

GRADE:

Applicazione alle network meta-analisi

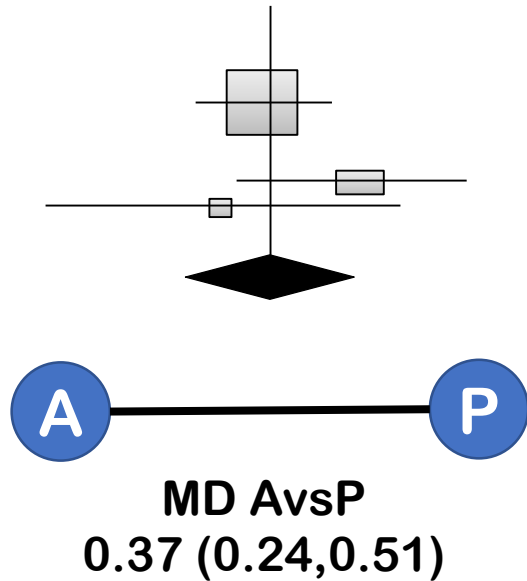
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Institute of Primary Health Care (BIHAM)

University of Bern, Switzerland

Cochrane Italy

Confidence in pairwise meta-analysis results



Confidence in this evidence?

GRADE system

⊕⊕⊕⊕ High

Further research is very unlikely to change our confidence in estimated of effect

⊕⊕⊕○ Moderate

Further research is likely to have impact on our confidence in the estimate of effect and may change the estimate

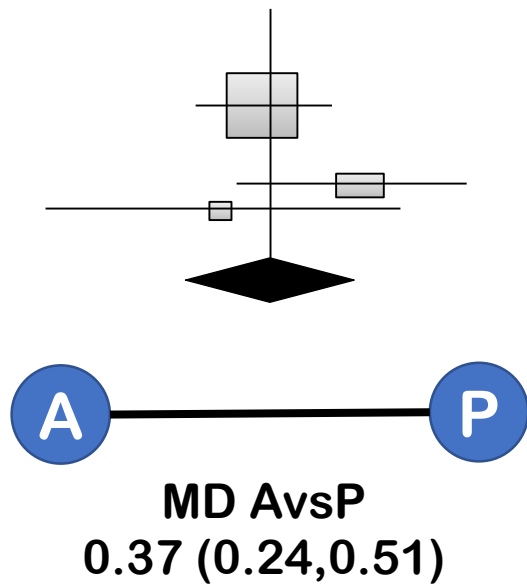
⊕⊕○○ Low

Further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate

⊕○○○ Very low

Any estimate of effect is very uncertain

Confidence in pairwise meta-analysis results



GRADE system

⊕⊕⊕⊕ High

⊕⊕⊕○ Moderate

⊕⊕○○ Low

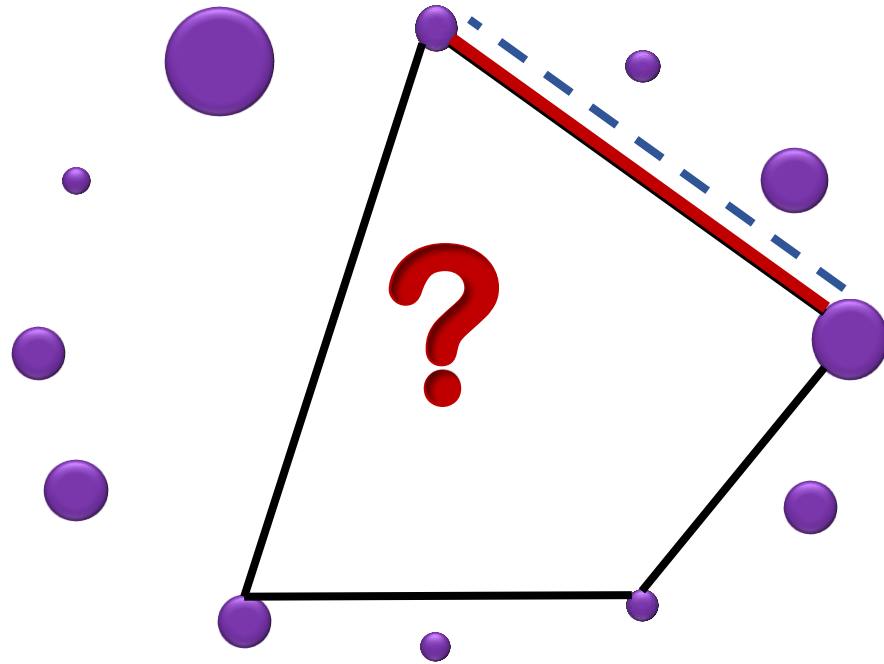
⊕○○○ Very low



1. Study limitations
2. Imprecision
3. Inconsistency
4. Indirectness
5. Publication bias

- Not serious
- Serious
- Very serious

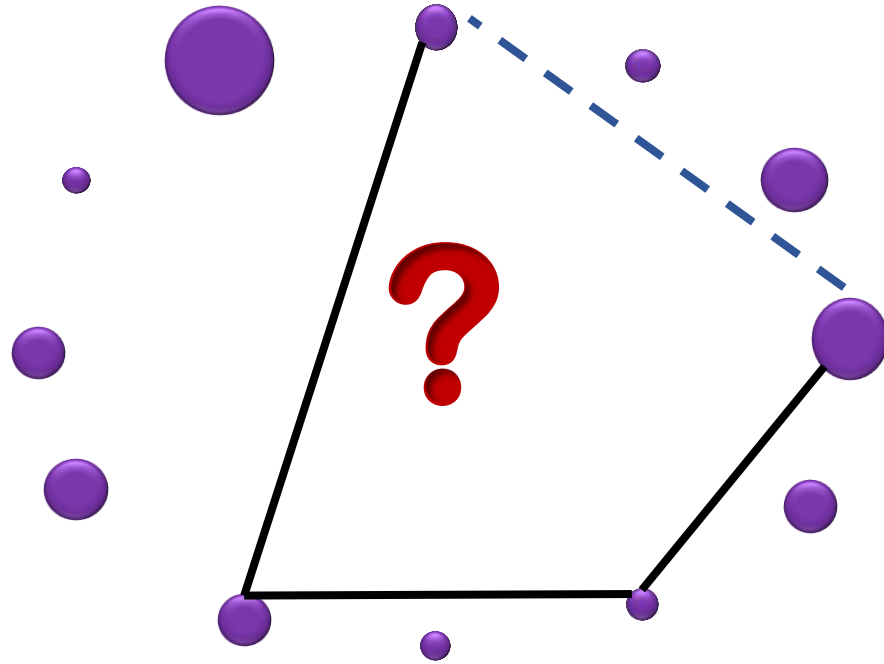
Network meta-analysis



“which are the most appropriate treatments, for which population and under which setting”

direct evidence + indirect evidence → mixed evidence

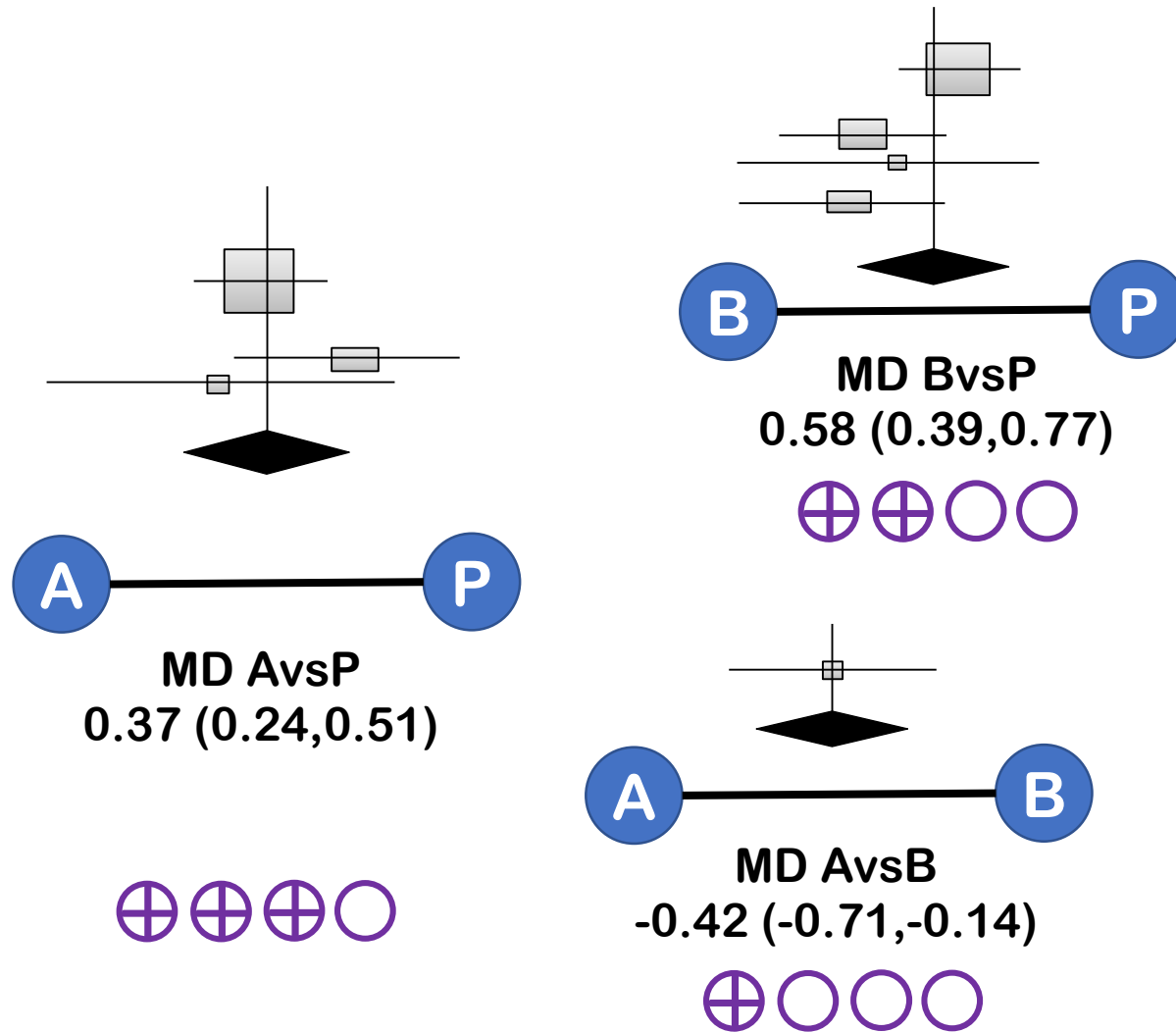
Network meta-analysis



“which are the most appropriate treatments, for which population and under which setting”

