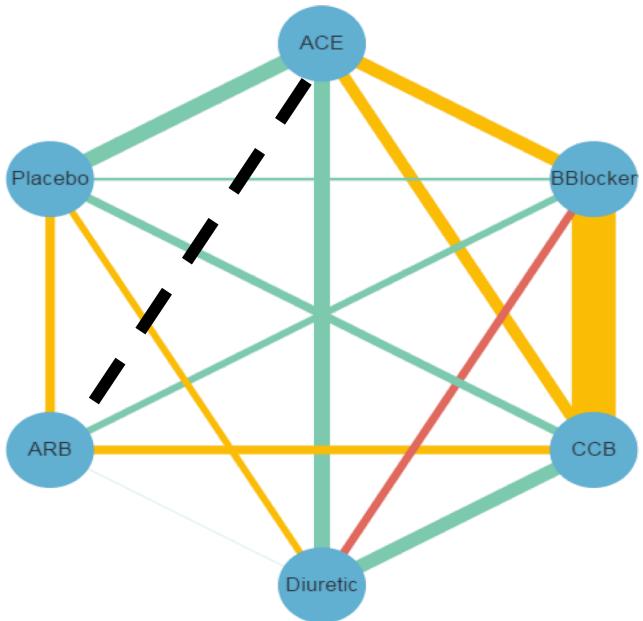


**Studies with high risk of bias
contribute to the estimation of
the OR CCB vs Diuretics!**

Comparison

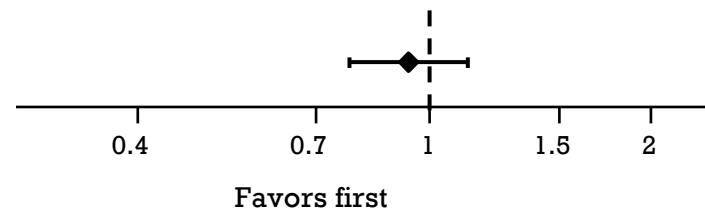
OR from NMA

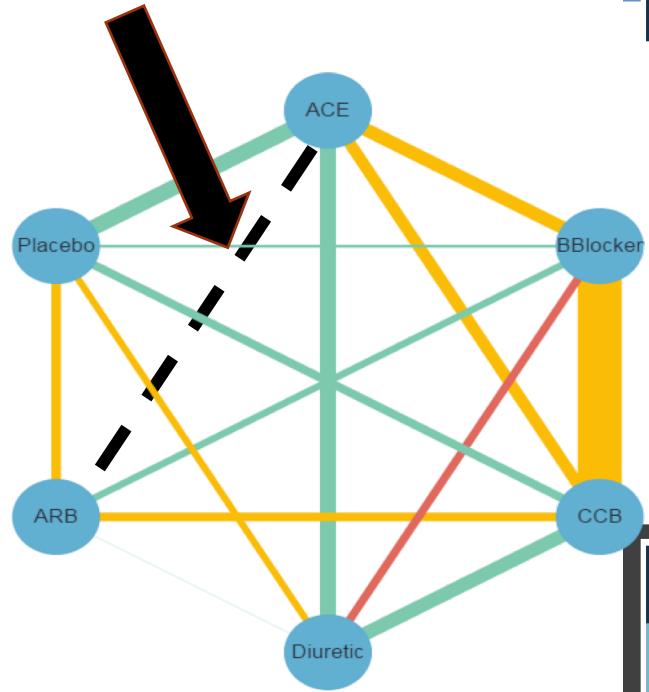
What is your judgement about study limitations for this (indirect) OR for ACE vs ARB estimated in NMA?



- Major concerns
- Some concerns
- No concerns

ARB vs ACE





our judgement about study limitations for the indirect OR between
ARB estimated in network meta-analysis?

Major concerns
Some concerns
No concerns

Start the presentation to activate live content

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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

