Lecture 8

CINeMA: a framework and software to evaluate Confidence in Network Meta-Analysis

Adriani Nikolakopoulou

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

BMJ 2014;349:g5630 doi: 10.1136/bmj.g5630 (Published 24 September 2014)

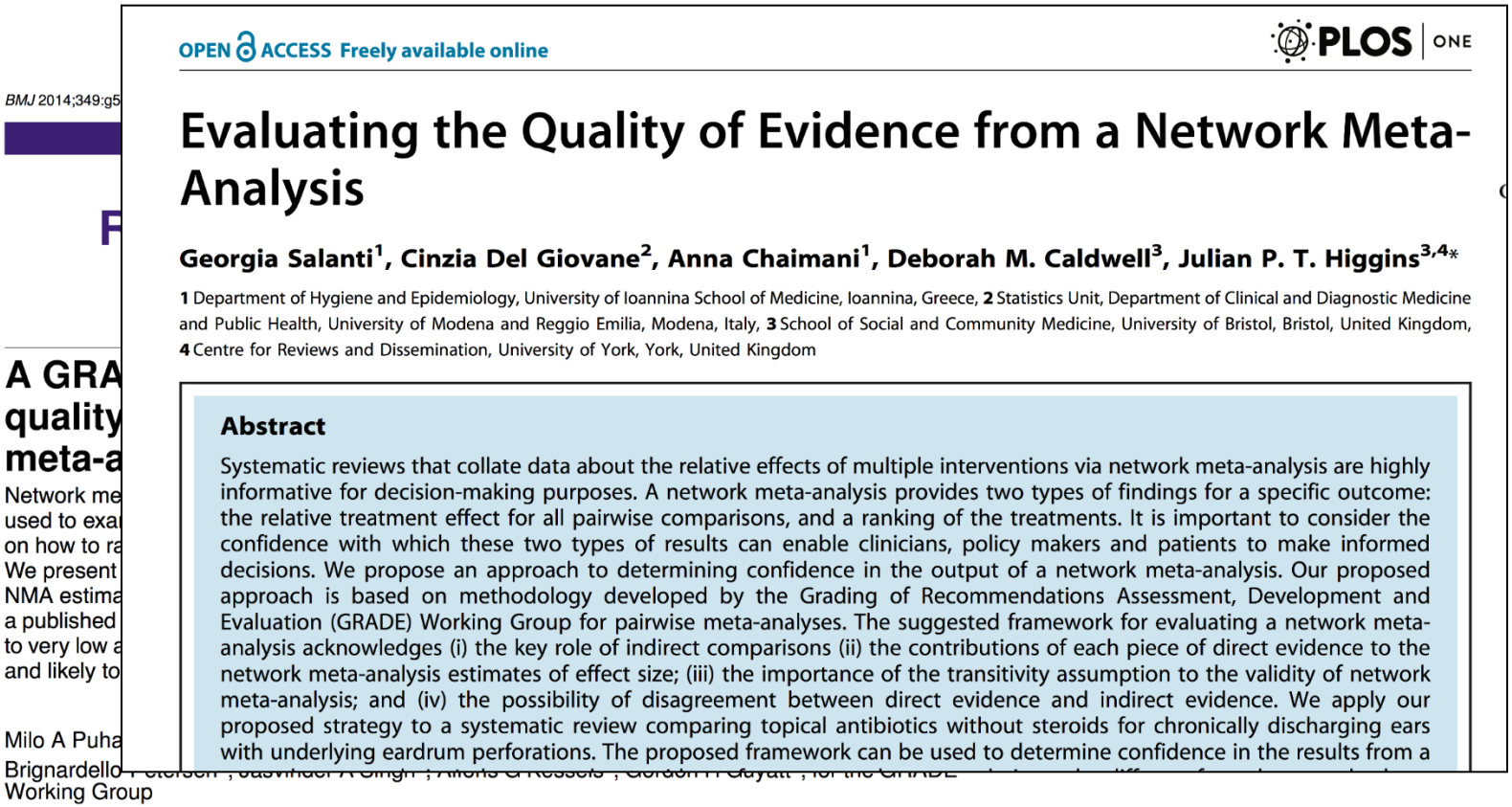
RESEARCH METHODS & REPORTING

A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis

Network meta-analysis (NMA), combining direct and indirect comparisons, is increasingly being used to examine the comparative effectiveness of medical interventions. Minimal guidance exists on how to rate the quality of evidence supporting treatment effect estimates obtained from NMA. We present a four-step approach to rate the quality of evidence in each of the direct, indirect, and NMA estimates based on methods developed by the GRADE working group. Using an example of a published NMA, we show that the quality of evidence supporting NMA estimates varies from high to very low across comparisons, and that quality ratings given to a whole network are uninformative and likely to mislead.

Milo A Puhan [1], Holger J Schünemann [2], Mohammad Hassan Murad [3], Tianjing Li [4], Romina Brignardello-Petersen [5], Jasvinder A Singh [6], Alfons G Kessels [7], Gordon H Guyatt [2], for the GRADE Working Group

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



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PLOS ONE

Evaluating the Quality of Evidence from a Network Meta-Analysis

Georgia Salanti[1], Cinzia Del Giovane[2], Anna Chaimani[1], Deborah M. Caldwell[3], Julian P. T. Higgins[3,4]*

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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

CINeMA **framework**

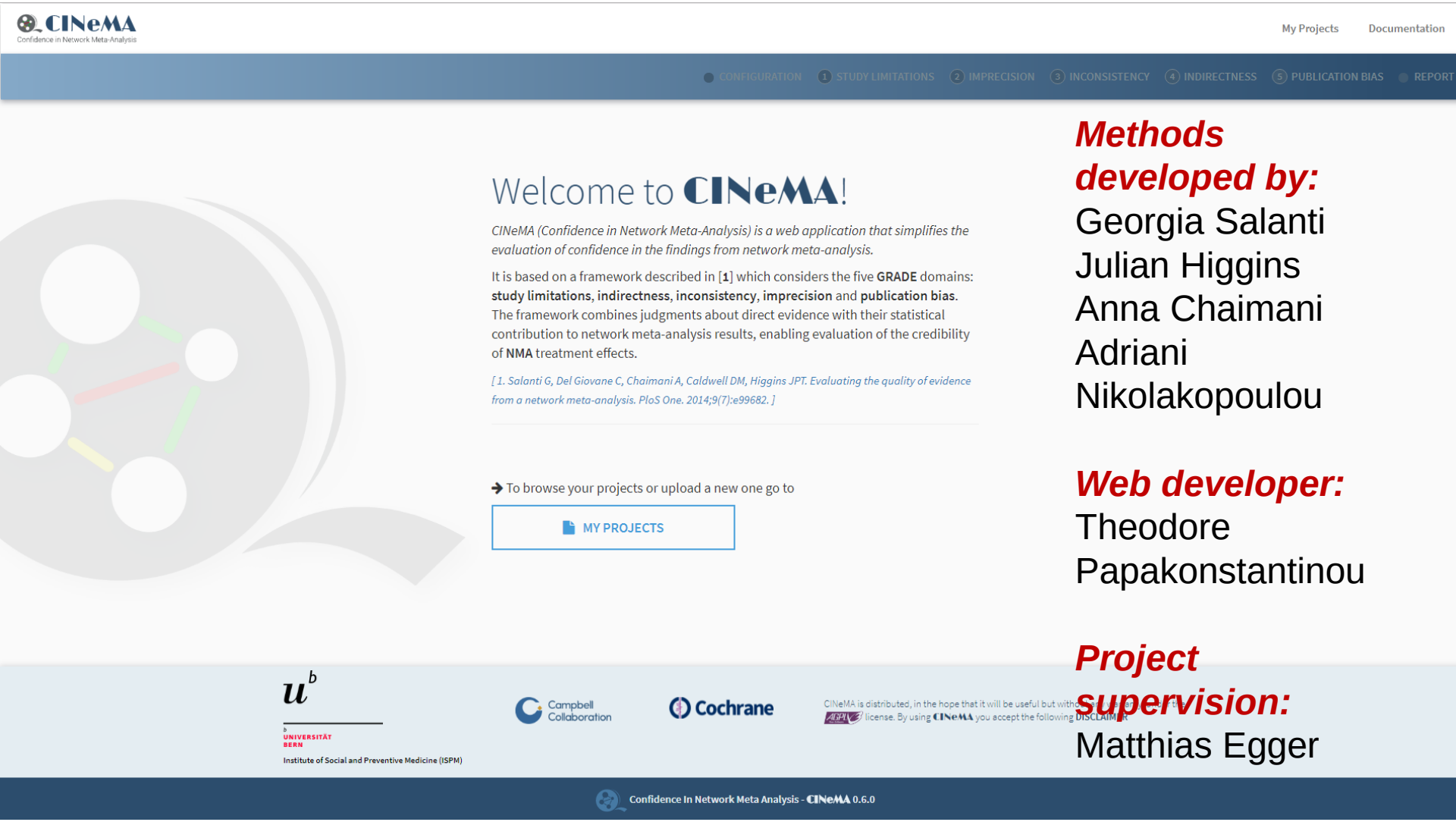
Consider the **network estimates**

Study limitations
Indirectness
Inconsistency (heterogeneity, incoherence)
Imprecision
Publication bias

⇩

Rate each **network estimate**
No concerns
Some concerns
Major concerns

Network estimate	**Study limitations**	**Indirectness**	**Inconsistency**		**Imprecision**	**Publication bias**	**Confidence**
			Heterogeneity	Incoherence			
A vs B	Some concerns	Some concerns	Major concerns	Some concerns	Some concerns	undetected	Very low
A vs C	No concerns	No concerns	No concerns	Major concerns	No concerns	suspected	Low
….							