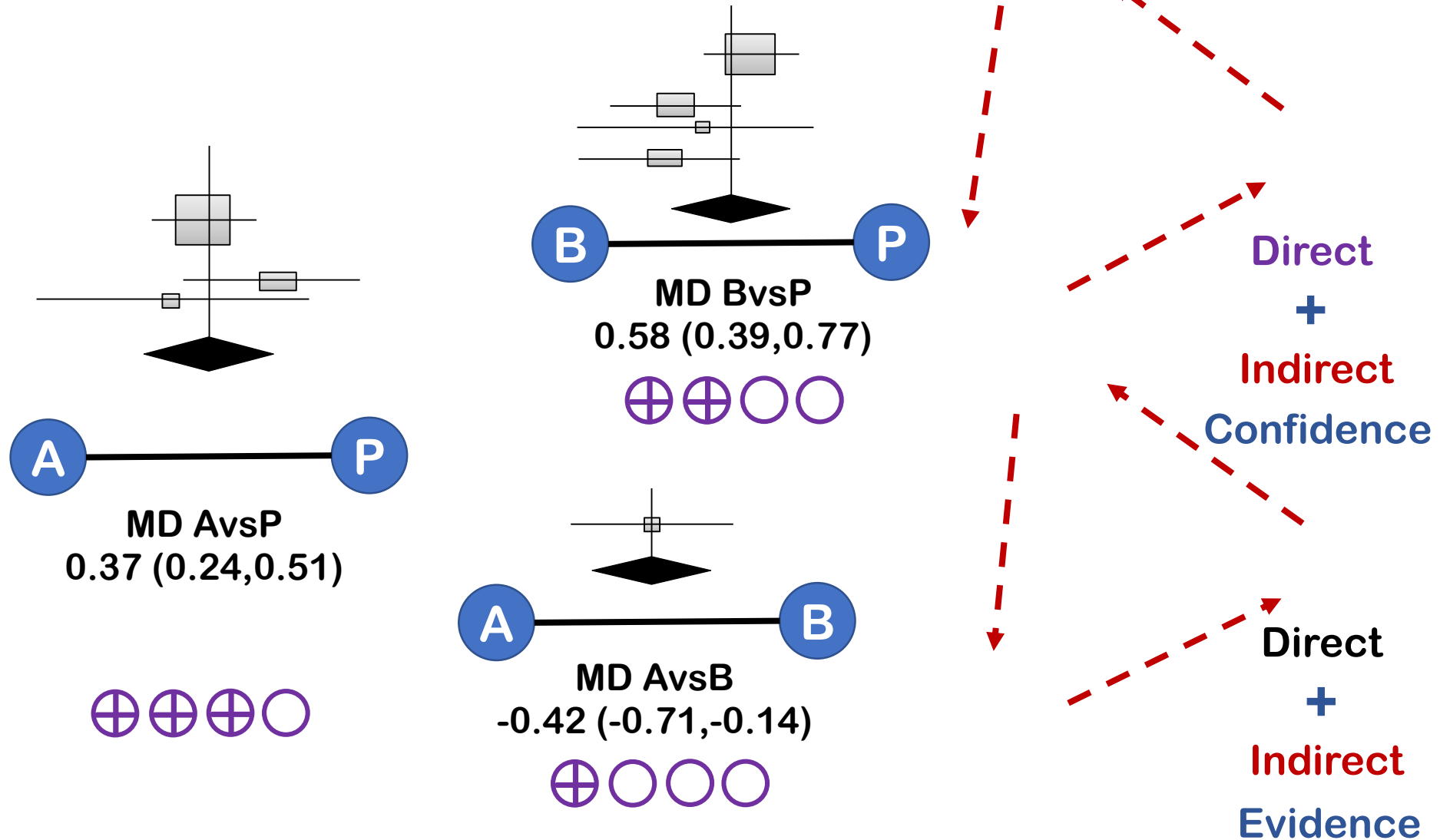
indirect
evidence

Extending GRADE into NMA



Background

confidence in network meta-analysis results



Evaluating the Quality of Evidence from a Network Meta-Analysis

Georgia Salanti¹, Cinzia Del Giovane², Anna Chaimani¹, Deborah M. Caldwell³, 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 network meta-analysis. Judgements about evidence from a network meta-analysis can be different from those made about evidence from pairwise meta-analyses.

Citation: Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT (2014) Evaluating the Quality of Evidence from a Network Meta-Analysis. PLoS ONE 9(7): e99682. doi:10.1371/journal.pone.0099682

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Competing Interests: The authors have declared that no competing interests exist.

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An alternative equivalent approach is presented in:

J Clin Epidemiol. 2017. *Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis*. Brignardello-Petersen R1, Bonner A1, Alexander PE2, Siemieniuk RA3, Furukawa TA4, Rochweg B5, Hazlewood GS6, Alhazzani W5, Mustafa RA7, Murad MH8, Puhan MA9, Schünemann HJ1, Guyatt GH10; GRADE Working Group.

Time for CINeMA

cinema.ispm.ch

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, imprecision and publication bias. The framework combines judgments about direct evidence with their statistical contribution to network meta-analysis results, enabling evaluation of the credibility

1. Salanti G, Del Giovane C, Chaimani A, evidence from a network meta-analysis. P

To browse you projects or upload a new o



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

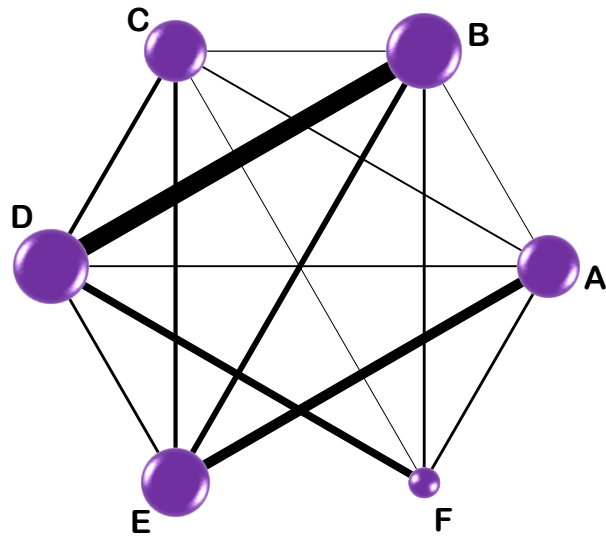
Advantages

The rules can be overw

1. Semi-automatic process
2. Fast
3. Results easily reproducible

Example

antihypertensives & incidence of diabetes



A=placebo
B=beta-blockers
C=Diuretics
D=CCB
E=ACE inhibitors
F=ARB

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.

Methods We undertook a systematic review up to Sept 15, 2006, and identified 48 randomised groups of 22 clinical trials with 143153 participants who did not have diabetes at randomisation and so were eligible for inclusion in our analysis. 17 trials enrolled patients with hypertension, three enrolled high-risk patients, and one enrolled those with heart failure. The main outcome was the proportion of patients who developed diabetes.

Findings Initial drug therapy used in the trials (and the number of patients with diabetes of the total number at risk) included: an ARB (1189 of 14185, or 8.38%), ACE inhibitor (1618 of 22941, or 7.05%), calcium-channel blocker (CCB, 2791 of 38607, or 7.23%), placebo (1686 of 24767, or 6.81%), β blocker (2705 of 35745, or 7.57%), or diuretic (998 of 18699, or 5.34%). With an initial diuretic as the standard of comparison (eight groups), the degree of incoherence (a measure of how closely the entire network fits together) was small ($\omega=0.000017$, eight degrees of freedom). The odds ratios were: ARB (five groups) 0.57 (95% CI 0.46–0.72, $p<0.0001$); ACE inhibitor (eight groups) 0.67 (0.56–0.80, $p<0.0001$); CCB (nine groups): 0.75 (0.62–0.90, $p=0.002$); placebo (nine groups) 0.77 (0.63–0.94, $p=0.009$); β blocker (nine groups) 0.90 (0.75–1.09, $p=0.30$). These estimates changed little in many sensitivity analyses.

Interpretation The association of antihypertensive drugs with incident diabetes is therefore lowest for ARB and ACE inhibitors followed by CCB and placebo, β blockers and diuretics in rank order.

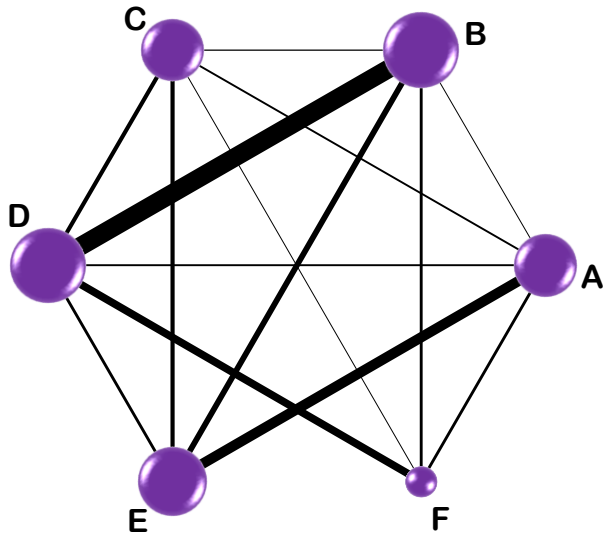
Lancet 2007; 369: 201–07

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Example

antihypertensives & incidence of diabetes



A=placebo
B=beta-blockers
C=Diuretics
D=CCB
E=ACE inhibitors
F=ARB

study	id	t	r	n	rob
AASK	1	ACE	45	410	1
AASK	1	BBlocker	70	405	1
AASK	1	CCB	32	202	1
ALLHAT	2	ACE	119	4096	1
ALLHAT	2	CCB	154	3954	1
ALLHAT	2	Diuretic	302	6766	1
ALPINE	3	ARB	1	196	1
ALPINE	3	Diuretic	8	196	1
ANBP-2	4	ACE	138	2800	1
ANBP-2	4	Diuretic	200	2826	1
ASCOT	5	BBlocker	799	7040	1
ASCOT	5	CCB	567	7072	1
CAPPP	6	ACE	337	5183	2
CAPPP	6	BBlocker	380	5230	2
CHARM	7	ARB	163	2715	1
CHARM	7	Placebo	202	2721	1
DREAM	8	ACE	449	2623	1
DREAM	8	Placebo	489	2646	1
EWPHÉ	9	Diuretic	29	416	2
EWPHÉ	9	Placebo	20	424	2
FEVER	10	CCB	177	4841	1
FEVER	10	Placebo	154	4870	1

1 LOW RoB
2 UNCLÉAR RoB
3 HIGH RoB

Data upload

A demo dataset can be downloaded [here](#). It is a network of six intervention for diabetes mellitus by Elliot et al
W. J. Elliott and P. M. Meyer. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *The Lancet*, 369(9557):201 – 207, 2007

CINeMA uses the netmeta R-package for performing Network meta-analysis of the data.