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

The contribution matrix

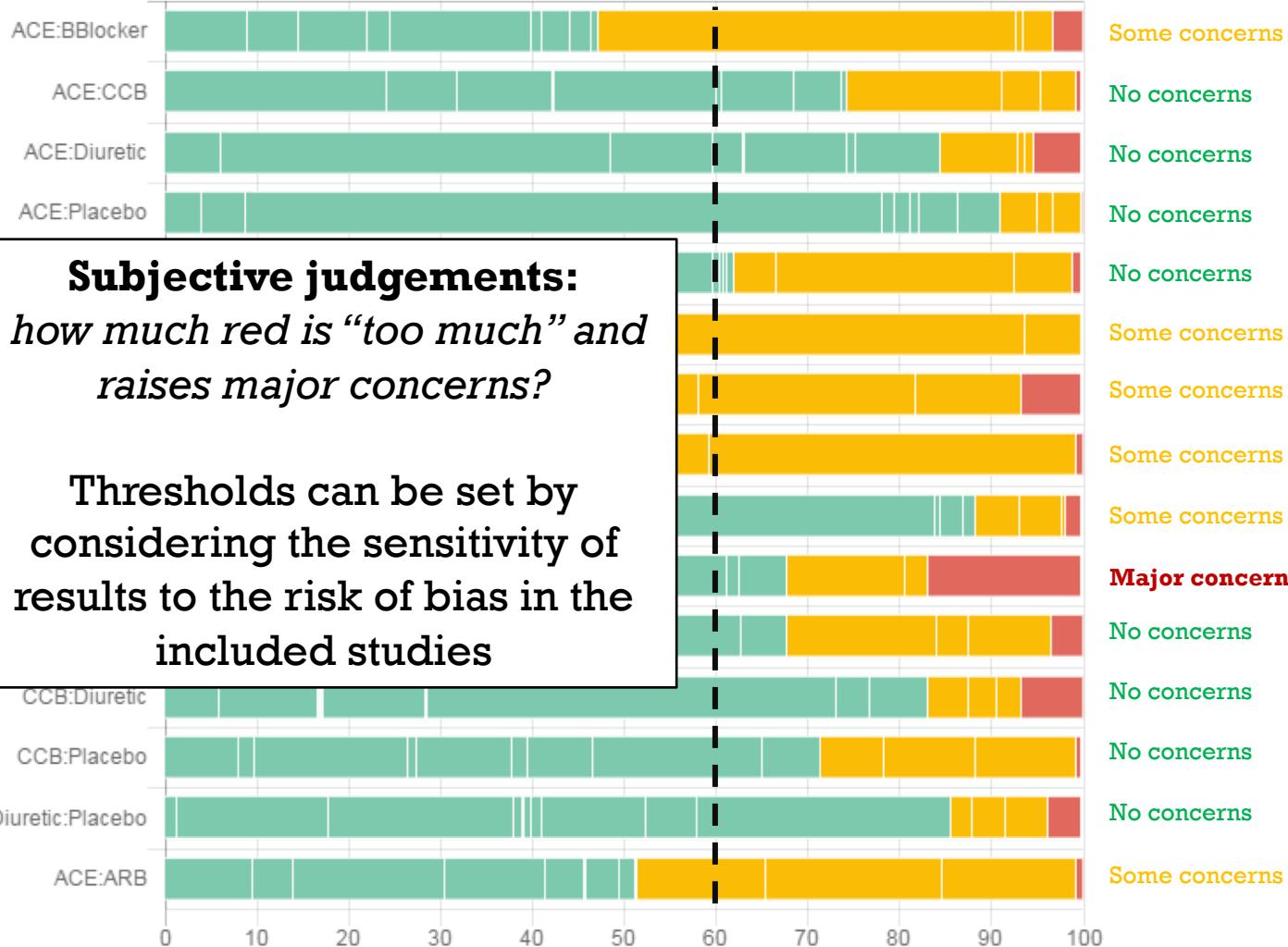
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ACE:Diuretic	3	28	0	21	0	5	0	4	2	1	5	3	5	0
ACE:Placebo	2	6	0	4	0	3	2	23	1	5	0	15	0	0
ARB:BBlocker	2	0	0	0	5	3	6	2	0	1	2	1	0	5
ARB:CCB	1	3	0	0	4	0	7	2	0	5	0	1	2	4
ARB:Diuretic	1	12	1	4	0	1	10	2	2	0	6	1	8	0
ARB:Placebo	1	3	0	0	0	2	29	3	1	5	1	2	1	0
BBlocker:CCB	6	5	0	0	19	4	0	0	0	2	3	0	2	19
BBlocker:Diureti	3	14	0	7	5	7	1	0	1	1	17	0	8	5
BBlocker:Placeb	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	3											