Methods developed by:

Georgia Salanti
Julian Higgins
Anna Chaimani
Adriani Nikolakopoulou

Web developer:

Theodore Papakonstantinou

Project supervision:

Matthias Egger

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

William J Elliott, Peter M Meyer

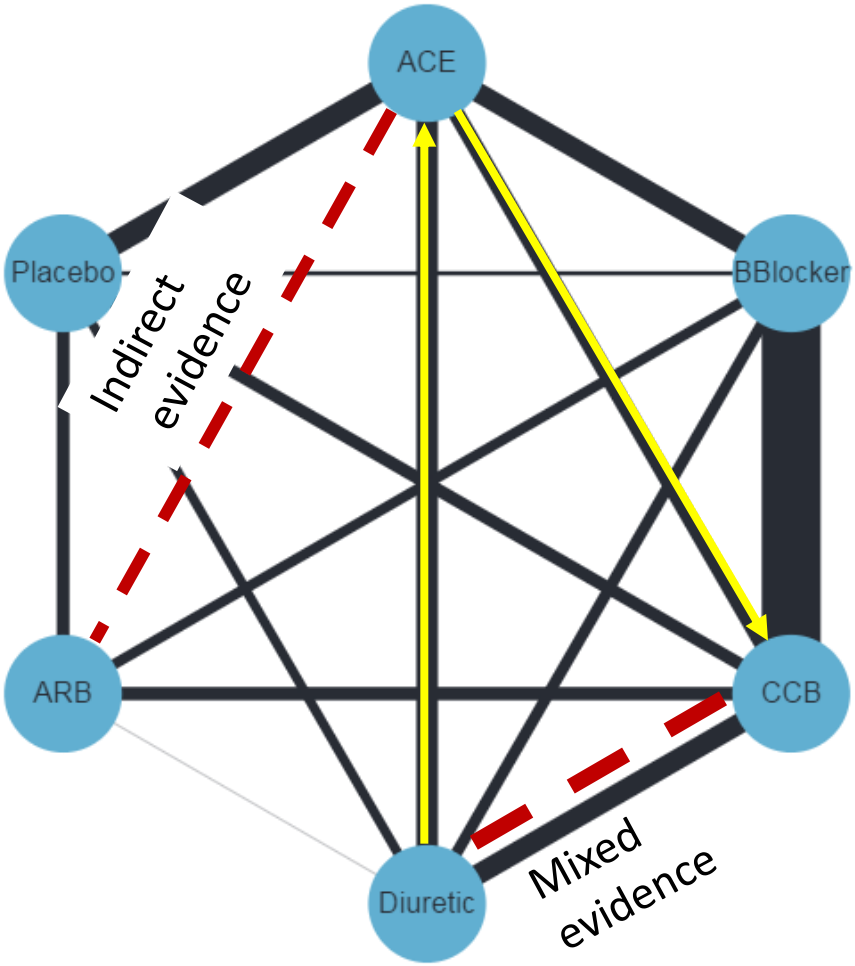
Summary

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


ACE
Placebo
BBlocker
ARB
CCB
Diuretic
Indirect evidence
Mixed evidence

				Inconsistency				
Comparison	Number of Studies	Study Limitations	Imprecision	Heterogeneity	Incoherence	Indirectness	Publication bias	CONFIDENCE
			Mixed evidence					
ACE vs BBlocker	3	No concerns	No concerns	Some concerns	Some concerns	No concerns	Undetected	MODERATE
ACE vs CCB	3	No concerns	Some concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
ACE vs Diuretic	2	No concerns	No concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
ACE vs Placebo	3	No concerns	Some concerns	Some concerns	No concerns	No concerns	Suspected	LOW
ARB vs BBlocker	1	No concerns	No concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
ARB vs CCB	1	Some concerns	No concerns	Some concerns	No concerns	No concerns	Undetected	LOW
ARB vs Diuretic	1	No concerns	No concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
ARB vs Placebo	2	Some concerns	Some concerns	No concerns	No concerns	No concerns	Suspected	VERY LOW
BBlocker vs CCB	5	No concerns	Some concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
BBlocker vs Diuretic	2	No concerns	Some concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
BBlocker vs Placebo	1	No concerns	Some concerns	Some concerns	Some concerns	No concerns	Suspected	VERY LOW
CCB vs Diuretic	2	No concerns	Some concerns	No concerns	No concerns	No concerns	Undetected	MODERATE
CCB vs Placebo	1	No concerns	Some concerns	Some concerns	No concerns	No concerns	Suspected	LOW
Diuretic vs Placebo	3	No concerns	No concerns	Some concerns	No concerns	No concerns	Suspected	LOW
			Indirect evidence					
ACE vs ARB	--	No concerns	Some concerns	Some concerns	No concerns	No concerns	Undetected	LOW

				Inconsistency				CONFIDENCE
Comparison	Number of Studies	Study Limitations	Imprecision	Heterogeneity	Incoherence	Indirectness	Publication bias	
			Mixed evidence					
ACE vs BBlocker	3	No concerns	No concerns	Some concerns	Some concerns	No concerns	Undetected	MODERATE
ACE vs CCB	3	No concerns	Some concerns	Some concerns	No concerns	No concerns	Undetected	MODERATE
ACE vs Diuretic	2							MODERATE
ACE vs Placebo	3							LOW
ARB vs BBlocker	1							MODERATE
ARB vs CCB	1							LOW
ARB vs Diuretic	1							MODERATE
ARB vs Placebo	2							VERY LOW
BBlocker vs CCB	5							MODERATE
BBlocker vs Diuretic	2							MODERATE
BBlocker vs Placebo	1							VERY LOW
CCB vs Diuretic	2							MODERATE
CCB vs Placebo	1	No concerns	Some concerns	Some concerns	No concerns	No concerns	Suspected	LOW
Diuretic vs Placebo	3	No concerns	No concerns	Some concerns	No concerns	No concerns	Suspected	LOW
			Indirect evidence					
ACE vs ARB	--	No concerns	Some concerns	Some concerns	No concerns	No concerns	Undetected	LOW

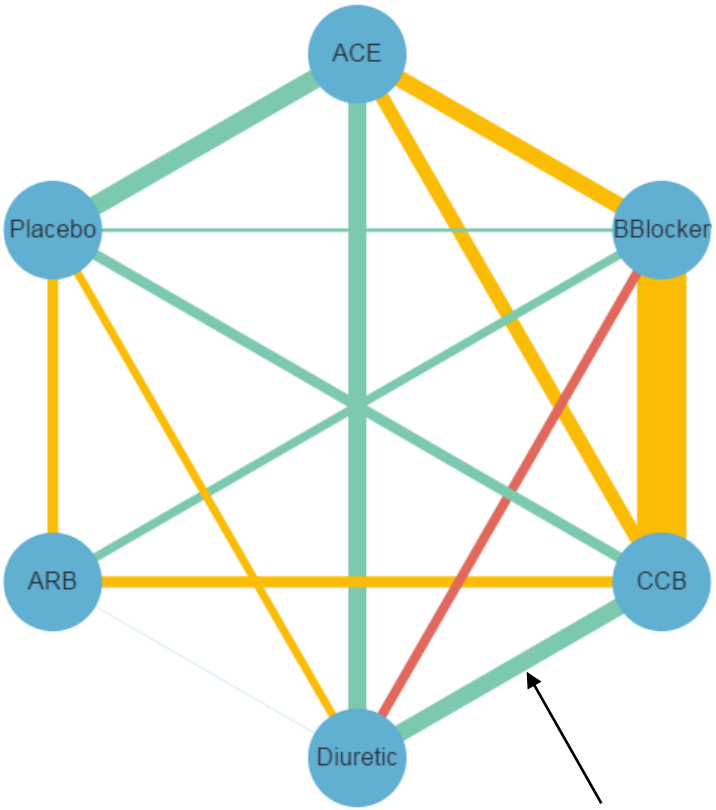
Semi-automated process

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

The rules can be overwritten!