G. Rücker, G. Schwarzer, U. Krahn, and J. König. netmeta: *Network Meta-Analysis using Frequentist Methods*, 2017. R package version 0.9-5. <https://CRAN.R-project.org/package=netmeta>

Below you can find a brief guide of using CINeMA to evaluate confidence in network meta-analysis treatment effects.

My projects

CINeMA requires a .csv file with the study outcome data and study-level risk of bias (RoB) judgements which you can upload in [My Projects](#). We describe below how the data should be formatted.

Binary data

If your outcome is binary, there are two possible formats to upload your data. The first is a long format, where each treatment arm occupies one row.

Example binary format 1:

id	t	r	n	rob
1	A	5	12	2
1	B	7	15	2
2	A	6	9	3
2	B	7	10	3
2	C	2	8	3

id specifies the study and has to be numeric

t specifies the treatment code and it can be either numeric or string

r is the number of events

n is the sample size

rob specifies risk of bias. It can take either 1, 2 and 3 or L, U, H values for low, unclear and high risk of bias

In the second format, each row represents a comparison. The number of rows that each study occupies equals the number of comparisons that it examines. Two arm

Data upload

CINEMA My Projects Documentation Configuration Study Limitations Imprecision Inconsistency Indirectness Publication Bias Repo

diabetes

File upload success

Studies	22
Interventions	6
Comparisons	14



...Evaluation starts!

Configuration – network plot

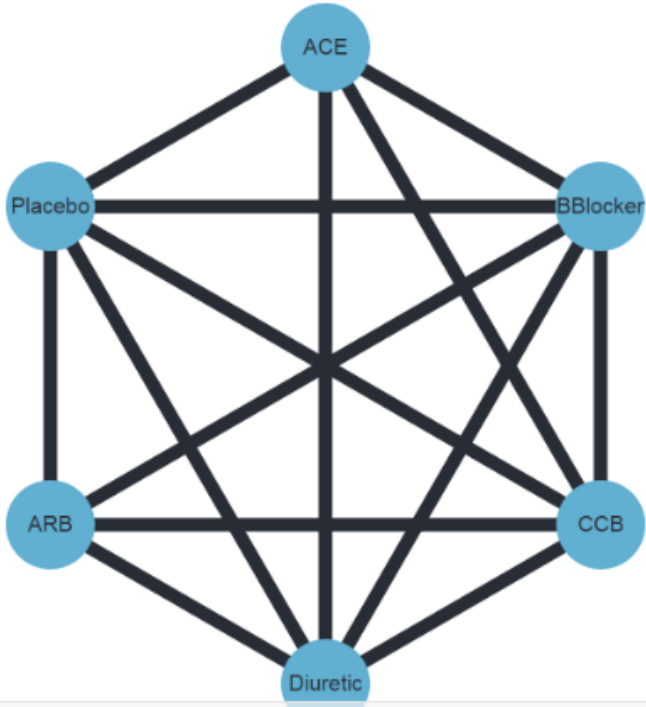
CINeMA My Projects Documentation Configuration Study Limitations Imprecision Inconsistency Indirectness Publication Bias Report

**Sample size
Number of studies**

Network Plot

Node size by: Equal size Node color by: No color Edge width by: Equal size Edge color by: No color

Redraw Save Plot



study id t1 r1 n1 rob t2 r2 n2

1	AASK	1	ACE	45	410	1	BBLOCKER	70	405
2	AASK	1	ACE	45	410	1	CCB	32	202
3	AASK	1	BBLOCKER	70	405	1	CCB	32	202
4	ALLHAT	2	ACE	119	4096	1	CCB	154	3954
5	ALLHAT	2	ACE	119	4096	1	Diuretic	302	6766
6	ALLHAT	2	CCB	154	3954	1	Diuretic	302	6766
7	ALPINE	3	ARB	1	196	1	Diuretic	8	196
8	ANBP-2	4	ACE	138	2800	1	Diuretic	200	2826
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12	DREAM	8	ACE	449	2623	1	Placebo	489	2646
13	EWPH	9	Diuretic	29	416	2	Placebo	20	424
14	FEVER	10	CCB	177	4841	1	Placebo	154	4870
15	HAPPY	11	BBLOCKER	86	3297	3	Diuretic	75	3272
16	HOPE	12	ACE	102	2837	1	Placebo	155	2883
17	INSIGHT	13	CCB	136	2508	1	Diuretic	176	2511
18	INVEST	14	BBLOCKER	665	8078	1	CCB	569	8098
19	LIFE	15	ARB	242	4020	1	BBLOCKER	320	3979
20	MRC	16	BBLOCKER	37	1102	1	Diuretic	43	1081
21	MRC	16	BBLOCKER	37	1102	1	Placebo	34	2213
22	MRC	16	Diuretic	43	1081	1	Placebo	34	2213
23	NORDIL	17	BBLOCKER	251	5059	1	CCB	216	5095

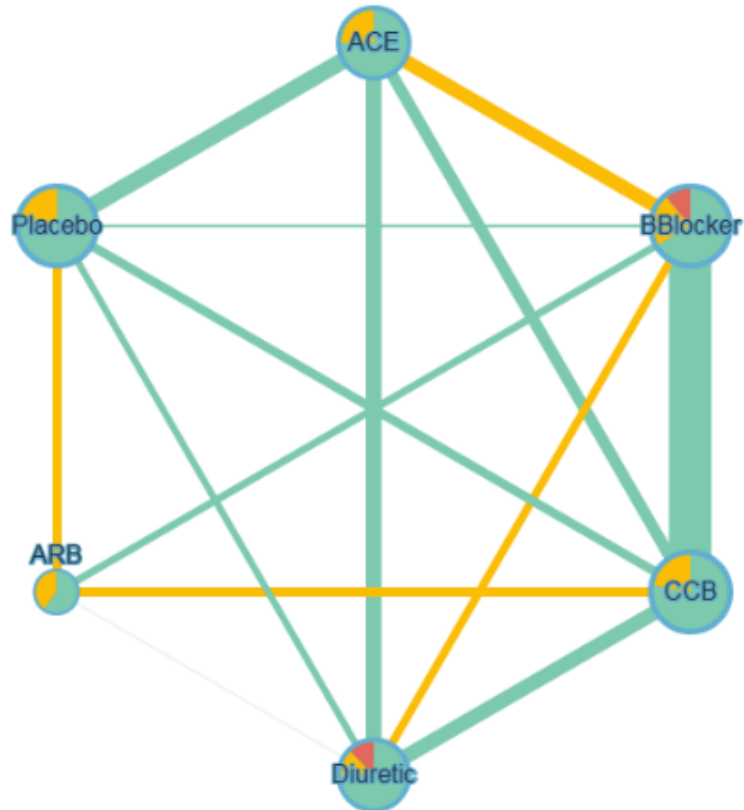
Confidence In Network Meta Analysis - CINeMA v0.4.0- α

Configuration – network plot

Network Plot

Node size by: Number of studies ▼ Node color by: Risk of Bias ▼ Edge width by: Sample Size ▼ **Edge color by: Average RoB ▼**

Redraw Save Plot



	study	id	t1	r1	n1	rob	t2	r2	n2
1	AASK	1	ACE	45	410	1	BBLOCKER	70	405
2	AASK	1	ACE	45	410	1	CCB	32	202
3	AASK	1	BBLOCKER	70	405	1	CCB	32	202
4	ALLHAT	2	ACE	119	4096	1	CCB	154	3954
5	ALLHAT	2	ACE	119	4096	1	Diuretic	302	6766
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7	ALPINE	3	ARB	1	196	1	Diuretic	8	196
8	ANBP-2	4	ACE	138	2800	1	Diuretic	200	2826
9	ASCOT	5	BBLOCKER	799	7040	1	CCB	567	7072
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21	MRC	16	BBLOCKER	37	1102	1	Placebo	34	2213
22	MRC	16	Diuretic	43	1081	1	Placebo	34	2213
23	NORDIL	17	BBLOCKER	251	5059	1	CCB	216	5095

Setting up the evaluation

Define your analysis

Analysis model: **Fixed effect** **Random effects**

Effect measure:

Select intervention comparisons for evaluation


Interventions: ACE BBLOCKER CCB Diuretic ARB Placebo

Select comparisons:

Containing any of the above interventions

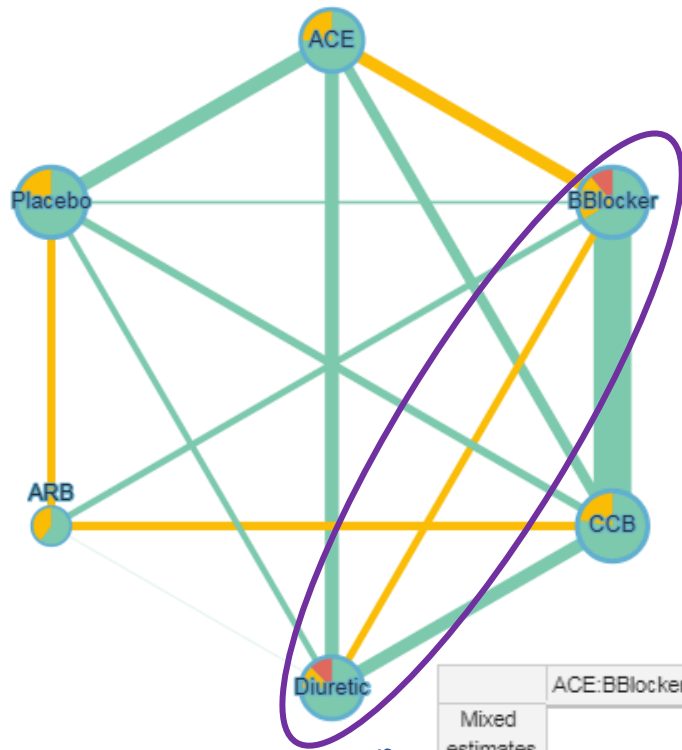
Between the above interventions

You have selected the following 15 comparisons. Confidence in the results will be graded for:

 Analysis is performed including all studies



Contribution matrix



Contribution of each direct evidence to each network estimate

Direct comparisons in the network

Network meta-analysis estimates

	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	43.4	10.8	6.7	7.2	2.7	0.1	0	2.8	14.5	5.3	2.2	2.0	1.6	0.6
ACE:CCB	13.5	33.5	8.3	9.0	0.1	2.8	0	2.7	14.7	0.6	0.5	8.4	5.1	0.7
ACE:Diuretic	8.6	8.4	40.5	11.3	0	0.3	0.1	0.4	1.6	7.1	0.1	10.8	0.5	10.4
ACE:Placebo	5.3	6.1	6.8	58.6	1.9	1.7	0	3.6	0.9	0.4	2.1	0.2	5.1	7.3
ARB:BBLOCKER	5.6	0.1	0.1	5.4	34.7	16.4	0.3	11.3	17.6	2.6	2.2	0.1	1.4	2.3
ARB:CCB	0.1	3.8	0.4	4.4	13.2	40.9	0.3	12.1	13.8	0.1	0.5	3.2	4.8	2.4
ARB:Diuretic	2.5	1.5	8.2	4.2	11.6	16.4	0.9	17.0	0.5	8.7	0	15.6	0.2	12.6
ARB:Placebo	3.9	3.0	0.3	7.2	7.6	10.7	0.3	51.8	0.2	1.4	2.1	2.4	5.4	3.7
BBLOCKER:CCB	7.4	6.0	0.6	0.8	4.1	4.0	0	0.1	64.5	4.0	1.4	4.7	2.2	0.1
BBLOCKER:Diuretic	12.3	1.2	12.6	0.9	2.7	0.1	0.2	2.3	17.7	24.9	2.1	15.5	1.1	6.4
BBLOCKER:Placebo	14.3	2.8	0.3	17.5	6.8	2.1	0	8.9	14.8	5.9	8.6	2.3	7.6	7.9
CCB:Diuretic	2.6	8.3	10.7	0.3	0	2.5	0.2	2.2	11.5	8.4	0.5	41.2	4.3	7.3
CCB:Placebo	4.2	10.2	0.8	15.1	1.7	7.2	0	8.9	9.8	1	2.9	8.8	20.4	9.0
Diuretic:Placebo	1.4	1.3	13.4	16.1	1.7	2.3	0.2	4.3	0.3	5.1	2.2	9.8	5.9	36.1
Indirect estimates														
ACE:ARB	13.2	11.1	4.9	18.2	13.3	14.2	0.3	19.5	0.7	0.8	0	2.3	0.1	1.4

Configuration – network plot

CINeMA My Projects Documentation Configuration **Study Limitations** Imprecision Inconsistency Indirectness Publication Bias Report

Network Plot

Node size by: Equal size Node color by: No color Edge width by: Equal size Edge color by: No color

Redraw Save Plot

The network plot displays six nodes: ACE (top), Placebo (left), BBLOCKER (right), ARB (bottom-left), CCB (bottom-right), and Diuretic (bottom). All nodes are interconnected with thick black lines, forming a complete graph.

	study	id	t1	r1	n1	rob	t2	r2	n2
1	AASK	1	ACE	45	410	1	BBLOCKER	70	405
2	AASK	1	ACE	45	410	1	CCB	32	202
3	AASK	1	BBLOCKER	70	405	1	CCB	32	202
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19	LIFE	15	ARB	242	4020	1	BBLOCKER	320	3979
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23	NORDIL	17	BBLOCKER	251	5059	1	CCB	216	5095

Confidence In Network Meta Analysis - CINeMA v0.4.0- α

Study limitations (Risk of bias)

- In each study, we assign an overall risk of bias across the risk of bias domains (**low**, **unclear**, **high**)
- We assign numerical scores to these risk of bias judgments: **1 for low**, **2 for unclear** and **3 for high** risk of bias
- In each direct comparison, we judge the risk of bias as **low**, **moderate** and **high** considering the risk of bias assessment for the **majority/average/highest** of the studies included in the comparison
- Then, we derive the judgment for study limitations for each **pairwise network estimate (direct and indirect)** considering the combination of the risk of bias judgments from all direct estimates and the contribution of each direct estimate to the network estimates from the contributions matrix

22 total studies

16 : low 5 : moderate 1 : high

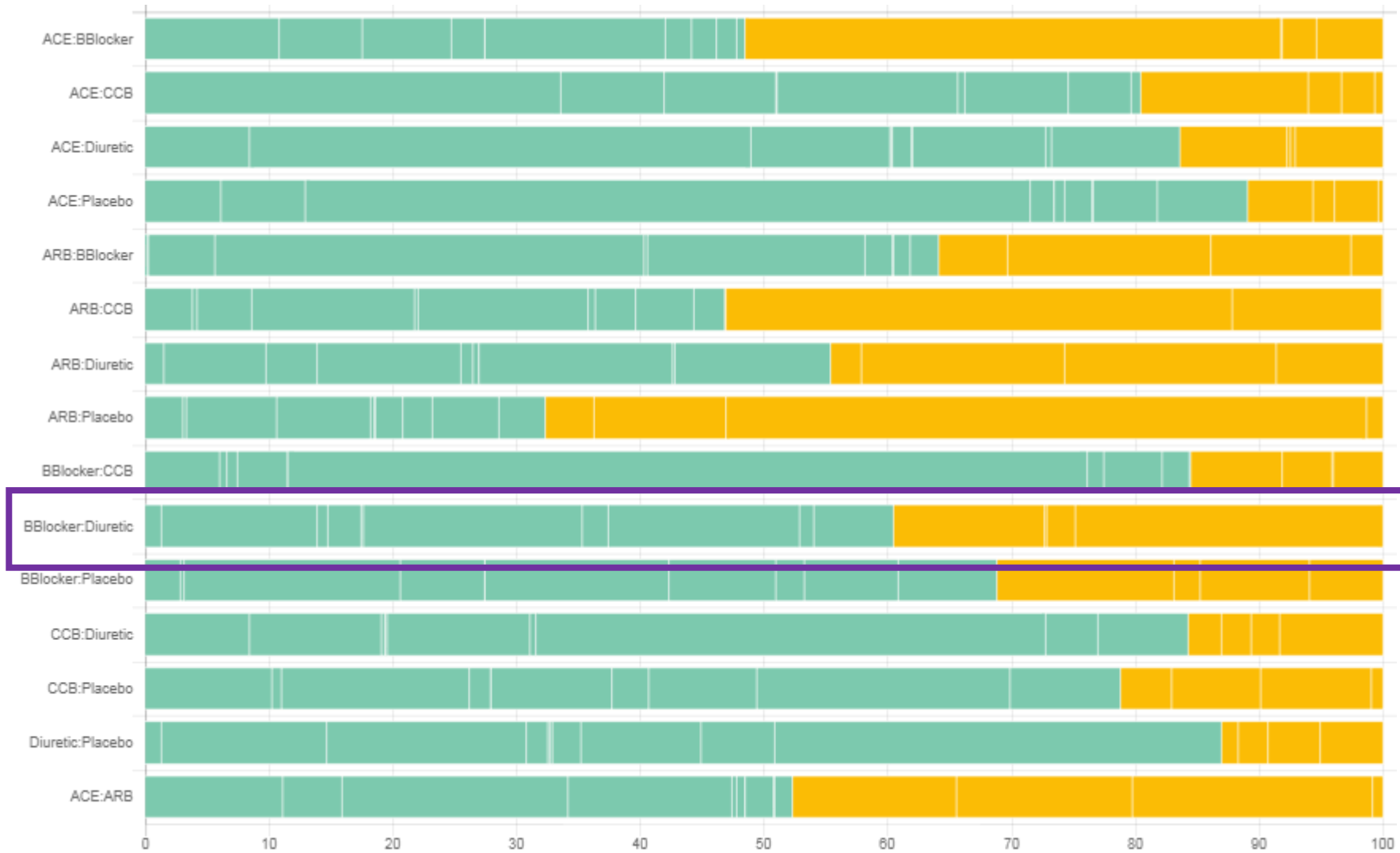
Selected rule: Average RoB

Reset Proceed

<p>Comparison: ACE:BBlocker</p> <p>Number of studies: 3</p> <p>Sample size: 15158</p> <p>Majority RoB: moderate</p> <p>Average RoB: moderate</p> <p>Highest RoB: moderate</p> <p>Direct RoB: <input type="text" value="moderate"/></p>	<p>Comparison: ACE:CCB</p> <p>Number of studies: 3</p> <p>Sample size: 12597</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: moderate</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: ACE:Diuretic</p> <p>Number of studies: 2</p> <p>Sample size: 16488</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: ACE:Placebo</p> <p>Number of studies: 3</p> <p>Sample size: 17893</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>
<p>Comparison: ARB:BBlocker</p> <p>Number of studies: 1</p> <p>Sample size: 7999</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: ARB:CCB</p> <p>Number of studies: 1</p> <p>Sample size: 10161</p> <p>Majority RoB: moderate</p> <p>Average RoB: moderate</p> <p>Highest RoB: moderate</p> <p>Direct RoB: <input type="text" value="moderate"/></p>	<p>Comparison: ARB:Diuretic</p> <p>Number of studies: 1</p> <p>Sample size: 392</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: ARB:Placebo</p> <p>Number of studies: 2</p> <p>Sample size: 9778</p> <p>Majority RoB: moderate</p> <p>Average RoB: moderate</p> <p>Highest RoB: moderate</p> <p>Direct RoB: <input type="text" value="moderate"/></p>
<p>Comparison: BBlocker:CCB</p> <p>Number of studies: 5</p> <p>Sample size: 44974</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: moderate</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: BBlocker:Diuretic</p> <p>Number of studies: 2</p> <p>Sample size: 8752</p> <p>Majority RoB: high</p> <p>Average RoB: moderate</p> <p>Highest RoB: high</p> <p>Direct RoB: <input type="text" value="moderate"/></p>	<p>Comparison: BBlocker:Placebo</p> <p>Number of studies: 1</p> <p>Sample size: 3315</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: CCB:Diuretic</p> <p>Number of studies: 2</p> <p>Sample size: 15739</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>
<p>Comparison: CCB:Placebo</p> <p>Number of studies: 1</p> <p>Sample size: 9711</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: low</p> <p>Direct RoB: <input type="text" value="low"/></p>	<p>Comparison: Diuretic:Placebo</p> <p>Number of studies: 3</p> <p>Sample size: 7343</p> <p>Majority RoB: low</p> <p>Average RoB: low</p> <p>Highest RoB: moderate</p> <p>Direct RoB: <input type="text" value="low"/></p>		

Risk of Bias bar chart

All possible comparisons



Inference for study limitations

Select how to summarize risk of bias across contributions for each network estimate