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

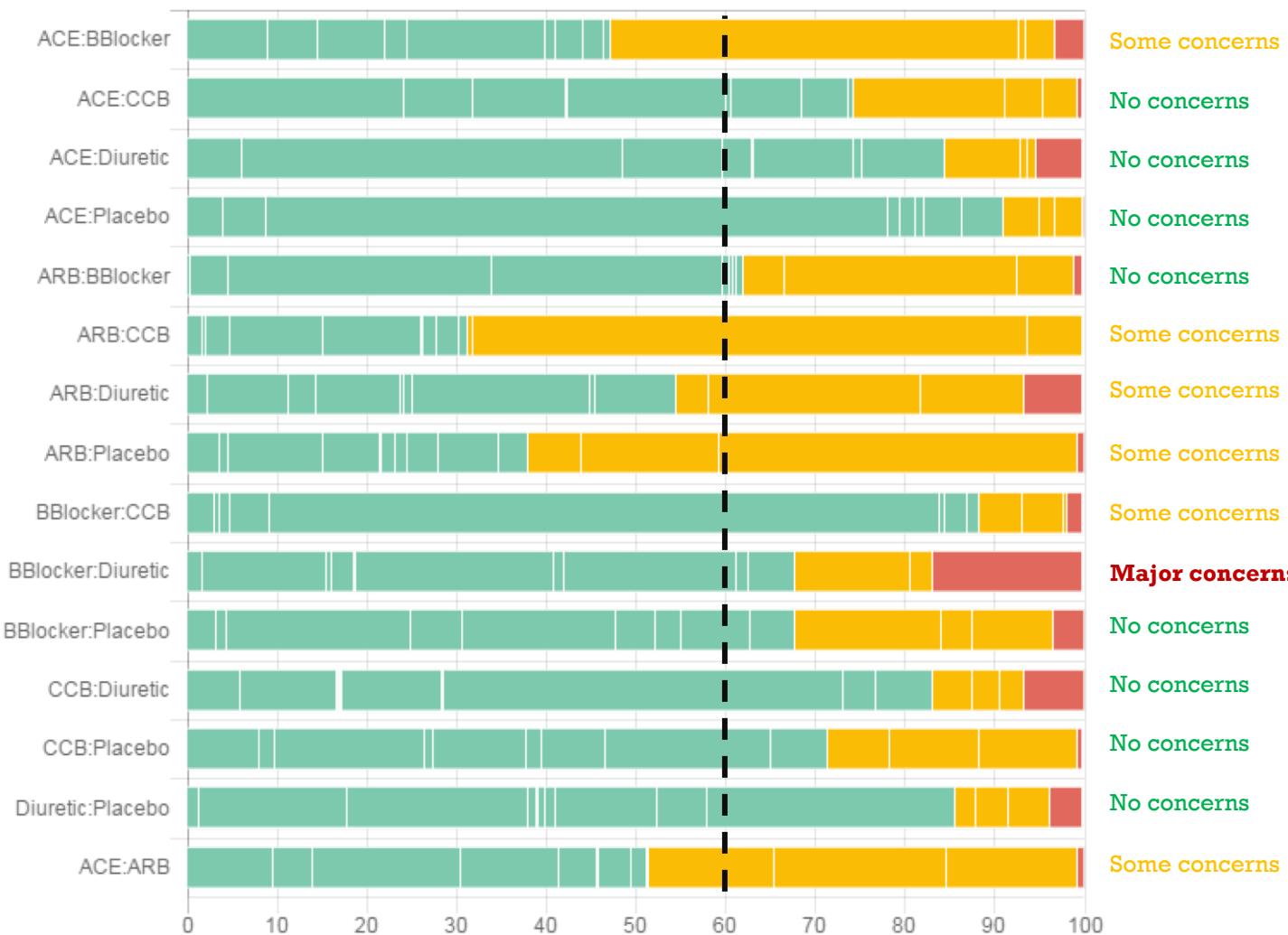
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ACE:Placebo	2	6	0	4	0	3	2	23	1	5	0	15	0	0
ARB:BBlocker	2	0	0	0	5	3	6	2	0	1	2	1	0	5
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BBlocker:Diureti	3	14	0	7	5	7	1	0	1	1	17	0	8	5
BBlocker:Placeb	4	3	0	0	4	8	5	7	2	8	4	4	1	4
CCB:Diuretic	2	30	0	6	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	0	10	15	20	30	40	45	50	55	60	70	80	90	100



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



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....



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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
 - Could be set using the Minimum Clinically Important Difference

NMA estimated odds ratios for diabetes

Comparison

BB vs Placebo

Diuretics

CCB

ACE

ARB

Diuretics vs BB

CCB

ACE

ARB

CCB vs Diuretics

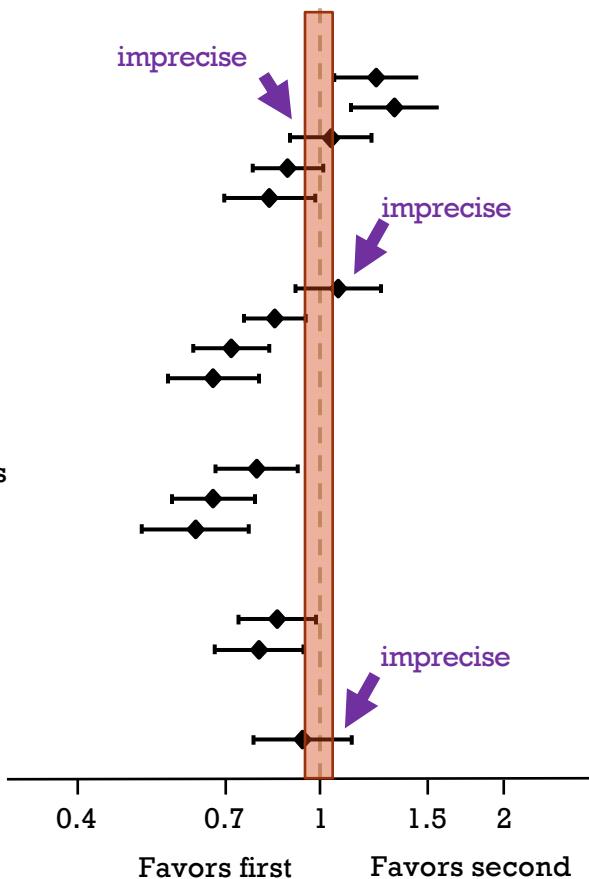
ACE

ARB

ACE vs CCB

ARB

ARB vs ACE



Imprecision:

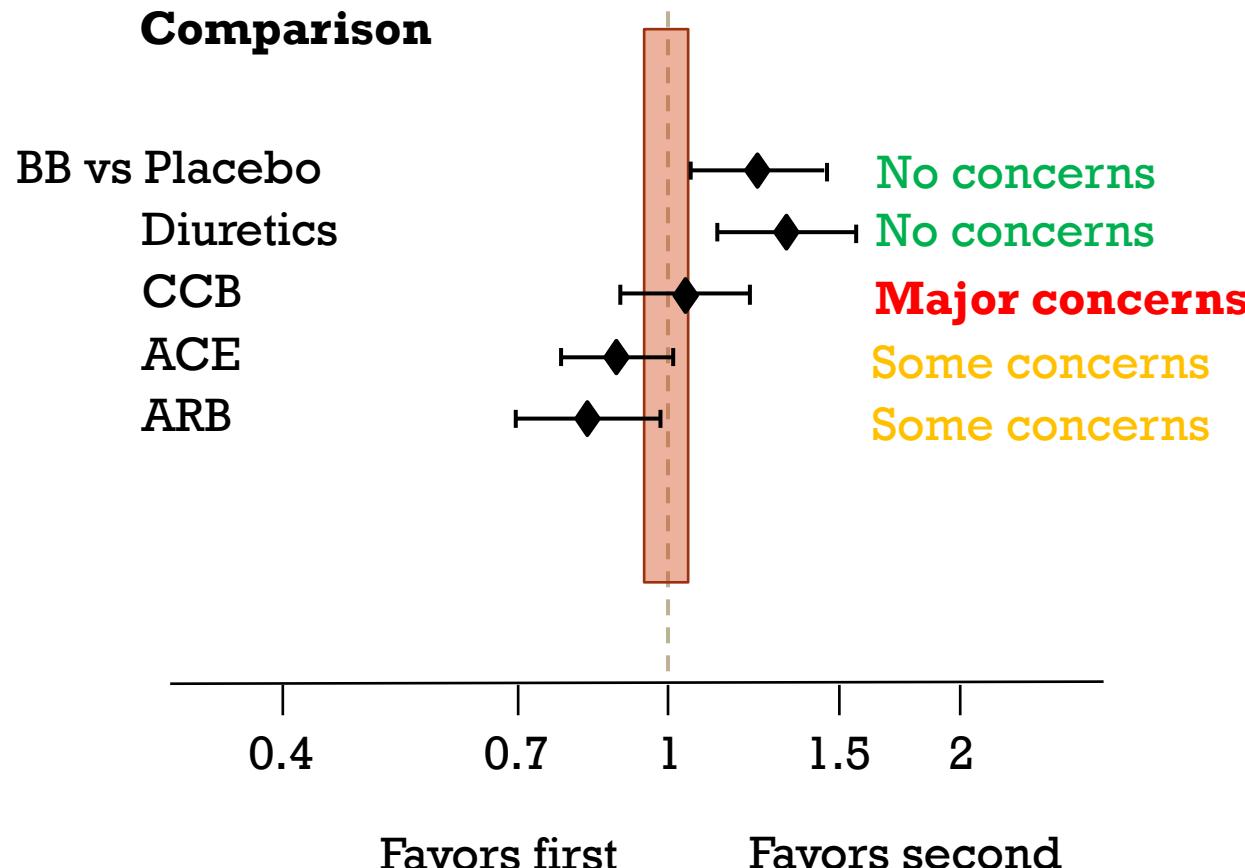
Confidence intervals include values that lead into different clinical decisions

Margin of equivalence:

OR=1.05 in either direction

Imprecision when the confidence interval **crosses both 0.95 and 1.05**

NMA estimated odds ratios for diabetes



IMPRECISION

Define clinically important size of effect: Odds ratio

1.05

Set

Effects lower than 0.952 and larger than 1.050 are considered to be clinically important

Comparison BBlocker:CCB

Evidence: mixed

95% Confidence interval:

*Confidence interval (1.049,1.341)
extends into clinically important
effects*

Imprecision judgement

Some concerns 

Comparison BBlocker:Diuretic

Evidence: mixed

95% Confidence interval:

*Confidence interval (0.789,1.104)
extends into clinically important
effects in both directions*

Imprecision judgement

Major concerns 

Comparison BBlocker:Placebo

Evidence: mixed

95% Confidence interval:

*Confidence interval (1.053,1.461)
does not cross clinically important
effect*

Imprecision judgement

No concerns 



Now it is time for....

CINeMA

VARIABILITY BEYOND CHANCE

Heterogeneity
between-study
variance within a
source 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