Study limitation

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



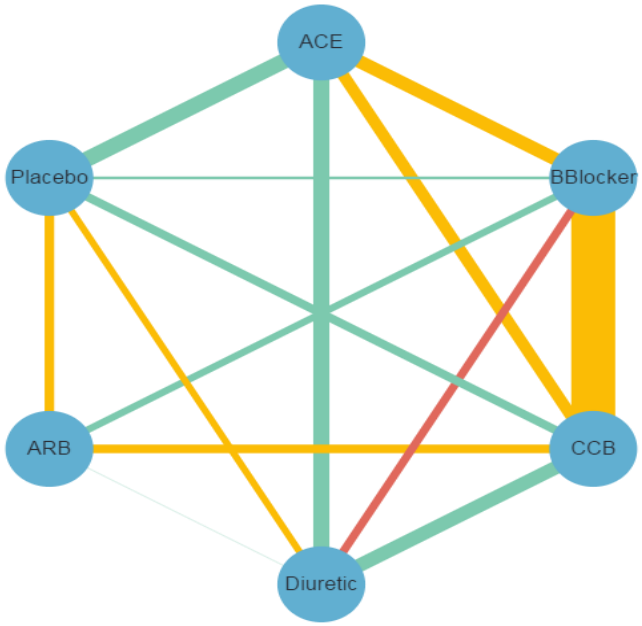
Plot direct comparison in green

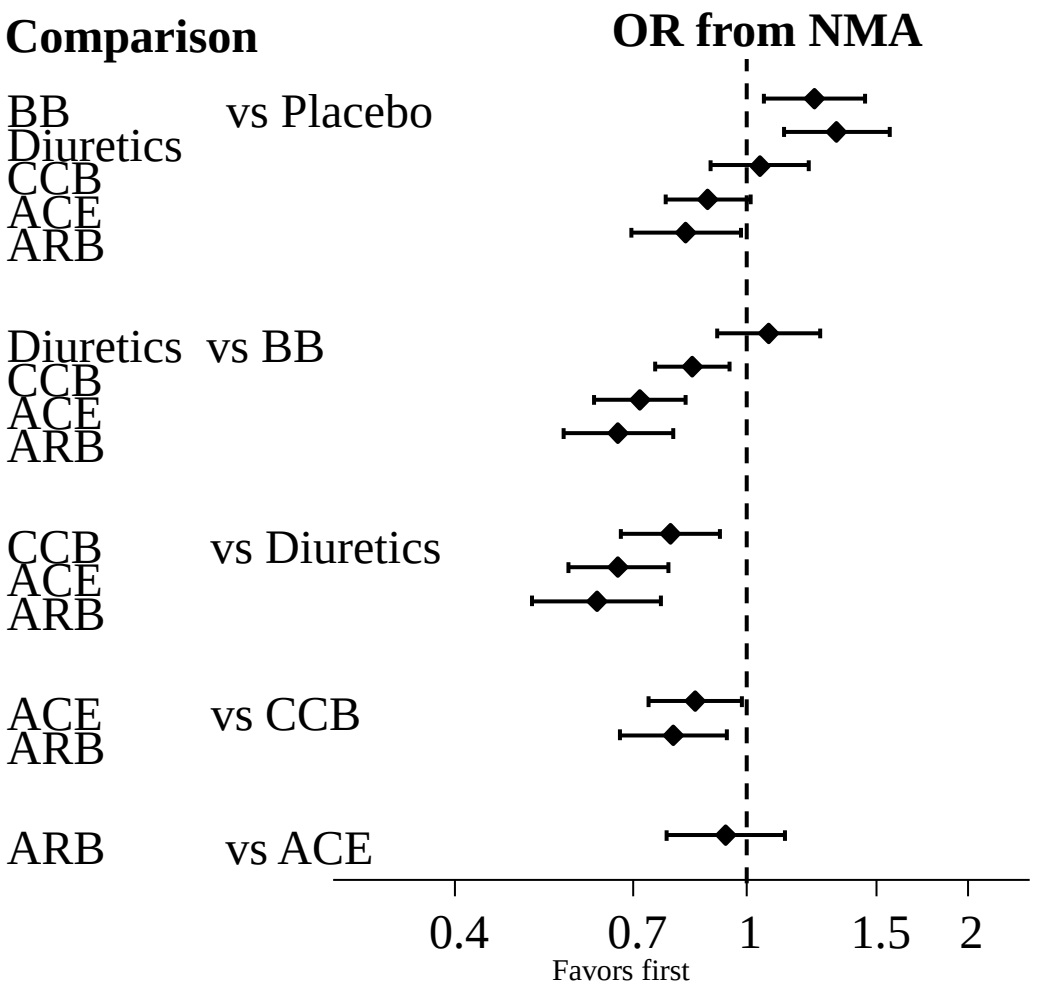
CCB vs Diuretics: overall low risk of bias

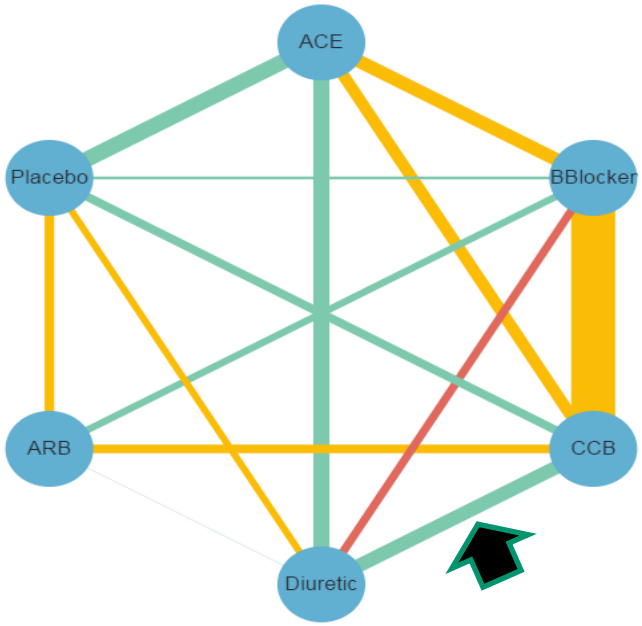
Form risk of bias judgements for each study

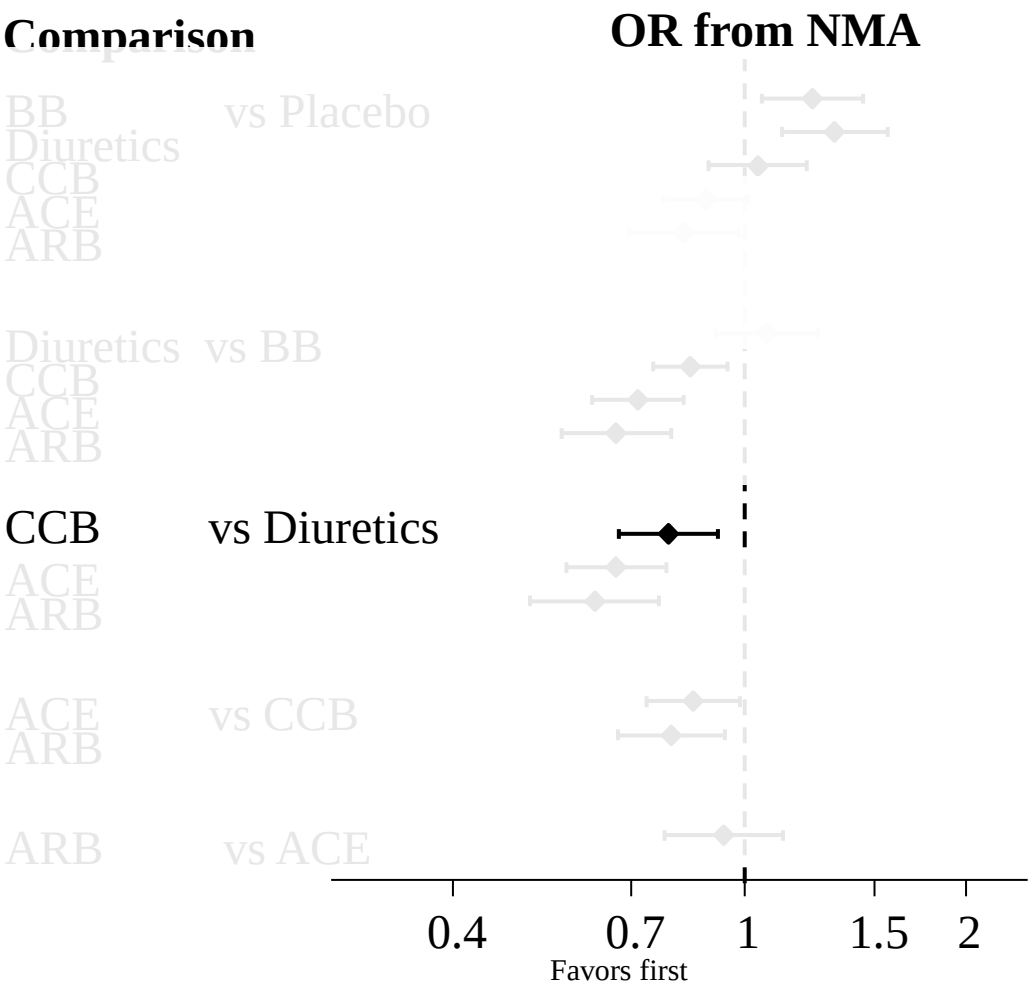
Consider selection, performance, attrition, detection and reporting bias

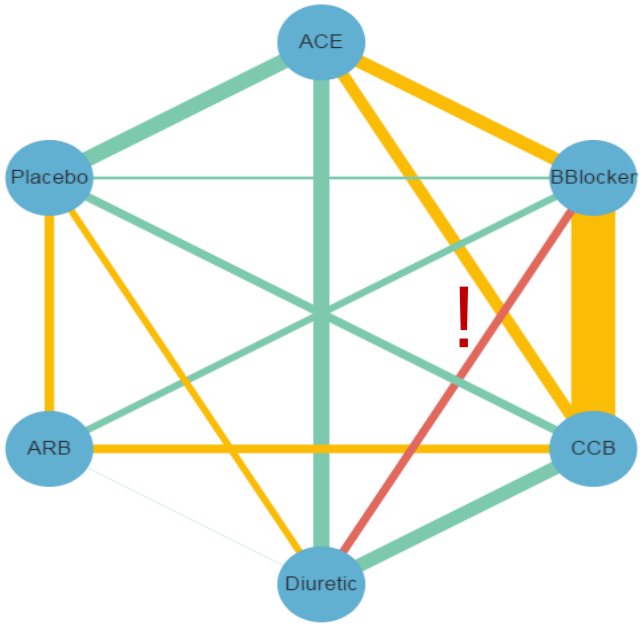
Study name	Risk of Bias
AASK	LOW
ALLHAT	LOW
ALPINE	LOW
ANBP-2	LOW
ASCOT	LOW
CAPPP	MODERATE
CHARM	LOW
DREAM	LOW
EWPHE	MODERATE
FEVER	LOW
HAPPHY	HIGH
HOPE	LOW
INSIGHT	LOW
INVEST	LOW
LIFE	LOW
MRC	LOW
NORDIL	LOW
PEACE	LOW
SCOPE	MODERATE
SHEP	LOW
STOP-2	MODERATE
VALUE	MODERATE