Selected rule: Average RoB

Reset

Proceed

Comparison	ACE:BBlocker
Evidence: mixed	
Majority RoB:	Some concerns
Average RoB:	Some concerns
Highest RoB:	Some concerns
NMA judgement	Some concerns ▼

Comparison	ACE:CCB
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	ACE:Diuretic
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	ACE:Placebo
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	ARB:BBlocker
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	ARB:CCB
Evidence: mixed	
Majority RoB:	Some concerns
Average RoB:	Some concerns
Highest RoB:	Some concerns
NMA judgement	Some concerns ▼

Comparison	ARB:Diuretic
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	ARB:Placebo
Evidence: mixed	
Majority RoB:	Some concerns
Average RoB:	Some concerns
Highest RoB:	Some concerns
NMA judgement	Some concerns ▼

Comparison	BBlocker:CCB
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	BBlocker:Diuretic
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	BBlocker:Placebo
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

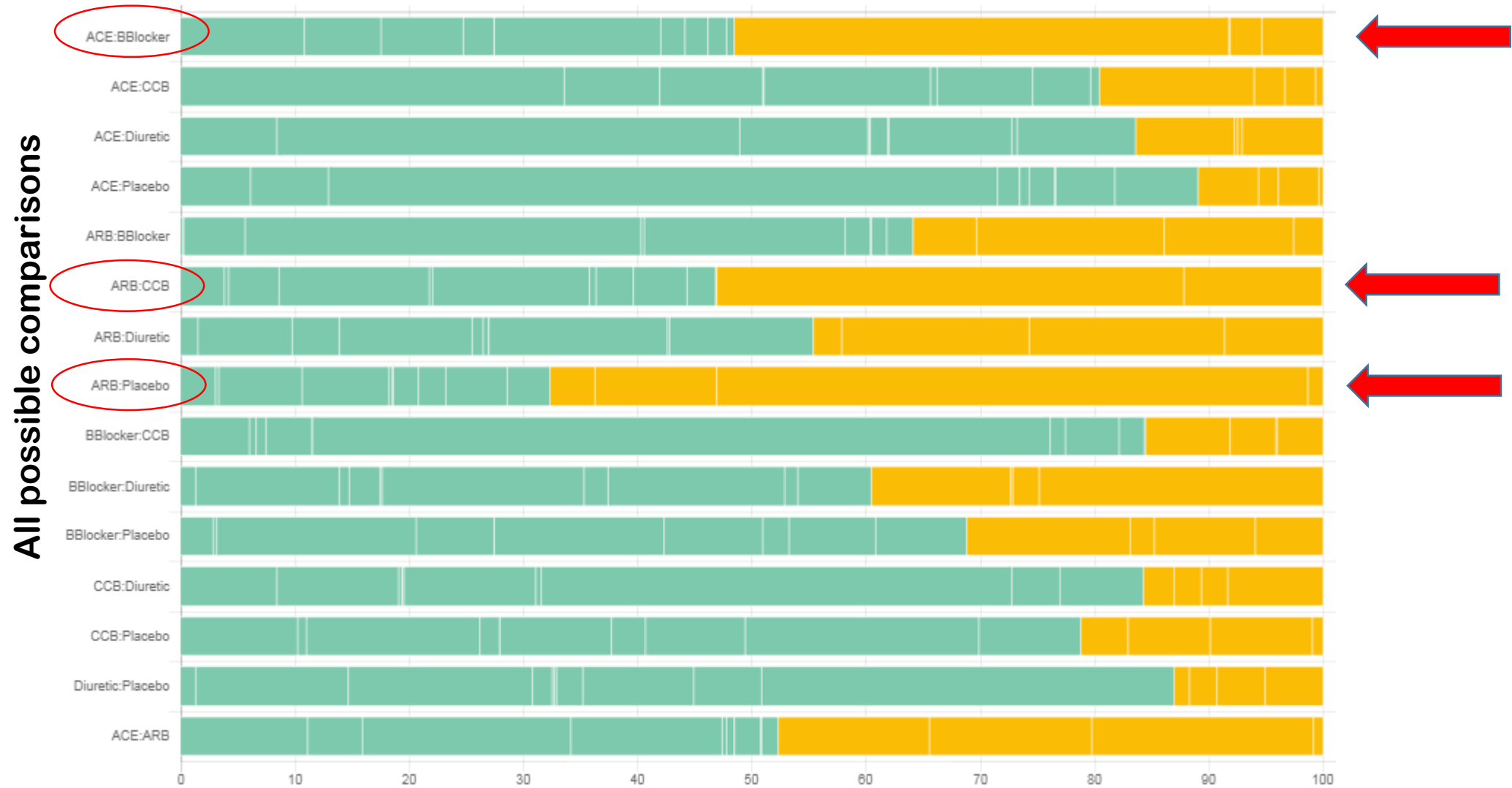
Comparison	CCB:Diuretic
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	CCB:Placebo
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Comparison	Diuretic:Placebo
Evidence: mixed	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

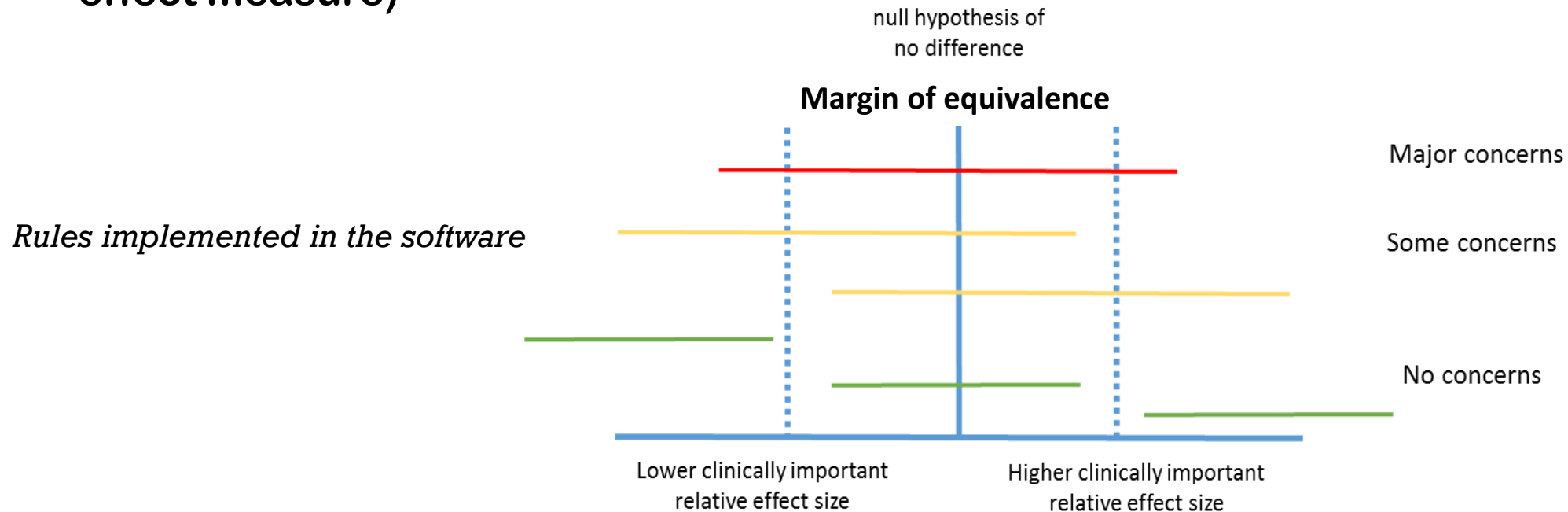
Comparison	ACE:ARB
Evidence: indirect	
Majority RoB:	No concerns
Average RoB:	No concerns
Highest RoB:	Some concerns
NMA judgement	No concerns ▼

Risk of Bias bar chart



Imprecision

- Importance of imprecise treatment effects depends on whether their confidence intervals include values that could lead into 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 (based on the scale of your effect measure)



Inference for imprecision

Imprecision

Define clinically important size of effect: Odds ratio

1.25

Effects lower than 0.800 and larger than 1.250 are considered to be clinically important

Set

Reset

Evaluation of imprecision

Reset

Proceed

Comparison ACE:BBlocker
Evidence: mixed
95% Confidence interval: (1.208,1.628)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison ACE:CCB
Evidence: mixed
95% Confidence interval: (1.017,1.374)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison ACE:Diuretic
Evidence: mixed
95% Confidence interval: (1.279,1.766)
Confidence interval does not cross clinically important effect
Imprecision judgement **No concerns**

Comparison ACE:Placebo
Evidence: mixed
95% Confidence interval: (0.983,1.300)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison ARB:BBlocker
Evidence: mixed
95% Confidence interval: (1.252,1.797)
Confidence interval does not cross clinically important effect
Imprecision judgement **No concerns**

Comparison ARB:CCB
Evidence: mixed
95% Confidence interval: (1.061,1.507)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison ARB:Diuretic
Evidence: mixed
95% Confidence interval: (1.303,1.983)
Confidence interval does not cross clinically important effect
Imprecision judgement **No concerns**

Comparison ARB:Placebo
Evidence: mixed
95% Confidence interval: (1.011,1.447)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison BBlocker:CCB
Evidence: mixed
95% Confidence interval: (0.746,0.953)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison BBlocker:Diuretic
Evidence: mixed
95% Confidence interval: (0.906,1.268)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison BBlocker:Placebo
Evidence: mixed
95% Confidence interval: (0.684,0.950)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison CCB:Diuretic
Evidence: mixed
95% Confidence interval: (1.083,1.493)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison CCB:Placebo
Evidence: mixed
95% Confidence interval: (0.817,1.119)
Confidence interval does not cross clinically important effect
Imprecision judgement **No concerns**

Comparison Diuretic:Placebo
Evidence: mixed
95% Confidence interval: (0.636,0.890)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Comparison ACE:ARB
Evidence: indirect
95% Confidence interval: (0.769,1.136)
Confidence interval extends into clinically important effects
Imprecision judgement **Some concerns**

Inconsistency

```
graph TD; A[Inconsistency] --> B[Heterogeneity]; A --> C[Incoherence];
```

Heterogeneity
between-study variance
within a comparison

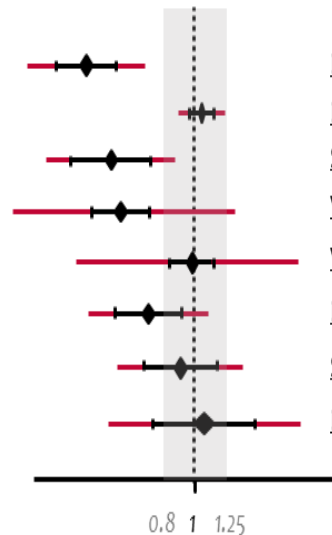
Incoherence
disagreement between
different sources of evidence

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
- We make use of prediction intervals and their agreement with the confident intervals in relation to the clinically important effects

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

Heterogeneity changes conclusions!