Treatment Effect

BB vs Placebo

Diuretics

CCB

ACE

ARB

Diuretics vs BB

CCB

ACE

ARB

CCB vs Diuretics

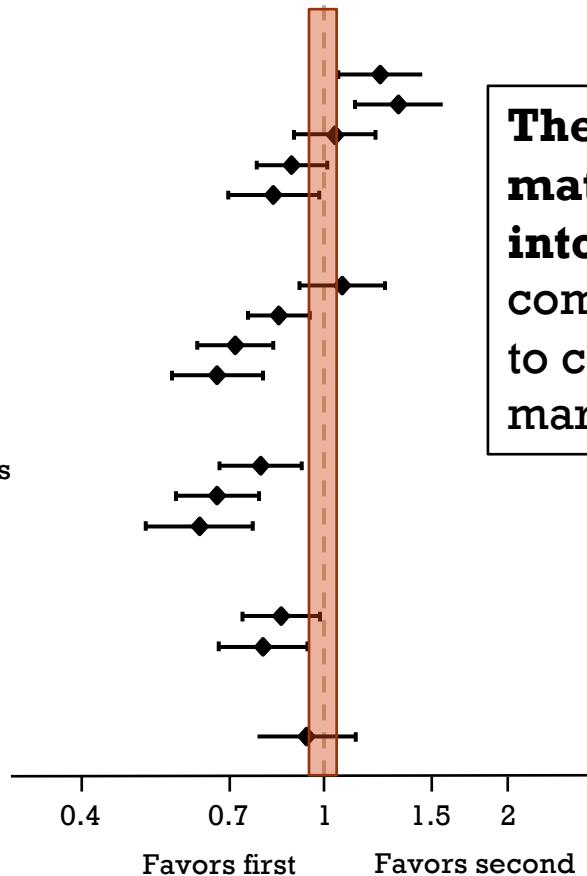
ACE

ARB

ACE vs CCB

ARB

ARB vs ACE



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

HETEROGENEITY

Treatment Effect

BB vs Placebo

Diuretics

CCB

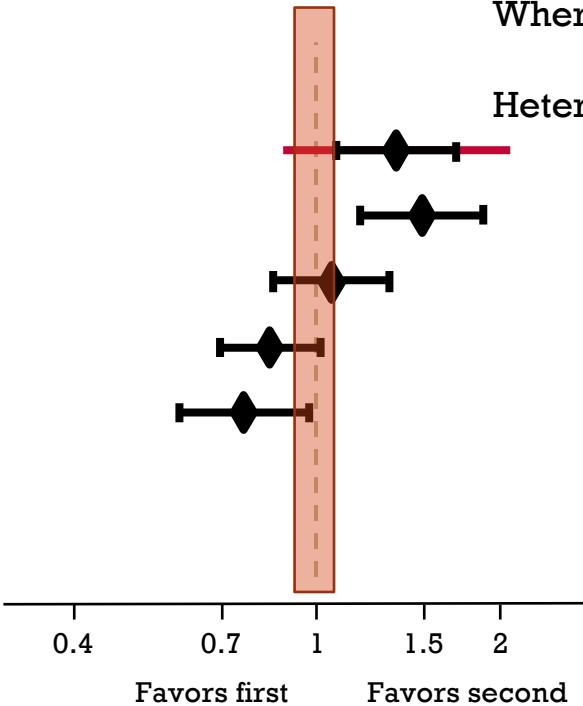
ACE

ARB

Prediction interval:

Where is the true effect in a new study?

Heterogeneity changes conclusions!



HETEROGENEITY

Treatment Effect

BB vs Placebo

Diuretics

CCB

ACE

ARB

Diuretics vs BB

CCB

ACE

ARB

CCB vs Diuretics

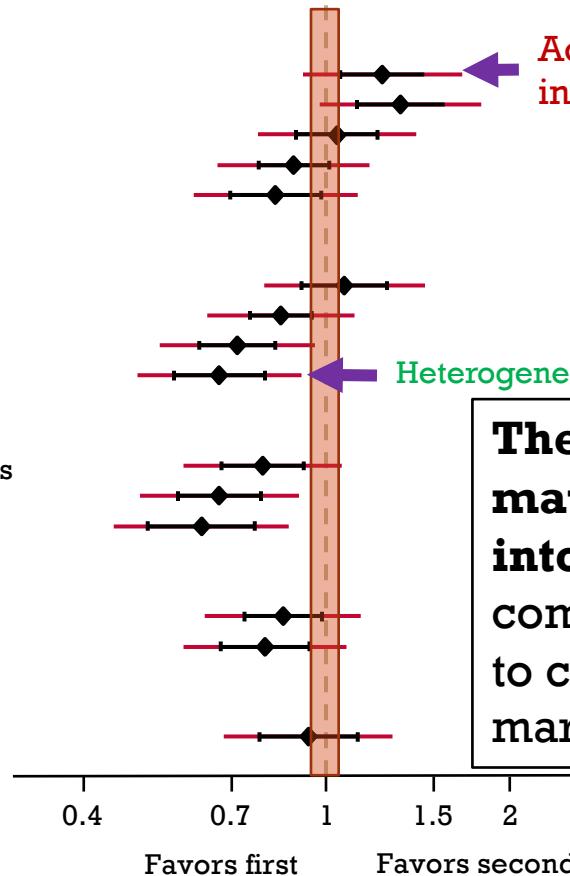
ACE

ARB

ACE vs CCB

ARB

ARB vs ACE



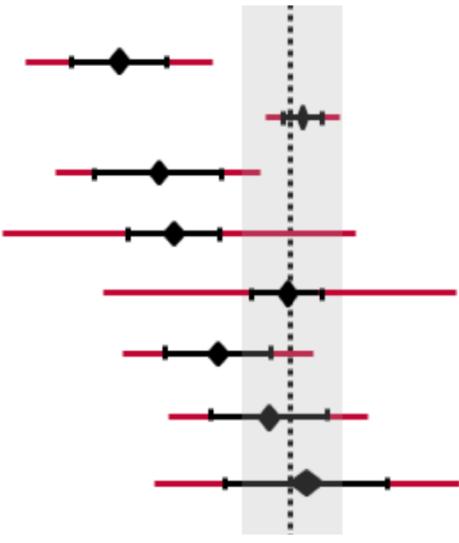
Accounting for heterogeneity leads into different clinical decisions!