ACE
Placebo
BBlocker
ARB
CCB
Diuretic

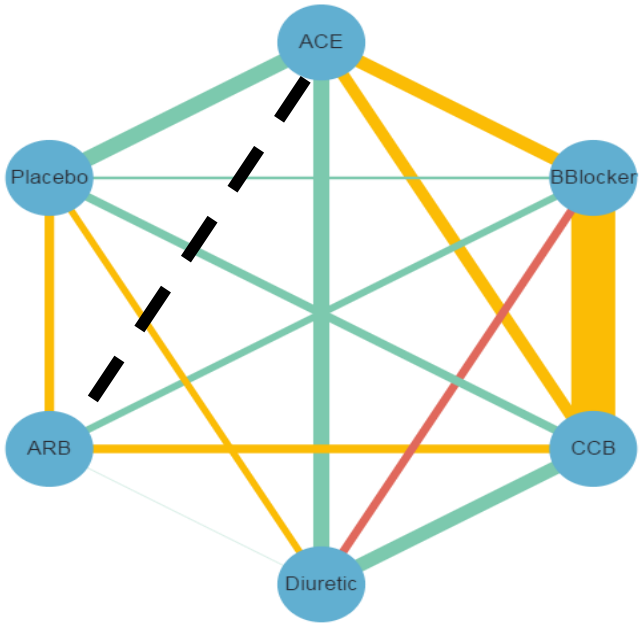

Comparison
OR from NMA
BB vs Placebo
Diuretics
CCB
ACE
ARB
Diuretics vs BB
CCB
ACE
ARB
CCB vs Diuretics
ACE
ARB
ACE vs CCB
ARB
ARB vs ACE
0.4
0.7
1
1.5
2
Favors first

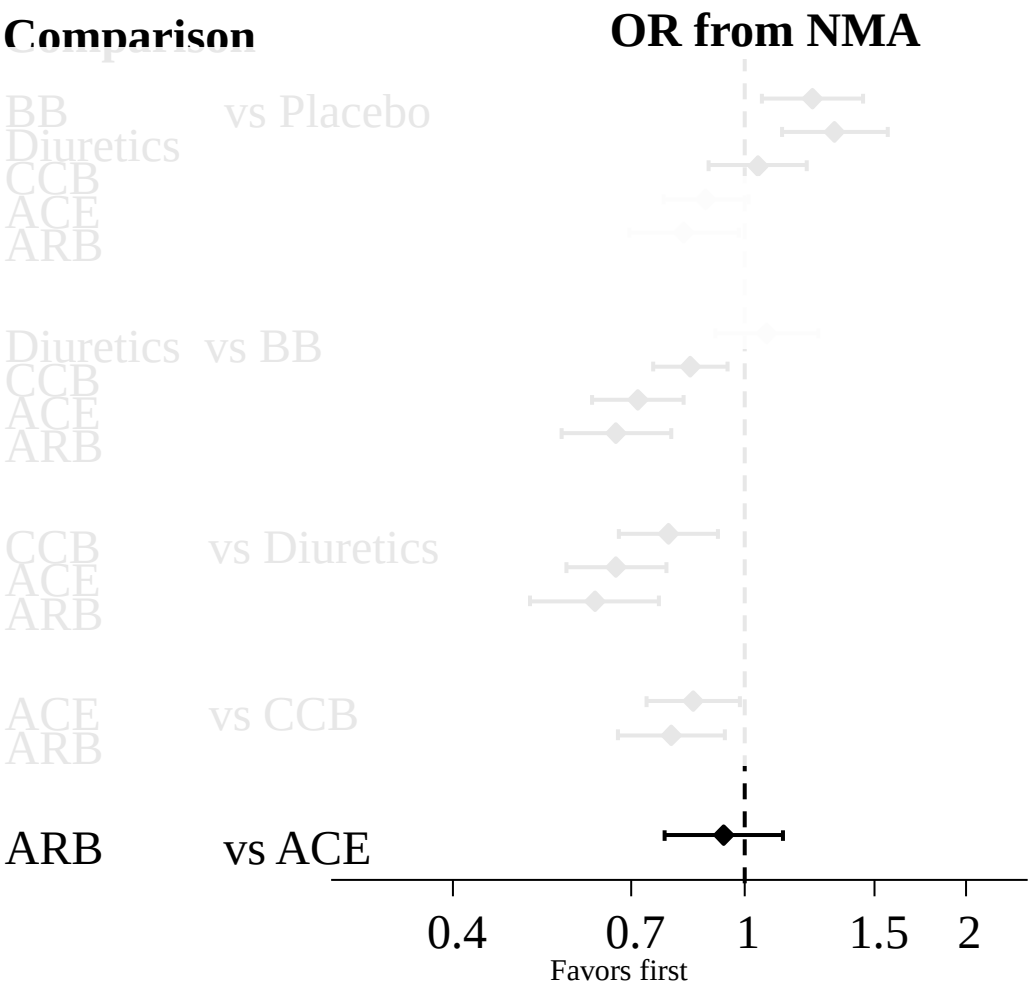

ACE
Placebo
BBlocker
ARB
CCB
Diuretic


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



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


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

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

The contribution matrix

	ACE: BBlocker	ACE: CCB	ACE: Diuretic	ACE: Placebo	ARB: BBlocker	ARB: CCB	ARB: Diuretic	ARB: Placebo	BBlocker: CCB	BBlocker: Diuretic	BBlocker: Placebo	CCB: Diuretic	CCB: Placebo	Diuretic: Placebo
Mixed estimates														
ACE:BBlocker	32	10	10	8	6	1	0	4	15	6	2	5	2	0
ACE:CCB	10	26	13	11	1	6	0	4	9	1	0	13	6	0
ACE:Diuretic	6	7	57	5	0	2	0	2	1	5	0	12	2	2
ACE:Placebo	5	7	5	56	3	3	0	6	1	0	2	3	8	2
ARB:BBlocker	4	1	0	3	41	21	0	5	19	2	2	2	1	0
ARB:CCB	1	2	1	2	8	67	0	6	8	1	0	2	4	0
ARB:Diuretic	3	2	11	5	10	27	0	8	0	7	0	25	0	2
ARB:Placebo	3	3	2	7	6	15	0	49	0	1	2	2	10	1
BBlocker:CCB	6	4	1	1	11	12	0	0	53	4	2	5	2	0
BBlocker:Diuretic	10	1	13	2	5	3	0	2	19	20	2	21	0	2
BBlocker:Placebo	10	2	2	14	13	3	0	16	16	4	8	1	11	2
CCB:Diuretic	2	6	11	3	1	3	0	2	7	6	0	56	3	2
CCB:Placebo	2	6	4	12	1	15	0	16	6	0	2	5	28	2
Diuretic:Placebo	0	0	20	20	2	7	0	9	0	5	2	17	11	7
Indirect estimates														
ACE:ARB	10	11	8	16	11	20	0	14	1	1	0	7	2	0

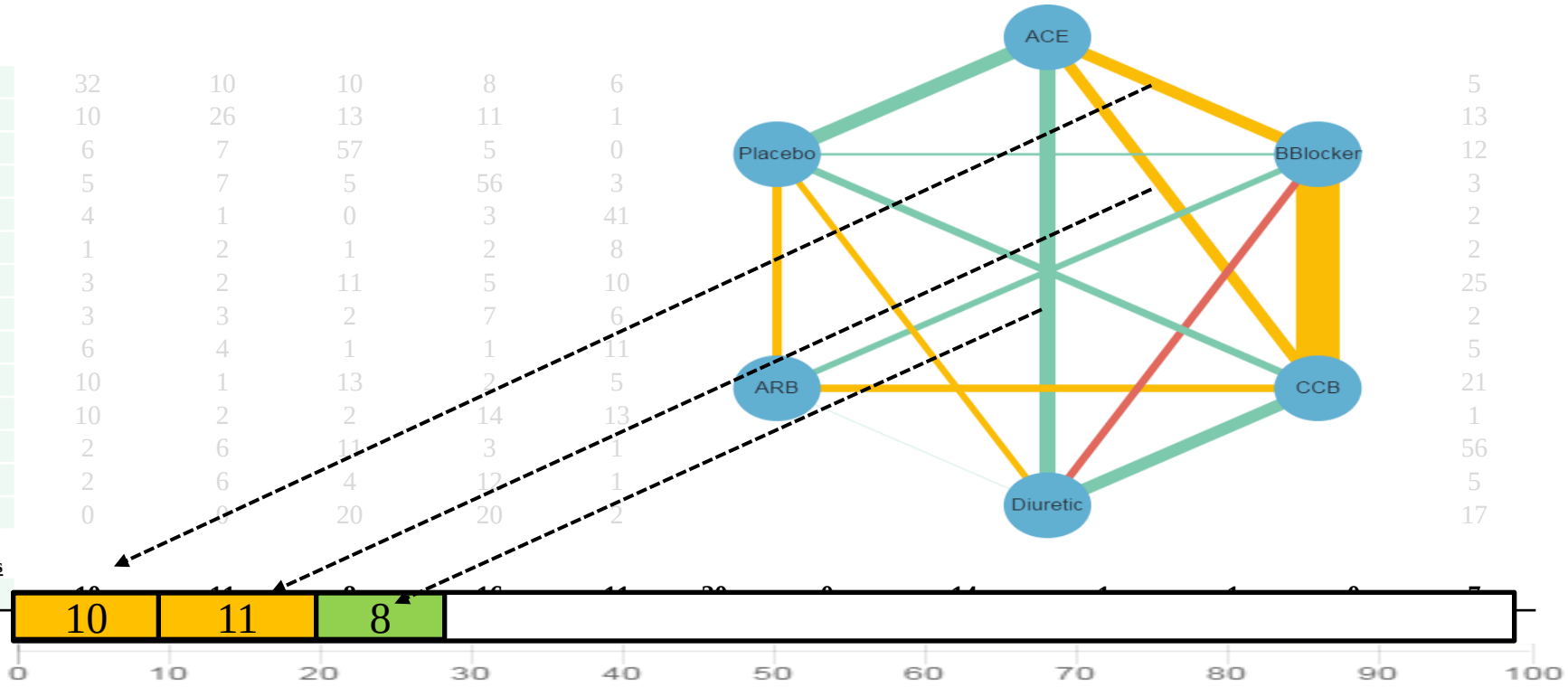
An indirect or mixed treatment effect is a combination of the available direct treatment effects