Rules implemented in the software

- No serious: Confidence and prediction intervals agree in relation to clinically important effect
- No serious: Confidence and prediction intervals agree in relation to clinically important effect
- Serious: Prediction interval extends into clinically important or unimportant effects
- Very serious: Prediction interval extends into clinically important effects in both directions
- Very serious: Prediction interval extends into clinically important effects in both directions
- No serious: Confidence and prediction intervals agree in relation to clinically important effect
- Serious: Prediction interval extends into clinically important or unimportant effects
- No serious: Confidence and prediction intervals agree in relation to clinically important effect

Prediction interval 
Confidence interval 

Hypothetical NMA treatment effects to illustrate our recommendations on judging imprecision based on a clinically important odds ratio of 0.8.

Heterogeneity

- Pairwise meta-analysis heterogeneity variances (τ^2) can be estimated (they make 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
- The common heterogeneity variance (τ^2) estimated in the entire network is also reported in the software

Inference for heterogeneity

Heterogeneity [Incoherence](#)

Importance of heterogeneity depends on the variability of effects in relation to a clinically important size of effect

Define clinically important size of effect: Odds ratio

1.25

Effects lower than 0.800 and larger than 1.250 are considered to be clinically important

Set

Reset

To view between-study variance estimates for each direct comparison along with reference intervals, select type of intervention and outcome (optional)

ACE: Pharmacological | ARB: Pharmacological | BBLOCKER: Pharmacological | CCB: Pharmacological | Diuretic: Pharmacological | Placebo: Placebo/Control

Outcome type: Semi-objective

Reset

View

Evaluation of heterogeneity

Reset

Proceed

The estimated value of between-study variance for the network meta-analysis is 0.016

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:	0.004
median:	0.040
third quantile:	0.429
95% intervals for NMA estimate	
Confidence interval:	(1.208,1.628)
Prediction interval:	(1.030,1.909)
Confidence and prediction intervals agree in relation to clinically important effect	

Comparison	ACE:CCB
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I^2 :	29.0%
Estimated τ^2 :	0.011
Reference Values for τ^2	
first quantile:	0.004
median:	0.040
third quantile:	0.429
95% intervals for NMA estimate	
Confidence interval:	(1.017,1.374)
Prediction interval:	(0.868,1.610)
Confidence and prediction intervals agree in relation to clinically important effect	

Comparison	ACE:Diuretic
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:	0.040
third quantile:	0.429
95% intervals for NMA estimate	
Confidence interval:	(1.279,1.766)
Prediction interval:	(1.096,2.061)
Prediction interval extends into clinically important or unimportant effects	

Comparison	ACE:Placebo
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I^2 :	58.9%
Estimated τ^2 :	0.011
Reference Values for τ^2	
first quantile:	0.005
median:	0.049
third quantile:	0.491
95% intervals for NMA estimate	
Confidence interval:	(0.983,1.300)
Prediction interval:	(0.834,1.531)
Confidence and prediction intervals agree in relation to clinically important effect	

Comparison	ARB:BBLOCKER
Evidence: mixed	
Reference Values for τ^2	
first quantile:	0.004
median:	0.040
third quantile:	0.429
95% intervals for NMA estimate	
Confidence interval:	(1.252,1.797)
Prediction interval:	(1.082,2.080)
Prediction interval extends into clinically important or unimportant effects	

Comparison	ARB:CCB
Evidence: mixed	
Reference Values for τ^2	
first quantile:	0.004
median:	0.040
third quantile:	0.429
95% intervals for NMA estimate	
Confidence interval:	(1.061,1.507)
Prediction interval:	(0.915,1.748)
Confidence and prediction intervals agree in relation to clinically important effect	

Inconsistency

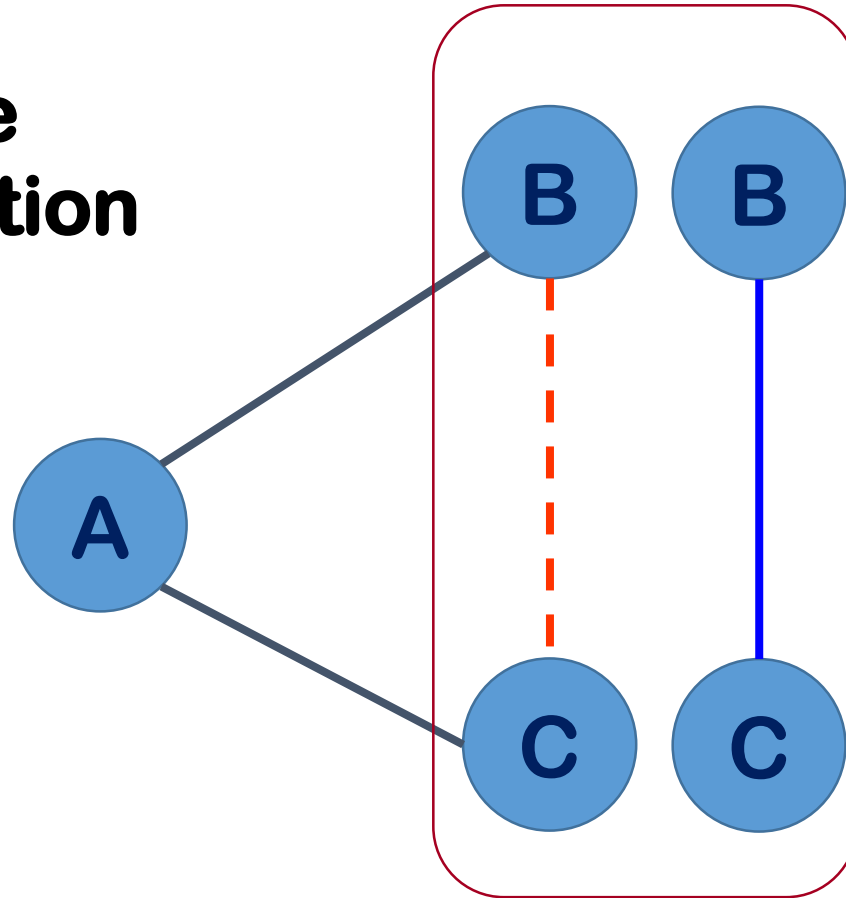
```
graph TD; A[Inconsistency] --> B[Heterogeneity]; A --> C[Incoherence];
```

Heterogeneity
between-study variance
within a comparison

Incoherence
disagreement between
different sources of evidence

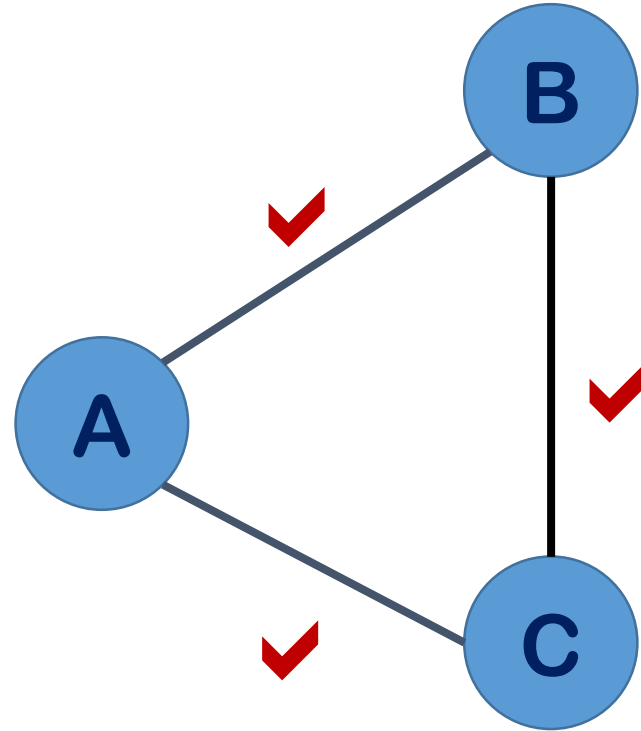
Coherence

**Testable
assumption**



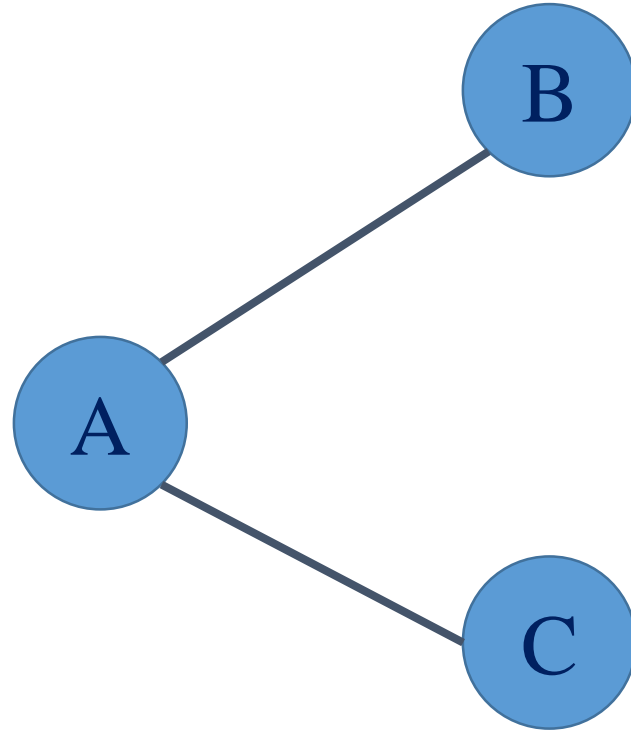
**Direct and
indirect
evidence are
in agreement**

Only a closed loop can be coherent (or incoherent)



Direct and indirect
evidence are in
(statistical) agreement:
the loop is coherent

Incoherence cannot be evaluated



Open loop: there is no indirect evidence

Incoherence

- We propose assessing incoherence using :
 - the *Design-by-Treatment Interaction Model (globally)*
 - the *Separate Indirect from Direct Evidence (SIDE, or node-splitting) (locally)*
 - Compare direct and indirect relative treatment effects using a Z-test
- We judge comparisons that only direct evidence exists as ‘**No concerns**’ with respect to incoherence
- The same judgement is made for comparisons that both direct and indirect evidence exists with the contribution of direct evidence being more than 90%
- For comparisons that only indirect evidence exists, we judge incoherence as ‘**No concerns**’, ‘**Some concerns**’ and ‘**Major concerns**’ depending on whether the p-value of the design by treatment interaction model is more 0.10, between 0.01 and 0.10 and less than 0.01 respectively

Incoherence

- We use the rules described in the table below to infer about our confidence regarding incoherence in network estimates informed by less than 90% from direct evidence

		<i>Design by treatment interaction model</i>		
		<i>p-value>0.1</i>	<i>0.01<p-value<0.1</i>	<i>p-value<0.01</i>
<i>SIDE</i>	<i>p-value>0.1</i>	No concerns	No concerns	Some concerns
	<i>0.01<p-value<0.1</i>	Some concerns	Some concerns	Major concerns
	<i>p-value<0.01</i>	Some concerns	Major concerns	Major concerns

Summary of recommendations on judging incoherence of NMA treatment effects for mixed evidence comparisons which are informed less than 90% by direct evidence.