Heterogeneity does not change 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



Margin of equivalence

Prediction interval —————
Confidence interval —————

- No concerns: Confidence and prediction intervals agree in relation to clinically important effect
- No concerns: Confidence and prediction intervals agree in relation to clinically important effect
- Some concerns: Prediction interval extends into clinically important or unimportant effects
- Major concerns: Prediction interval extends into clinically important effects in both directions
- Major concerns: Prediction interval extends into clinically important effects in both directions
- No concerns: Confidence and prediction intervals agree in relation to clinically important effect
- Some concerns: Prediction interval extends into clinically important or unimportant effects
- No concerns: Confidence and prediction intervals agree in relation to clinically important effect

HETEROGENEITY

Define clinically important size of effect: Odds ratio

1.05

Set

Effects lower than 0.952 and larger than 1.050 are considered to be clinically important

Comparison ARB:CCB
Evidence: mixed

95% intervals for NMA estimate

Confidence interval: (0.664,0.942)

Prediction interval: (0.572,1.093)

Prediction interval extends into clinically important effects in both directions

Heterogeneity judgement

Major concerns 

Comparison ARB:Diuretic
Evidence: mixed

95% intervals for NMA estimate

Confidence interval: (0.504,0.767)

Prediction interval: (0.440,0.879)

Confidence and prediction intervals agree in relation to clinically important effect

Heterogeneity judgement

No concerns 

Comparison ARB:Placebo
Evidence: mixed

95% intervals for NMA estimate

Confidence interval: (0.691,0.990)

Prediction interval: (0.597,1.146)

Prediction interval extends into clinically important or unimportant effects

Heterogeneity judgement

Some concerns 

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 τ^2 can be estimated
 - But their estimation makes sense when you have enough studies
 - The observed values of τ^2 are 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

HETEROGENEITY

Select type of intervention and outcome *optional*

All Pharmacological

All Non-pharmacological

Deselect all

ACE: Pharmacological ▲

ARB: Pharmacological ▲

BBlocker: Pharmacological ▲

Diuretic: Pharmacological ▲

Placebo: Placebo/Control ▲

Outcome type Objective ▲



HETEROGENEITY

Comparison	ARB:CCB
Evidence: mixed	
Reference Values for τ^2	

first quantile:	0.003
median:	0.014
third quantile:	0.061

95% intervals for NMA estimate	
Confidence interval:	(0.664,0.942)
Prediction interval:	(0.572,1.093)

Prediction interval extends into clinically important effects in both directions

Heterogeneity judgement
Major concerns 

Comparison	ARB:Diuretic
Evidence: mixed	
Reference Values for τ^2	

first quantile:	0.003
median:	0.014
third quantile:	0.061

95% intervals for NMA estimate	
Confidence interval:	(0.504,0.767)
Prediction interval:	(0.440,0.879)

Confidence and prediction intervals agree in relation to clinically important effect

Heterogeneity judgement
No concerns 

Comparison	ARB:Placebo
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I ² :	0.0%
Estimated τ^2 :	0.000
Reference Values for τ^2	
first quantile:	0.004
median:	0.017
third quantile:	0.071
95% intervals for NMA estimate	
Confidence interval:	(0.691,0.990)
Prediction interval:	(0.597,1.146)
Prediction interval extends into clinically important or unimportant effects	
Heterogeneity judgement	
Some concerns 	

VARIABILITY BEYOND CHANCE

Heterogeneity
between-study
variance within a
comparison

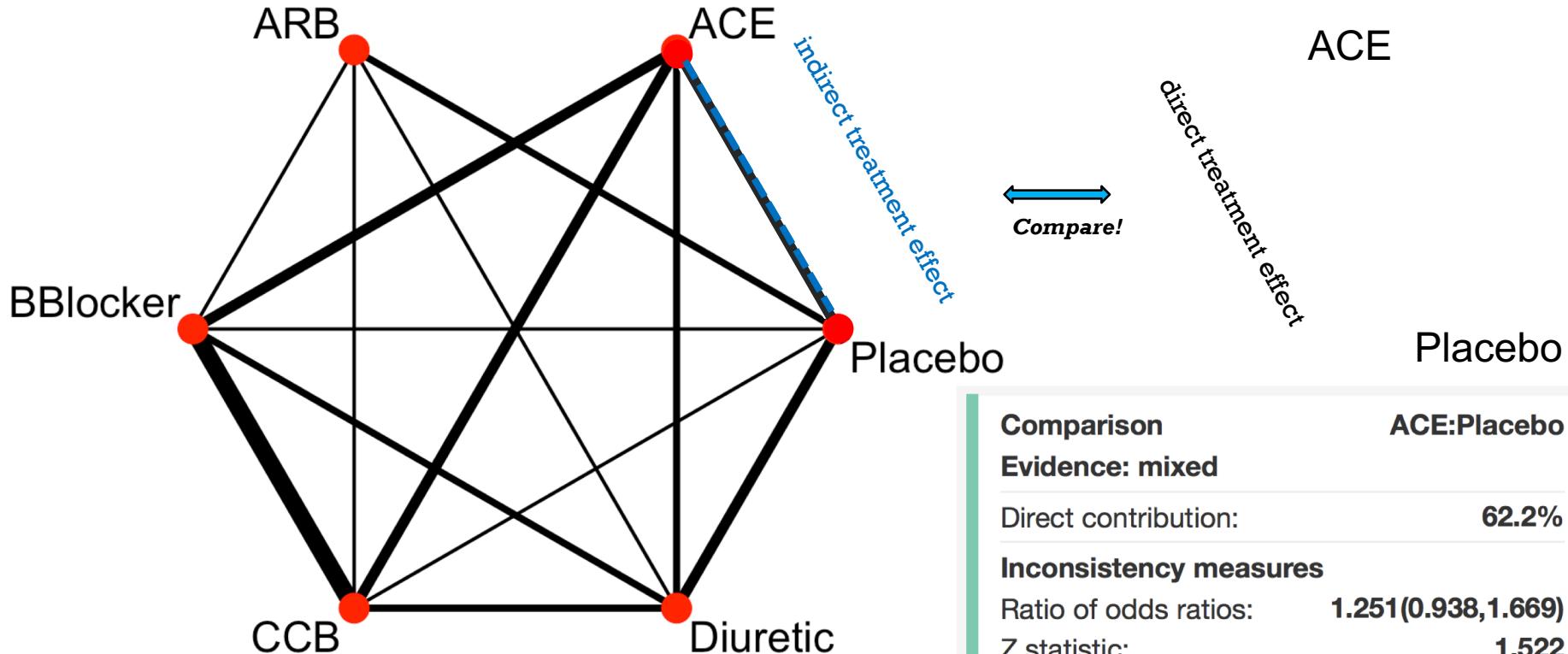
We consider prediction intervals for the **impact of heterogeneity** in clinical decision making