The contribution matrix

	ACE: BBlocker	ACE: CCB	ACE: Diuretic	ACE: Placebo	ARB: BBlocker	ARB: CCB	ARB: Diuretic	ARB: Placebo	BBlocker: CCB	BBlocker: Diuretic	BBlocker: Placebo	CCB: Diuretic	CCB: Placebo	Diuretic: Placebo
Mixed estimates														
ACE:BBlocker	32	10	10	8	6	1	0	4	15	6	2	5	2	0
ACE:CCB	10	26	13	11	1	6	0	4	9	1	0	13	6	0
ACE:Diuretic	6	7	57	5	0	2	0	2	1	5	0	12	2	2
ACE:Placebo	5	7	5	56	3	3	0	6	1	0	2	3	8	2
ARB:BBlocker	4	1	0	3	41	21	0	5	19	2	2	2	1	0
ARB:CCB	1	2	1	2	8	67	0	6	8	1	0	2	4	0
ARB:Diuretic	3	2	11	5	10	27	0	8	0	7	0	25	0	2
ARB:Placebo	3	3	2	7	6	15	0	49	0	1	2	2	10	1
BBlocker:CCB	6	4	1	1	11	12	0	0	53	4	2	5	2	0
BBlocker:Diuretic	10	1	13	2	5	3	0	2	19	20	2	21	0	2
BBlocker:Placebo	10	2	2	14	13	3	0	16	16	4	8	1	11	2
CCB:Diuretic	2	6	11	3	1	3	0	2	7	6	0	56	3	2
CCB:Placebo	2	6	4	12	1	15	0	16	6	0	2	5	28	2
Diuretic:Placebo	0	0	20	20	2	7	0	9	0	5	2	17	11	7
Indirect estimates														
ACE:ARB	10	11	8	16	11	20	0	14	1	1	0	7	2	0

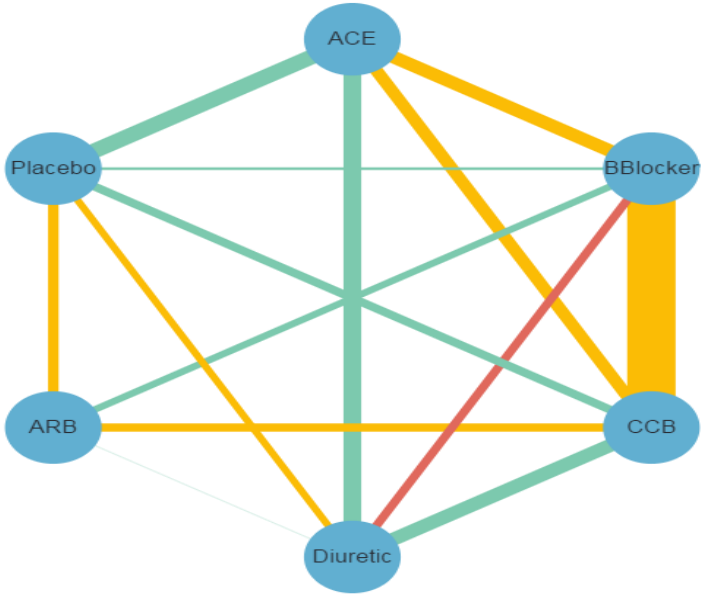
The contribution matrix

	ACE: BBlocker	ACE: CCB	ACE: Diuretic	ACE: Placebo	ARB: BBlocker	ARB: CCB	ARB: Diuretic	ARB: Placebo	BBlocker: CCB	BBlocker: Diuretic	BBlocker: Placebo	CCB: Diuretic
Mixed estimates												
ACE:BBlocker	32	10	10	8	6							5
ACE:CCB	10	26	13	11	1							13
ACE:Diuretic	6	7	57	5	0							12
ACE:Placebo	5	7	5	56	3							3
ARB:BBlocker	4	1	0	3	41							2
ARB:CCB	1	2	1	2	8							2
ARB:Diuretic	3	2	11	5	10							25
ARB:Placebo	3	3	2	7	6							2
BBlocker:CCB	6	4	1	1	11							5
BBlocker:Diuretic	10	1	13	2	5							21
BBlocker:Placebo	10	2	2	14	13							1
CCB:Diuretic	2	6	11	3	1							56
CCB:Placebo	2	6	4	12	1							5
Diuretic:Placebo	0	0	20	20	2							17
Indirect estimates												
ACE:ARB												



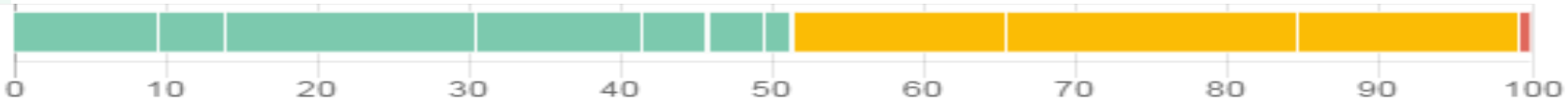
The contribution matrix

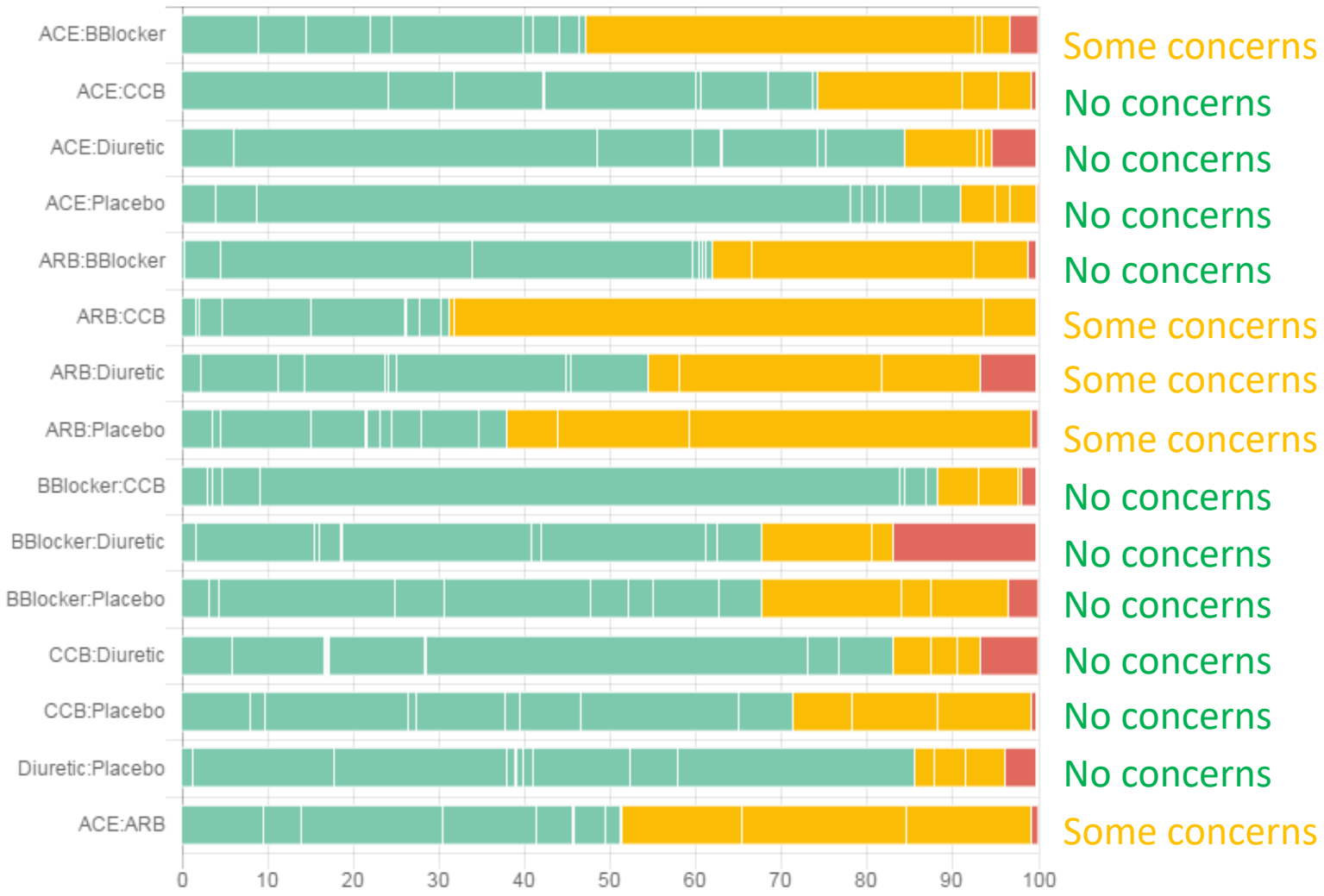
	ACE: BBlocker	ACE: CCB	ACE: Diuretic	ACE: Placebo	ARB: BBlocker	ARB: CCB	ARB: Diuretic	ARB: Placebo	BBlocker: CCB	BBlocker: Diuretic	BBlocker: Placebo	CCB: Diuretic
Mixed estimates												
ACE:BBlocker	32	10	10	8	6							5
ACE:CCB	10	26	13	11	1							13
ACE:Diuretic	6	7	57	5	0							12
ACE:Placebo	5	7	5	56	3							3
ARB:BBlocker	4	1	0	3	41							2
ARB:CCB	1	2	1	2	8							2
ARB:Diuretic	3	2	11	5	10							25
ARB:Placebo	3	3	2	7	6							2
BBlocker:CCB	6	4	1	1	11							5
BBlocker:Diuretic	10	1	13	2	5							21
BBlocker:Placebo	10	2	2	14	13							1
CCB:Diuretic	2	6	11	3	1							56
CCB:Placebo	2	6	4	12	1							5
Diuretic:Placebo	0	0	20	20	2							17



Indirect estimates

ACE:ARB




ACE:BBlocker
ACE:CCB
ACE:Diuretic
ACE:Placebo
ARB:BBlocker
ARB:CCB
ARB:Diuretic
ARB:Placebo
BBlocker:CCB
BBlocker:Diuretic
BBlocker:Placebo
CCB:Diuretic
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
No concerns
No concerns
No concerns
No concerns
No concerns
No concerns
Some concerns

Indirectness

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

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….