Inference for incoherence

Heterogeneity Incoherence

Incoherence is assessed both globally and locally

Global test for incoherence

Based on a random-effects design-by-treatment interaction model

χ^2 statistic: 19.325 (13 degrees of freedom), P value: 0.113 **Design by treatment interaction model**

Reset Proceed

Local tests for incoherence

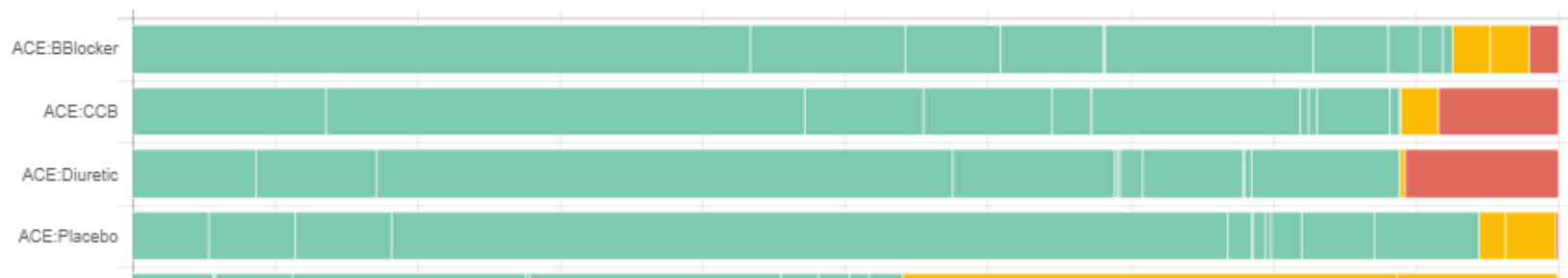
Separating indirect from direct evidence

Comparison	ACE:BBlocker	Comparison	ACE:CCB	Comparison	ACE:Diuretic	Comparison	ACE:Placebo	Comparison	ARB:BBlocker
Evidence: mixed		Evidence: mixed		Evidence: mixed		Evidence: mixed		Evidence: mixed	
NMA odds ratio:	1.402(1.208,1.628)	NMA odds ratio:	1.182(1.017,1.374)	NMA odds ratio:	1.503(1.279,1.766)	NMA odds ratio:	1.130(0.983,1.300)	NMA odds ratio:	1.500(1.252,1.797)
Direct odds ratio:	1.194(0.970,1.471)	Direct odds ratio:	1.249(0.989,1.577)	Direct odds ratio:	1.515(1.199,1.916)	Direct odds ratio:	1.230(1.030,1.469)	Direct odds ratio:	1.365(1.009,1.848)
Indirect odds ratio:	1.662(1.341,2.059)	Indirect odds ratio:	1.137(0.934,1.383)	Indirect odds ratio:	1.492(1.194,1.864)	Indirect odds ratio:	0.983(0.783,1.235)	Indirect odds ratio:	1.580(1.261,1.978)
Direct contribution:	51.4%	Direct contribution:	41.5%	Direct contribution:	47.4%	Direct contribution:	62.2%	Direct contribution:	35.5%
SIDE test									
Inconsistency measures		Inconsistency measures		Inconsistency measures		Inconsistency measures		Inconsistency measures	
Ratio of odds ratios:	0.719(0.533,0.965)	Ratio of odds ratios:	1.099(0.810,1.490)	Ratio of odds ratios:	1.015(0.735,1.403)	Ratio of odds ratios:	1.251(0.938,1.669)	Ratio of odds ratios:	0.864(0.593,1.260)
P value:	0.030	P value:	0.545	P value:	0.926	P value:	0.128	P value:	0.449
Incoherence judgement:	Some concerns	Incoherence judgement:	No concerns	Incoherence judgement:	No concerns	Incoherence judgement:	No concerns	Incoherence judgement:	No concerns
Comparison	ARB:CCB	Comparison	ARB:Diuretic	Comparison	ARB:Placebo	Comparison	BBlocker:CCB	Comparison	BBlocker:Diuretic
Evidence: mixed		Evidence: mixed		Evidence: mixed		Evidence: mixed		Evidence: mixed	
NMA odds ratio:	1.264(1.061,1.507)	NMA odds ratio:	1.608(1.303,1.983)	NMA odds ratio:	1.209(1.011,1.447)	NMA odds ratio:	0.843(0.746,0.953)	NMA odds ratio:	1.072(0.906,1.268)
Direct odds ratio:	1.273(0.971,1.670)	Direct odds ratio:	8.298(1.013,67.979)	Direct odds ratio:	1.251(0.978,1.601)	Direct odds ratio:	0.816(0.706,0.943)	Direct odds ratio:	0.985(0.718,1.349)
Indirect odds ratio:	1.258(1.000,1.583)	Indirect odds ratio:	1.581(1.281,1.953)	Indirect odds ratio:	1.164(0.896,1.511)	Indirect odds ratio:	0.916(0.728,1.155)	Indirect odds ratio:	1.109(0.909,1.353)

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

Inference for indirectness



Selected rule: Average

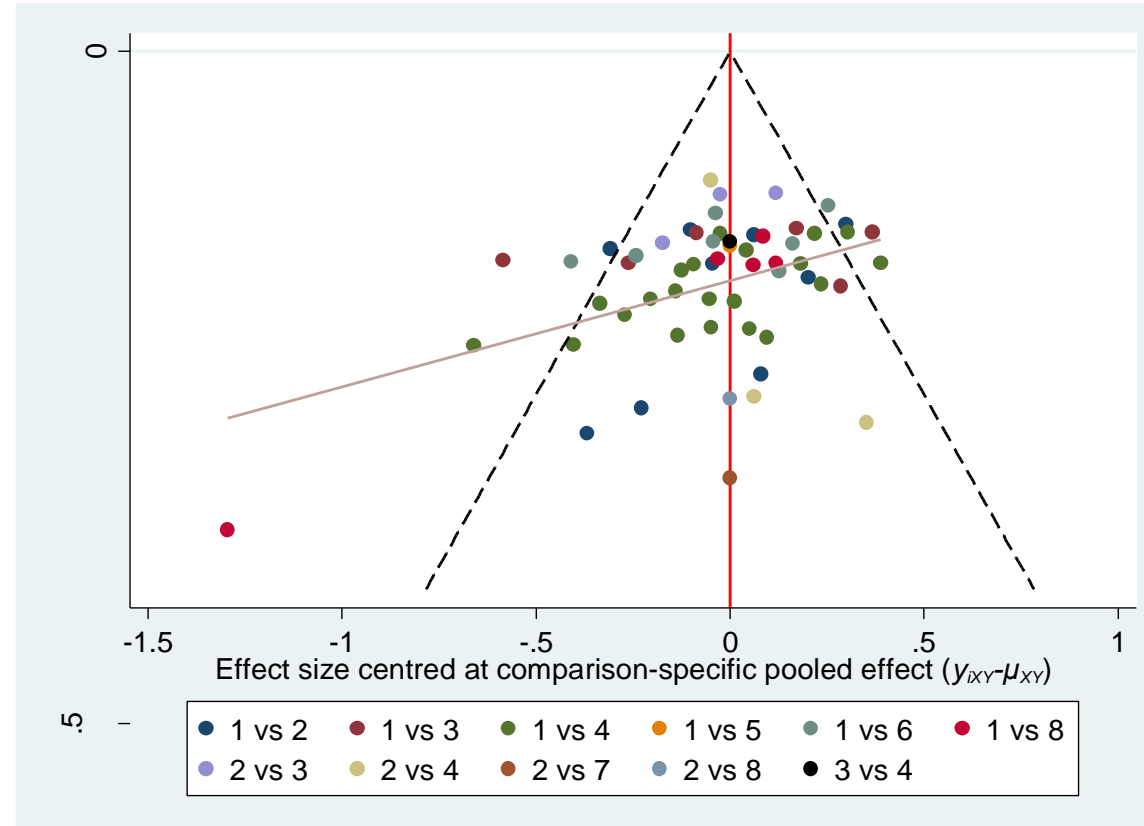
Reset

Proceed

<p>Comparison ACE:BBlocker Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison ACE:CCB Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison ACE:Diuretic Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison ACE:Placebo Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison ARB:BBlocker Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>
<p>Comparison ARB:CCB Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison ARB:Diuretic Evidence: mixed</p> <p>Majority: No concerns Average: Some concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="Some concerns"/></p>	<p>Comparison ARB:Placebo Evidence: mixed</p> <p>Majority: Some concerns Average: Some concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="Some concerns"/></p>	<p>Comparison BBlocker:CCB Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison BBlocker:Diuretic Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>
<p>Comparison BBlocker:Placebo Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison CCB:Diuretic Evidence: mixed</p> <p>Majority: No concerns Average: Some concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="Some concerns"/></p>	<p>Comparison CCB:Placebo Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison Diuretic:Placebo Evidence: mixed</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>	<p>Comparison ACE:ARB Evidence: indirect</p> <p>Majority: No concerns Average: No concerns Highest: Major concerns</p> <p>NMA judgement <input type="text" value="No concerns"/></p>

Publication bias

- We look at the search strategy
- We look at the comparison-adjusted funnel plot to check the presence of publication bias