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

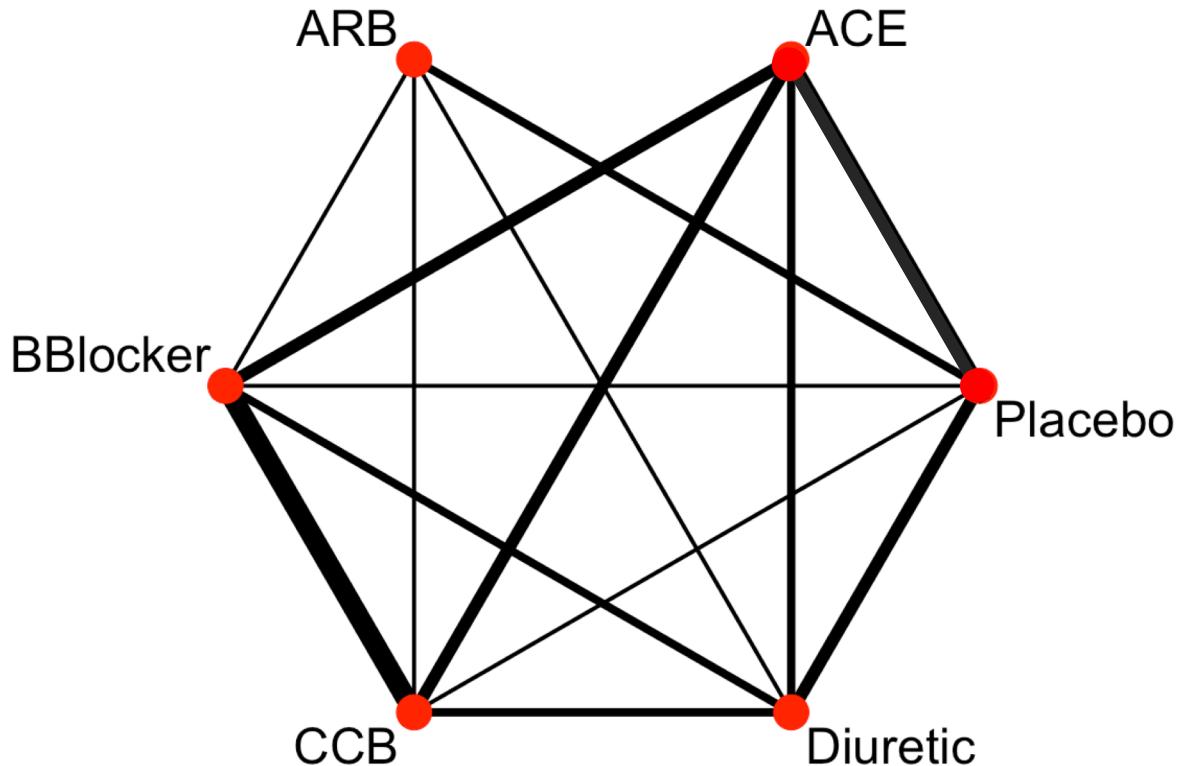
INCOHERENCE

Separate Indirect from Direct Evidence test



INCOHERENCE

Design-by-treatment χ^2 test



Does the assumption of coherence hold for the entire network?