CINeMA

`cinema.ispm.ch`

Imprecision

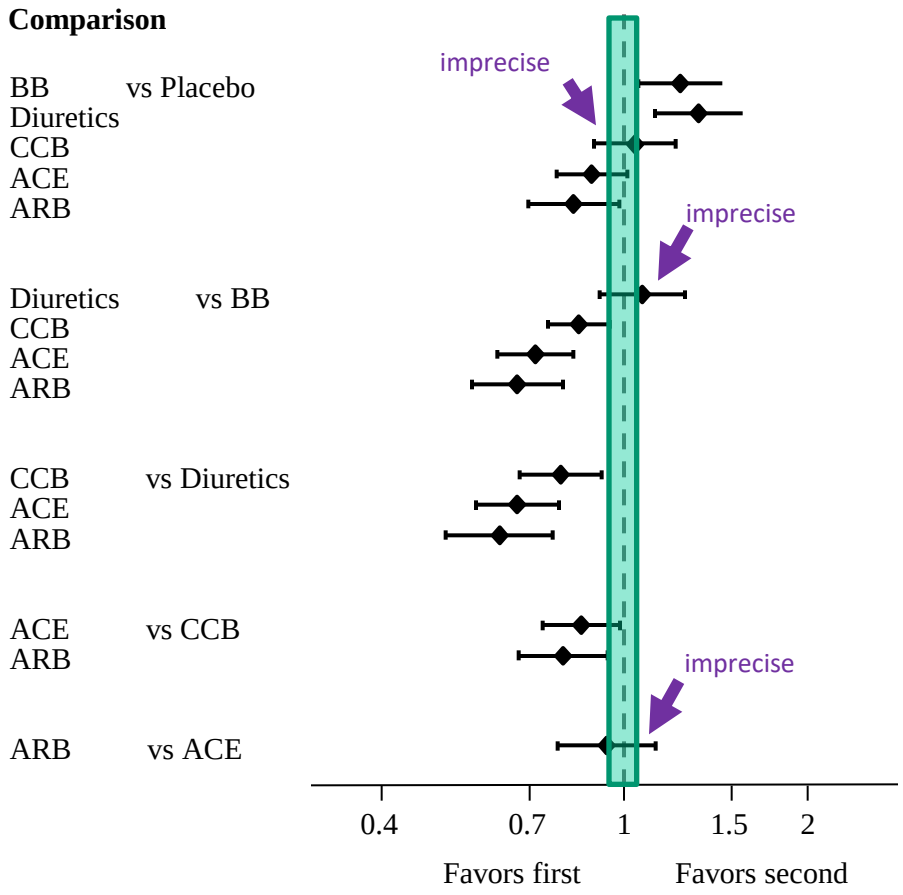
- ❑ Major concerns
- ❑ Some concerns
- ❑ No concerns

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

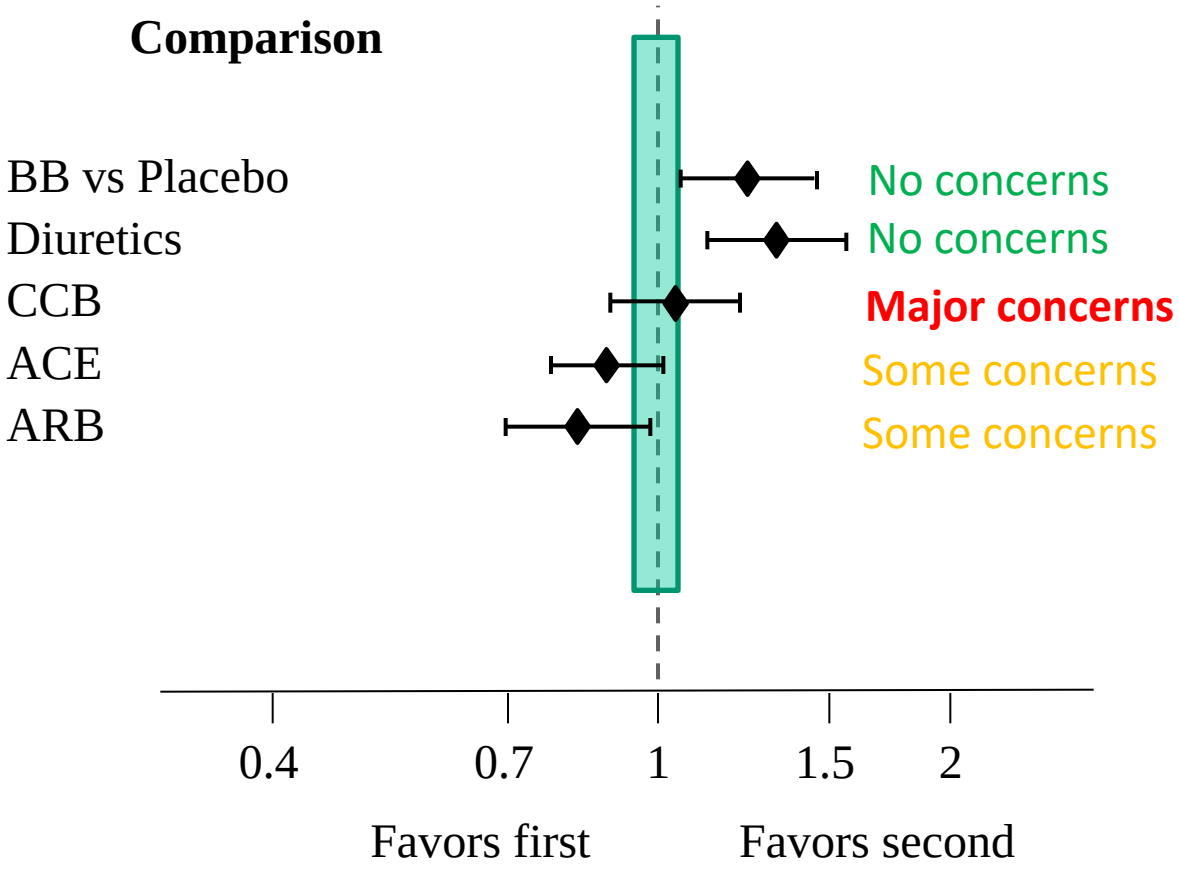
NMA estimated odds ratios for diabetes



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

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

NMA estimated odds ratios for diabetes



Now it is time for….

CINeMA

INCONSISTENCY

HETEROGENEITY

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

INCOHERENCE

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

INCONSISTENCY

Heterogeneity
between-study variance
within a comparison
evidence

INCONSISTENCY

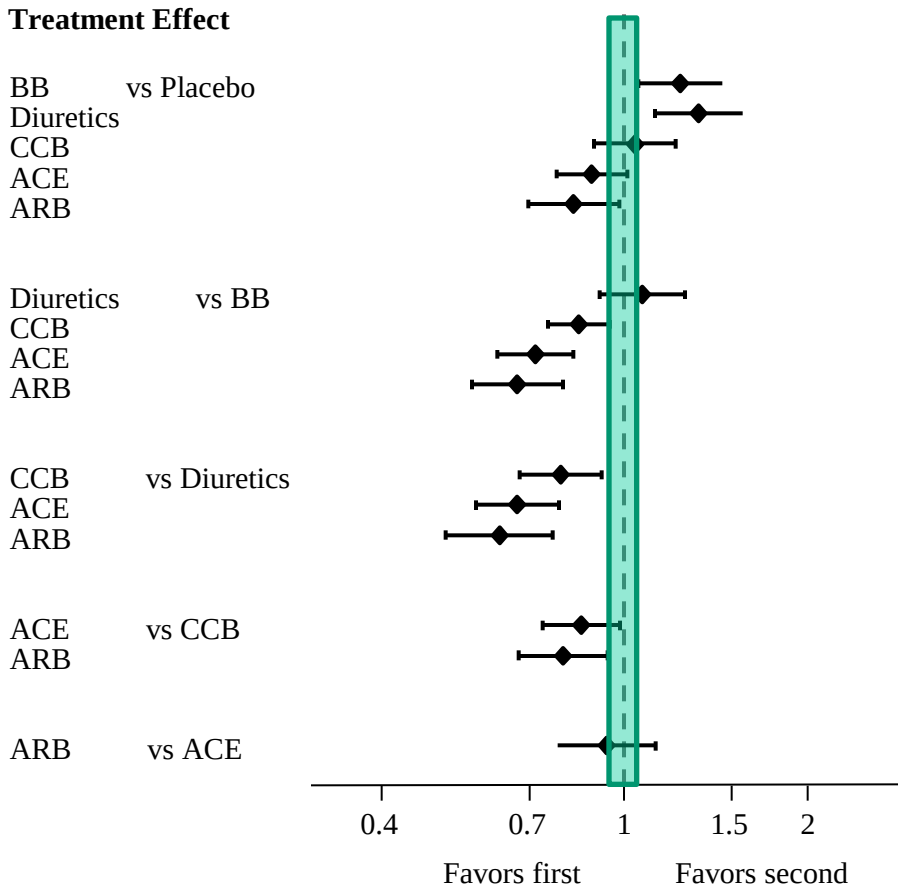
Heterogeneity
between-study variance within a comparison