Inference for publication bias

Evaluation of publication bias

Reset

Proceed

Comparison ACE:BBlocker
Evidence: mixed
Publication bias judgement

Comparison ACE:CCB
Evidence: mixed
Publication bias judgement

Comparison ACE:Diuretic
Evidence: mixed
Publication bias judgement

Comparison ACE:Placebo
Evidence: mixed
Publication bias judgement

Comparison ARB:BBlocker
Evidence: mixed
Publication bias judgement

Comparison ARB:CCB
Evidence: mixed
Publication bias judgement

Comparison ARB:Diuretic
Evidence: mixed
Publication bias judgement

Comparison ARB:Placebo
Evidence: mixed
Publication bias judgement

Comparison BBlocker:CCB
Evidence: mixed
Publication bias judgement

Comparison BBlocker:Diuretic
Evidence: mixed
Publication bias judgement

Comparison BBlocker:Placebo
Evidence: mixed
Publication bias judgement

Comparison CCB:Diuretic
Evidence: mixed
Publication bias judgement

Comparison CCB:Placebo
Evidence: mixed
Publication bias judgement

Comparison Diuretic:Placebo
Evidence: mixed
Publication bias judgement

Comparison ACE:ARB
Evidence: indirect
Publication bias judgement

Report

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

Final GRADE judgments

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

Final judgment

- ✓ The final rating of confidence is not necessarily obtained by aggregating the domain-specific judgements and may be different from the degree of downgrading suggested by the separate considerations for each domain.
- ✓ Imprecision, inconsistency and indirectness are related
- ✓ Intransitivity could produce inconsistency
- ✓ Incoherence can produce imprecision
- ✓ Heterogeneity: confidence interval narrow and the prediction interval extends into clinically unimportant effects but it does not cross the null hypothesis of no difference which might be considered 'no serious' instead of 'serious'
 - See ACE:Diuretics and ARB:BBlocker

Discussion

- ✓ Applications of network meta-analysis surge in medical literature
- ✓ Critical appraisal of results should become every-day practice in the field
- ✓ A user-friendly and freely available tool is necessary to facilitate the evaluation process and force researchers to incorporate such considerations in their manuscripts
- ✓ CINeMA is the only tool so far that applies GRADE into network meta-analysis using the most up-to-date methodology and considering the totality of the evidence

NMA toolkit

<http://cmim.cochrane.org/network-meta-analysis-toolkit>

cmim.cochrane.org/network-meta-analysis-toolkit

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- ♦ [Publications on Methodological Issues](#)
- ♦ [Publications That Include a Network Meta-Analysis](#)
- ♦ [Links to Other Relevant Sites](#)

Available Online Material & Software for Network Meta-Analysis

Please leave us a comment (at the bottom of this page) if you know of additional resources we should include.

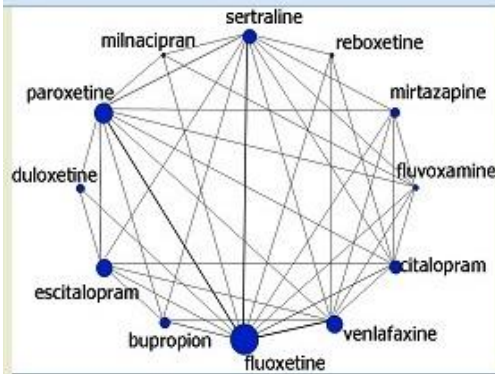
mvmeta command – performing NMA in STATA

- Source: <http://www.mrc-bsu.cam.ac.uk/Software/stata.html#Software>

The mvmeta command in STATA employs a recent approach to network meta-analysis that handles the different treatment comparisons appeared in studies as different outcomes. The command can perform fixed and random effects network meta-analysis assuming either a common or different between-study variances across comparisons. Both consistency and inconsistency models (the ‘design-by-treatment model’ or ‘Lu & Ades model’) have been implemented as well as network meta-regression models that can incorporate covariates. The command contains also an option that enables the estimation of ranking probabilities.

Other Cochrane Resources for Network Meta-Analysis

- [Our discussion document that describes all relevant methodologies for indirect comparisons suggested in the scientific literature to date.](#)
- [Our bibliography of relevant methodological papers](#)
- [Our glossary of key terms](#)
- [Our list of available](#)



Multiple-Treatments Meta-Analysis

A Framework for Evaluating and Ranking Multiple Healthcare Technologies

You are here: Home

- HOME
- TUTORIAL and BIBLIOGRAPHY
- HOW TO DO AN MTM
- IMMA ERC starting Grant
- RESEARCH and PUBLICATIONS
- STATA routines for Network Meta-Analysis
- Material from Publications (software and protocols)
- Meta-analysis methods and tools
- TEAM

Multiple-Treatments Meta-analysis (MTM)

Meta-analysis is the statistical technique used to synthesize evidence from experiments addressing the same research question. It is often used to combine data from clinical trials regarding the relative effectiveness of two interventions in order, for example, to infer about whether antihypertensives A and B are equally effective in lowering blood pressure.

The main drawback of the current state of the art is that meta-analysis focuses on comparing only two alternatives. However, clinicians and patients need to know the relative ranking of a set of alternative options and not only whether option A is better than B.

The statistical methodology applied to synthesize information over a network of comparisons involving all alternative treatment options for the same condition is called **Multiple-Treatments Meta-Analysis**.

This site provides

- an introduction to statistical and methodological issues related to MTM
- links to training material
- support to statisticians with the analysis of networks of interventions
- ideas and discussions of research in MTM

Cochrane Training on NMA

<http://training.cochrane.org/search/site/network%20meta-analysis>

The screenshot shows a web browser window with the URL training.cochrane.org/search/site/network%20meta-analysis. The page features a purple navigation bar with links for Interactive Learning, Learning resources, Pathways, Workshops/courses, Handbooks, and a Log in button. Below the navigation bar, the search results are displayed under the heading "Search". The search results show 77 results for "network meta-analysis". The results are filtered by "Training & Workshops". The first result is "Introduction to network meta-analysis (NMA)", published on 30 May 2017. The second result is "A network meta-analysis (NMA) toolkit", published on 31 May 2017. The third result is "CINeMA - Confidence in Network meta-analysis", published in October 2017. On the left side of the page, there is a "Filter your results:" section with two categories: "Type of Review" and "Topics". The "Type of Review" section includes checkboxes for "All types of reviews (2)", "Diagnostic Test Accuracy reviews (3)", "Intervention reviews (29)", and "Other review types (2)". The "Topics" section includes a list of topics with counts and dropdown arrows: "Introduction to... (20)", "Planning a review (3)", "Gathering evidence (8)", "Analysing evidence (37)", "Software and tools (7)", "Editing a review (8)", and "Writing a review (4)". The Windows taskbar at the bottom shows the date as 09/11/2017 and the time as 21:05.

Search

77 search results for "network meta-analysis"

Filter your results:

Type of Review

- All types of reviews (2)
- Diagnostic Test Accuracy reviews (3)
- Intervention reviews (29)
- Other review types (2)

Topics

- Introduction to... (20) ▾
- Planning a review (3)
- Gathering evidence (8) ▾
- Analysing evidence (37) ▾
- Software and tools (7) ▾
- Editing a review (8) ▾
- Writing a review (4) ▾

Resource • Video • Published 30 May 2017

Introduction to network meta-analysis (NMA)

The following two videos will introduce you to the key concepts in **network meta-analysis** (NMA). ... reporting and critical appraisal of NMA. Understand what is a **network meta-analysis** and the terminology ... around it Describe rationale for conducting a **network meta-analysis** ...

Resource • Published 31 May 2017

A network meta-analysis (NMA) toolkit

software tools for conducting **network meta-analysis**. You can find it through the link below. Analysing ...

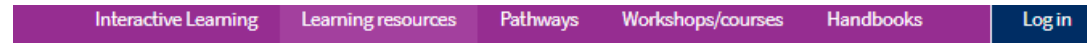
Resource • Video • Published October 2017

CINeMA - Confidence in Network meta-analysis

confidence that can be placed in results obtained from a **network meta-analysis** by adapting and extending the

CINeMA

<http://training.cochrane.org/resource/cinema-%E2%80%93-confidence-network-meta-analysis>



CINeMA – Confidence in Network meta-analysis

Date created
October 2017

Format
Video

Duration
50 minutes

Useful for...
Authors

Topics
Analysing evidence
GRADE and interpreting results
Advanced methods

Type of review
Intervention reviews

Learning resources

• Hosting a webinar

Description

In these videos from a Cochrane Learning Live webinar, Georgia Salanti and Theodore Papakonstantinou from the Institute of Social and Preventive Medicine, University of Bern, Switzerland present the CINeMA (Confidence in Network Meta-analysis) framework and web application developed to judge the confidence that can be placed in results obtained from a network meta-analysis by adapting and extending the GRADE domains (study limitations, inconsistency, indirectness, imprecision and publication bias).

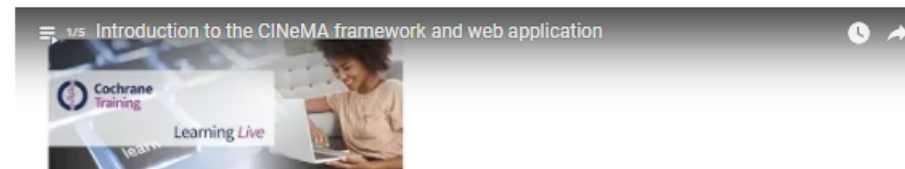
Below you will find slides from the webinar [PDF] as well as edited videos covering:

1. Introduction to the CINeMA framework and web application
2. Study limitations and indirectness
3. Imprecision
4. Inconsistency and publication bias
5. Questions and answers



Enter fullscreen mode

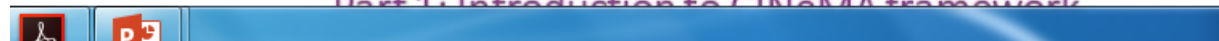
Part 1: Introduction to the CINeMA framework and web application



CINeMA – Confidence in Network meta-analysis

Prof Georgia Salanti and Theodoros Papakonstantinou
Institute of Social and Preventive Medicine, University of Bern, Switzerland

Part 1: Introduction to CINeMA framework



References

- Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT (2014) Evaluating the Quality of Evidence from a Network Meta-Analysis. *PLoS ONE* 9(7):e99682. doi:10.1371/journal.pone.0099682
- Cipriani A, Higgins JPT, Geddes JR, Salanti G (2013) Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 159(2): 130–137.
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924–6
- Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41:818-827.
- Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol*. 2015 Jan;68(1):52–60.
- Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, et al. (2013) Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 33(5): 641–656.
- Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L (2008) Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 61(10): 991-996.
- Tan SH, Cooper NJ, Bujkiewicz S, Welton NJ, Caldwell DM, et al. (2014) Novel presentational approaches were developed for reporting network meta-analysis. *J Clin Epidemiol* 67(6): 672–80.
- White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods*. 2012 Jun;3(2):111–25.
- Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012 Jun;3(2):98–110.
- Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010 Mar 30;29(7–8):932–44