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

INCOHERENCE

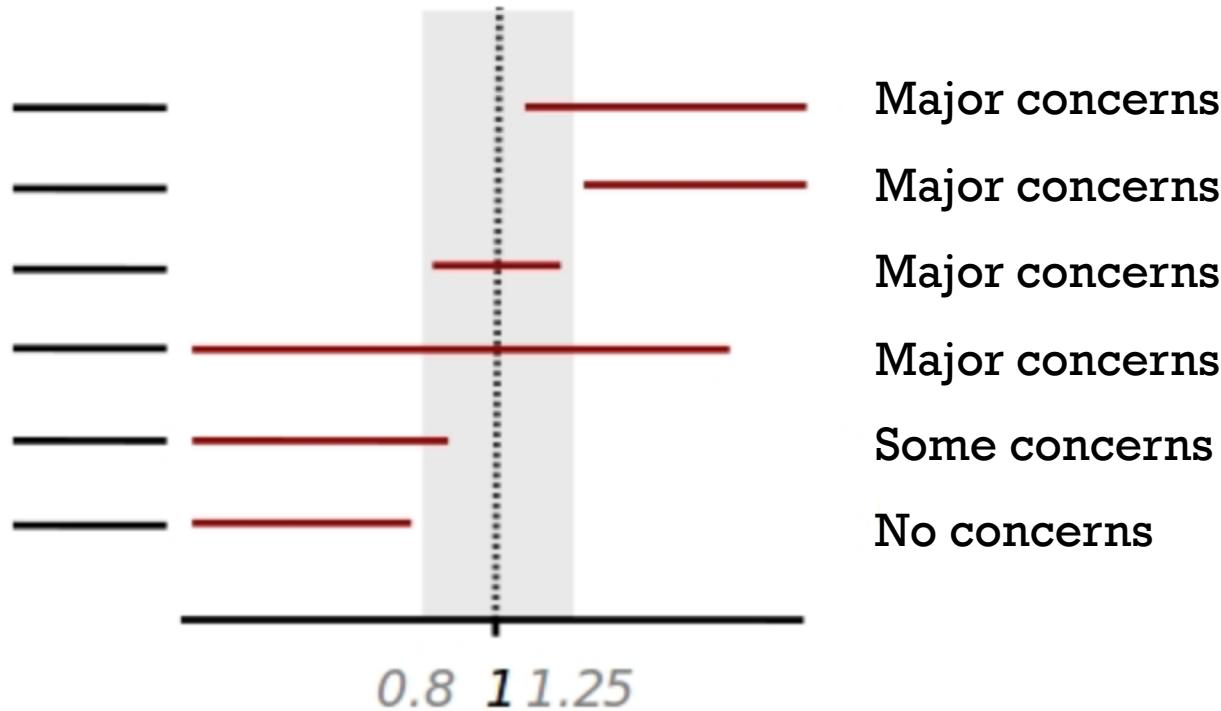
Comparisons with only direct evidence: incoherence is ‘no serious’

Comparisons with only indirect evidence: incoherence is ‘no serious’, ‘serious’ and ‘very serious’ according to p-value of the design by treatment interaction model being more than 0.10, between 0.01 and 0.10 and less than 0.01 respectively.

All other cases: we consider the overlap in the CIs and the margin of equivalence



INCOHERENCE



INCOHERENCE

Global test based on a random-effects design-by-treatment interaction model

χ^2 statistic: 19.325 (13 degrees of freedom), P value: 0.113

Comparison

ACE:ARB

Evidence: indirect

Indirect odds ratio:

1.070(0.880,1.300)

Inconsistency measures: Not applicable

Incoherence judgement

No concerns



INCOHERENCE

Comparison	BBlocker:Placebo
Evidence: mixed	
NMA odds ratio:	1.240(1.053,1.461)
Direct odds ratio:	2.226(1.307,3.794)
Indirect odds ratio:	1.167(0.982,1.386)
Direct contribution:	9.5%
Inconsistency measures	
Ratio of odds ratios:	1.908(1.090,3.340)
P value:	0.024
Incoherence judgement	Some concerns 

Comparison	ARB:BBlocker
Evidence: mixed	
NMA odds ratio:	0.667(0.557,0.799)
Direct odds ratio:	0.732(0.541,0.992)
Indirect odds ratio:	0.633(0.506,0.793)
Direct contribution:	35.5%
Inconsistency measures	
Ratio of odds ratios:	1.157(0.793,1.687)
P value:	0.449
Incoherence judgement	Some concerns 



BETWEEN-STUDIES BIAS

- Suspected
- Undetected

Comparison Evidence: mixed Publication bias judgement	ACE:BBBlocker <input checked="" type="checkbox"/> Undetected <input type="checkbox"/> Suspected	Comparison Evidence: mixed Publication bias judgement	ACE:CCB <input type="checkbox"/> Undetected
Comparison Evidence: mixed Publication bias judgement	ACE:Placebo <input type="checkbox"/> Undetected	Comparison Evidence: mixed Publication bias judgement	ARB:BBBlocker <input type="checkbox"/> Undetected
Comparison Evidence: mixed Publication bias judgement	ARB:Diuretic <input type="checkbox"/> Undetected	Comparison Evidence: mixed Publication bias judgement	ARB:Placebo <input type="checkbox"/> Undetected
Comparison Evidence: mixed Publication bias judgement	BBBlocker:Diuretic <input type="checkbox"/> Undetected	Comparison Evidence: mixed Publication bias judgement	BBBlocker:Placebo <input type="checkbox"/> Undetected
Comparison Evidence: mixed Publication bias judgement	CCB:Placebo <input type="checkbox"/> Undetected	Comparison Evidence: mixed Publication bias judgement	Diuretic:Placebo <input type="checkbox"/> Undetected

DISCLAIMER

You are welcome to use CINeMA with the understanding that it is still under development

- We will improve the data input module
- For some calculations CINeMA uses the `netmeta` package in R, so updates/debugging in `netmeta` affect CINeMA too
- Please notify us for any problems you come across
cinema.ispm@gmail.com
- If you use it in a publication you can cite

**CINeMA: Confidence in Network Meta-Analysis [Software].
University of Bern 2017. Available from cinema.ispm.ch**

Now it is time for....

CINeMA