Incoherence
disagreement between different sources of evidence

Inconsistency 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

INCONSISTENCY HETEROGENEITY



INCONSISTENCY HETEROGENEITY

Treatment Effect

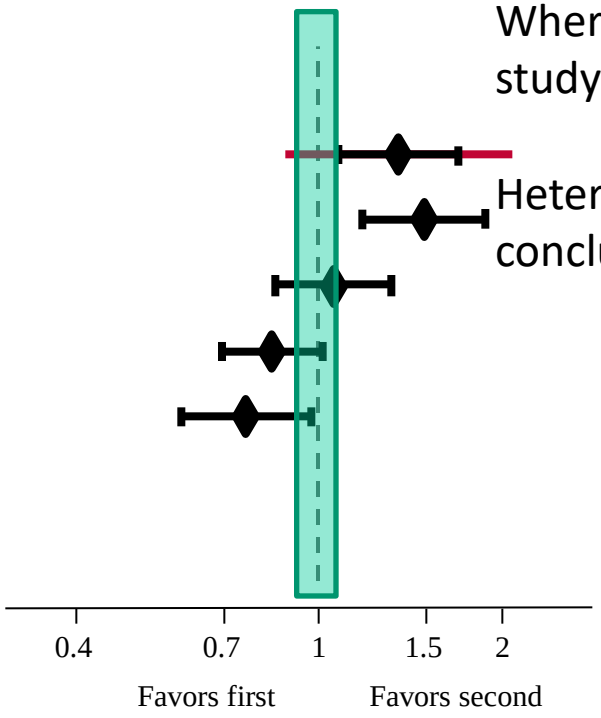
BB vs Placebo

Diuretics

CCB

ACE

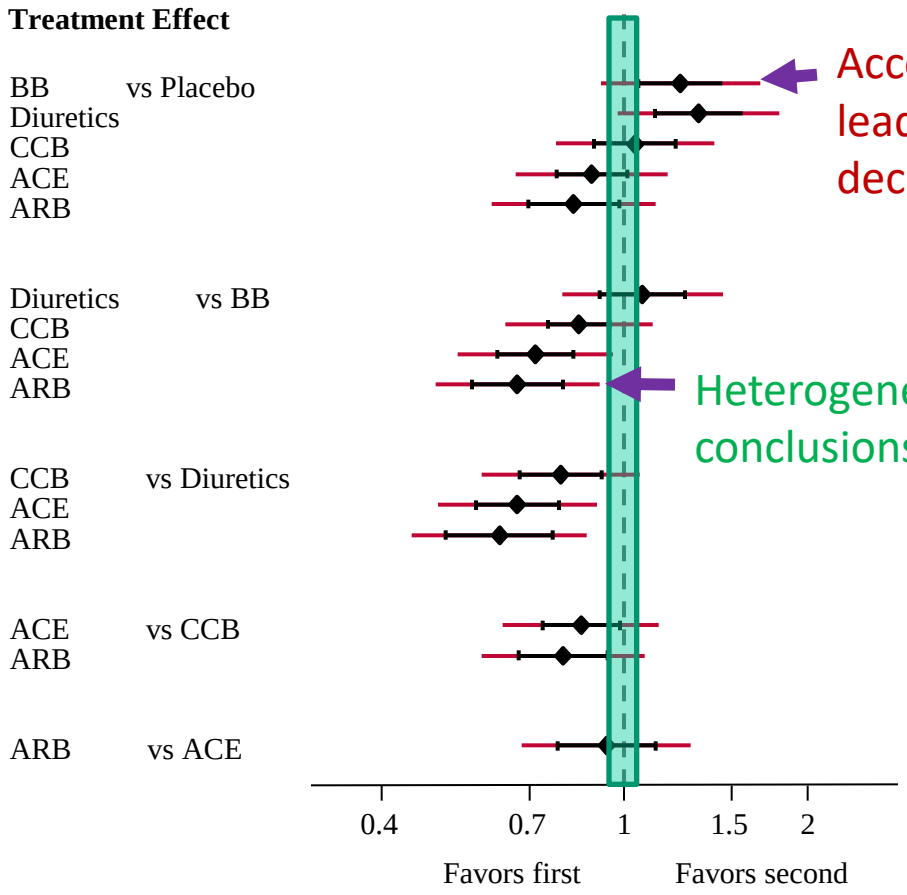
ARB



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

Heterogeneity changes conclusions!

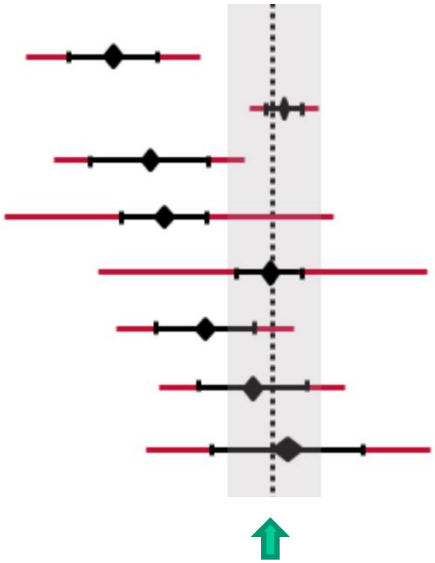
INCONSISTENCY HETEROGENEITY



Accounting for heterogeneity leads into different clinical decisions!

Heterogeneity does not change conclusions!

INCONSISTENCY HETEROGENEITY



Margin of equivalence

Rules implemented in the software

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

Prediction interval

Confidence interval

Inconsistency 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 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

Inconsistency heterogeneity

Comparison	ACE:BBlocker
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I^2:	**49.8%**
Estimated τ^2:	**0.019**
Reference Values for τ^2	
first quantile:	**0.003**
median:	**0.014**
third quantile:	**0.061**
95% intervals for NMA estimate	
Confidence interval:	**(1.245,1.498)**
Prediction interval:	**(0.992,1.879)**
*Prediction interval **extends into clinically important or unimportant effects***	
Heterogeneity judgement	Serious

Comparison	ARB:BBlocker
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I^2:	**NA**
Estimated τ^2:	**NA**
Reference Values for τ^2	
first quantile:	**0.003**
median:	**0.014**
third quantile:	**0.061**
95% intervals for NMA estimate	
Confidence interval:	**(1.372,1.657)**
Prediction interval:	**(1.094,2.077)**
*Confidence and prediction intervals **agree** in relation to clinically important effect*	
Heterogeneity judgement	No serious

Comparison	BBlocker:CCB
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I^2:	**62.5%**
Estimated τ^2:	**0.013**
Reference Values for τ^2	
first quantile:	**0.003**
median:	**0.014**
third quantile:	**0.061**
95% intervals for NMA estimate	
Confidence interval:	**(0.768,0.871)**
Prediction interval:	**(0.600,1.115)**
*Prediction interval extends into clinically important effects in **both** directions*	
Heterogeneity judgement	Very Serious

INCONSISTENCY

Heterogeneity
between-study variance within a comparison

Incoherence
disagreement between different sources of evidence

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

INCONSISTENCY

Heterogeneity
between-study variance within a comparison

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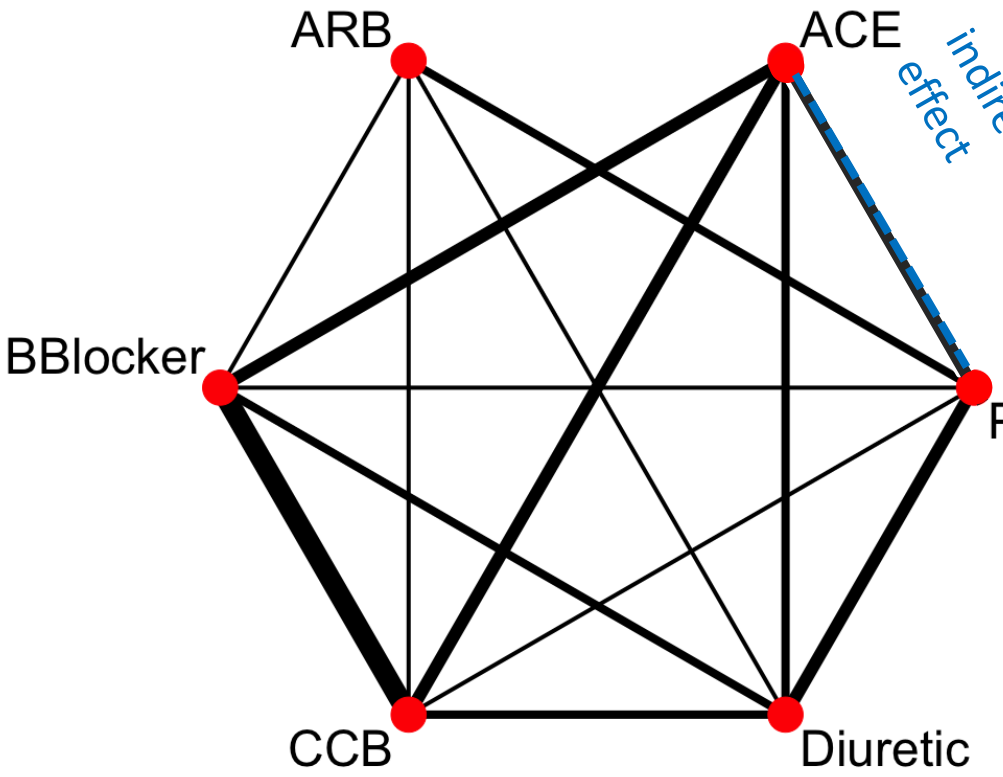
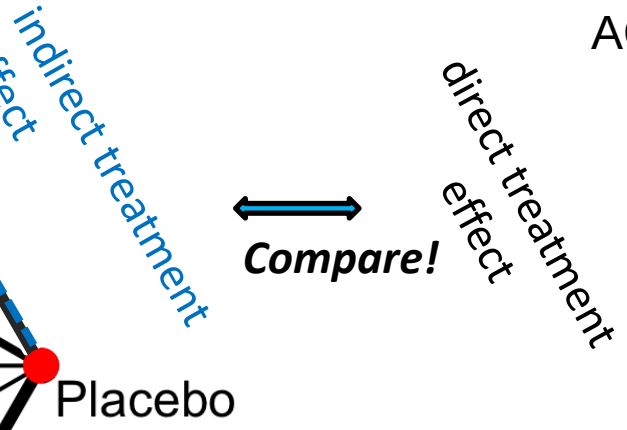
We consider prediction intervals for the **impact of heterogeneity** in clinical decision making

Separate Direct from Indirect Evidence test (node-splitting)
: Compare direct and indirect relative treatment effects using a Z-test
: one test for each treatment comparisons
Design-by-treatment test X^2
: one test for the network

INCONSISTENCY INCOHERENCE

Separate Direct from Indirect Evidence test

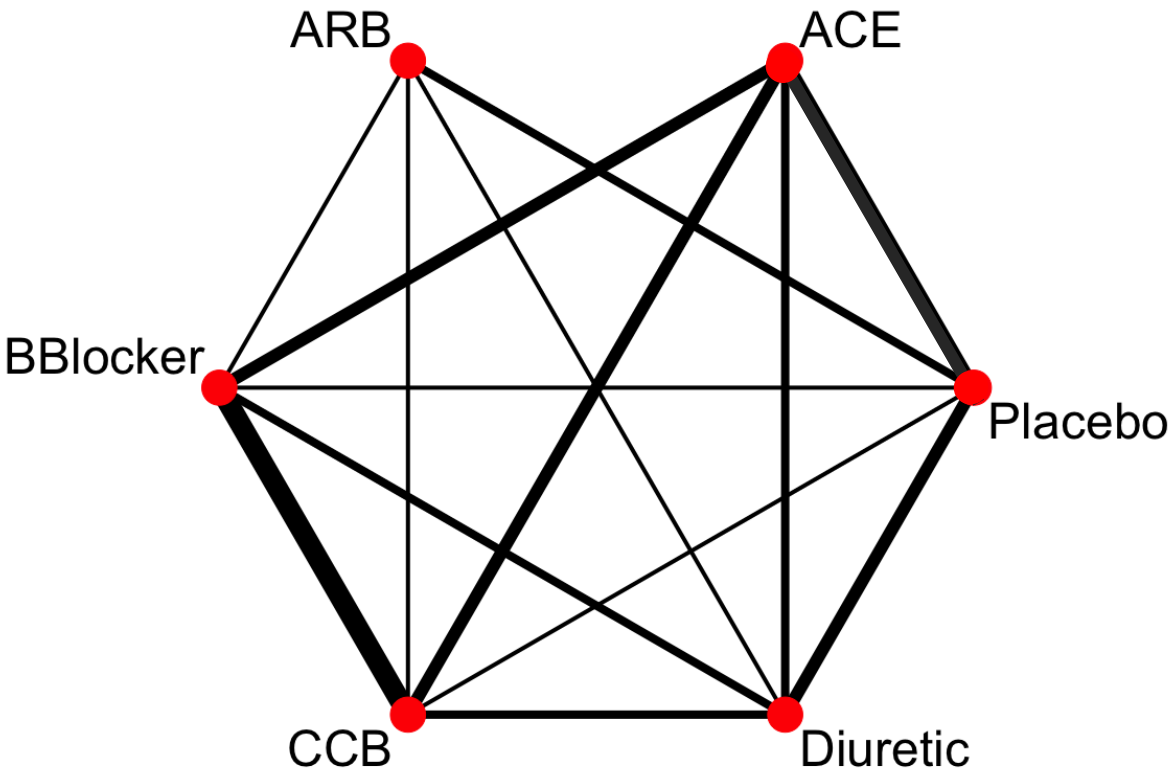




Comparison	ACE:Placebo
Evidence: mixed	
Direct contribution:	**62.2%**
Inconsistency measures	
Ratio of odds ratios:	**1.251(0.938,1.669)**
Z statistic:	**1.522**
P value:	**0.128**

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

INCONSISTENCY INCOHERENCE



Design-by-treatment X^2 test

Does the assumption of coherence hold for the entire network?

χ^2 =19.325 (13 df)
P-value=0.113

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

INCONSISTENCY INCOHERENCE

Treatment comparisons that take at least 90% of the information from direct evidence have no concerns for incoherence

For comparisons with at least 10% of information derived from indirect evidence we use the following rule

Design-by-treatment interaction model

		p-value>0.1	*0.01<p-value<0.1*	*p-value<0.01*
	p-value>0.1	No concerns	No concerns	Some concerns
SIDE	*0.01<p-value<0.1*	Some concerns	Some concerns	Major concerns
	p-value<0.01	Some concerns	Major concerns	Major concerns

INCONSISTENCY INCOHERENCE

Comparison	ACE:BBlocker
Evidence: mixed	
Direct contribution:	**51.4%**
Inconsistency measures	
Ratio of odds ratios:	**0.719(0.533,0.969)**
Z statistic:	**-2.165**
P value:	**0.030**
Incoherence judgement	Some concerns

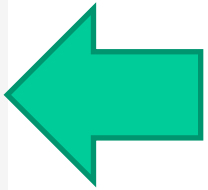
Comparison	ACE:CCB
Evidence: mixed	
Direct contribution:	**41.5%**
Inconsistency measures	
Ratio of odds ratios:	**1.099(0.810,1.490)**
Z statistic:	**0.605**
P value:	**0.545**
Incoherence judgement	No concerns

Comparison	ARB:CCB
Evidence: mixed	
Direct contribution:	**41.7%**
Inconsistency measures	
Ratio of odds ratios:	**1.012(0.709,1.444)**
Z statistic:	**0.066**
P value:	**0.948**
Incoherence judgement	No concerns

Comparison	ARB:Diuretic
Evidence: mixed	
Direct contribution:	**1.0%**
Inconsistency measures	
Ratio of odds ratios:	**5.247(0.634,43.445)**
Z statistic:	**1.537**
P value:	**0.124**
Incoherence judgement	No concerns

Comparison	BBlocker:Placebo
Evidence: mixed	
Direct contribution:	**9.5%**
Inconsistency measures	
Ratio of odds ratios:	**0.524(0.299,0.918)**
Z statistic:	**-2.261**
P value:	**0.024**
Incoherence judgement	Some concerns

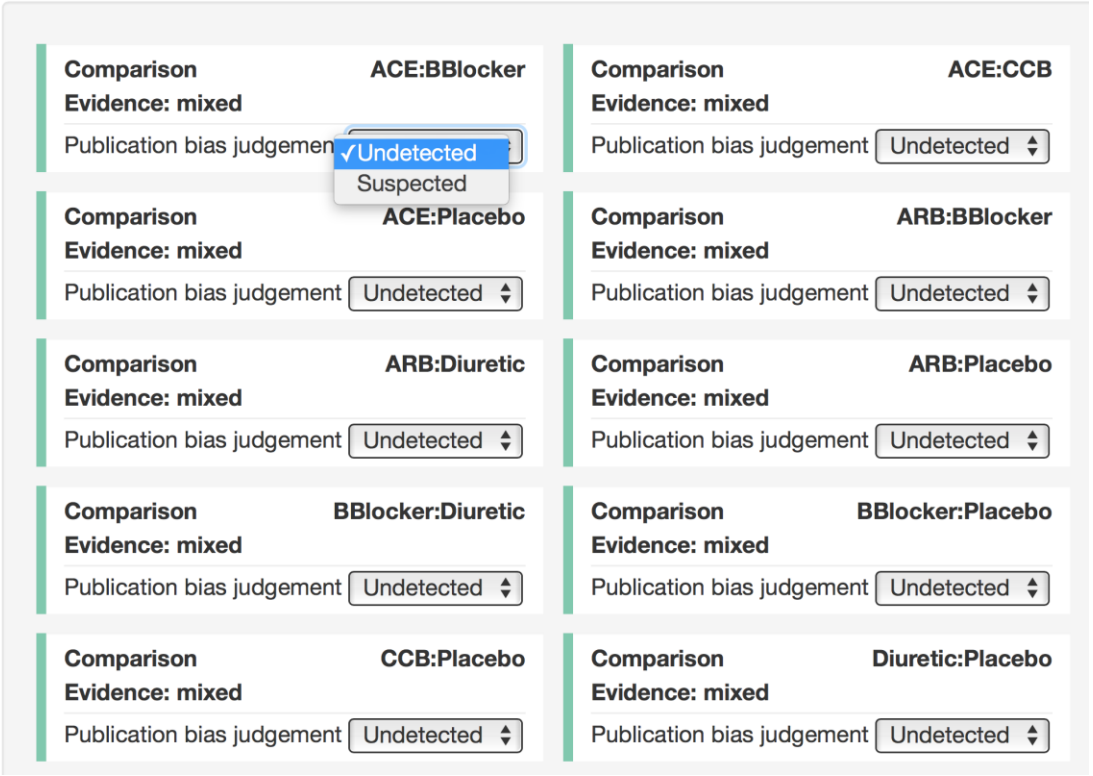
Comparison	CCB:Diuretic
Evidence: mixed	
Direct contribution:	**48.0%**
Inconsistency measures	
Ratio of odds ratios:	**0.932(0.676,1.286)**
Z statistic:	**-0.429**
P value:	**0.668**
Incoherence judgement	No concerns



Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis. Res Synth Meth 2012

publication bias

- Suspected
- Undetected



Now it is time for….

CINeMA

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 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