GRADE:
Applicazione alle network meta-analisi

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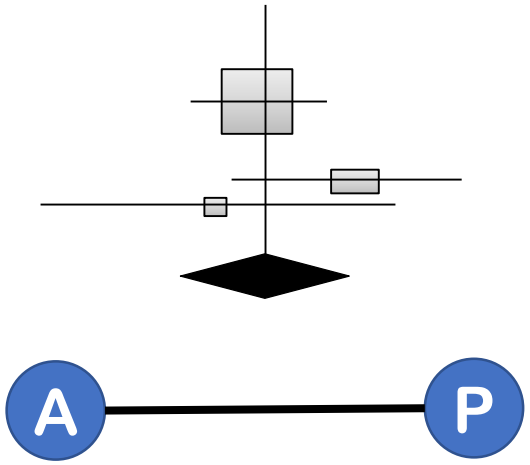
Confidence in pairwise meta-analysis results



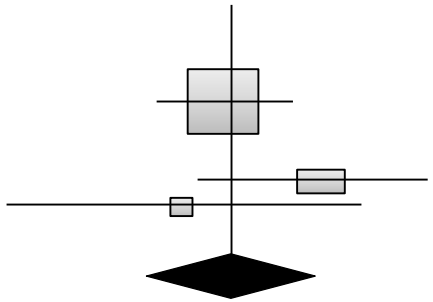
MD AvsP
0.37 (0.24,0.51)

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



MD AvsP
0.37 (0.24,0.51)

⊕⊕⊕◯

GRADE system

⊕⊕⊕⊕ High

⊕⊕⊕◯ Moderate

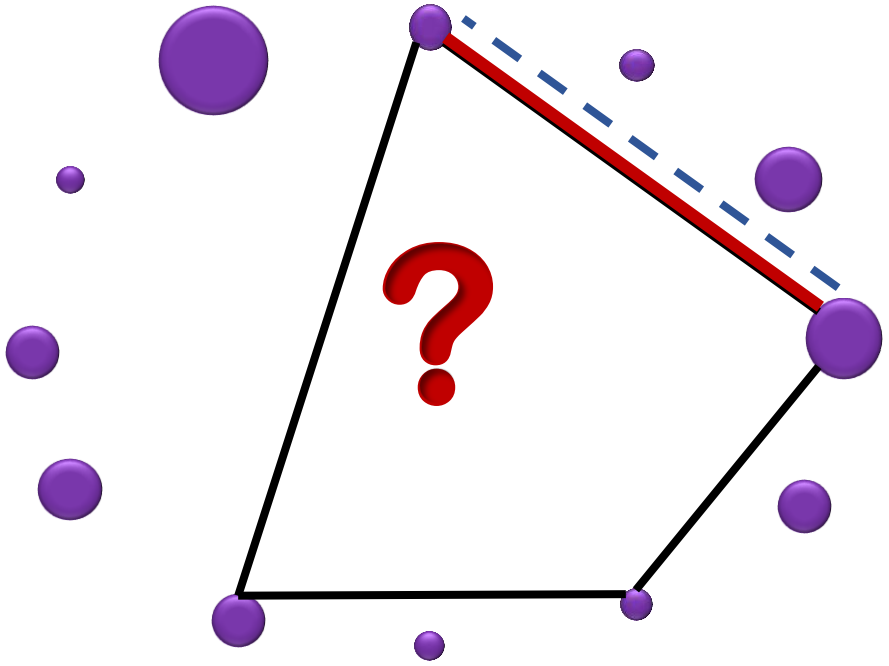
⊕⊕◯◯ Low

⊕◯◯◯ Very low

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

- Not serious
- Serious
- Very serious

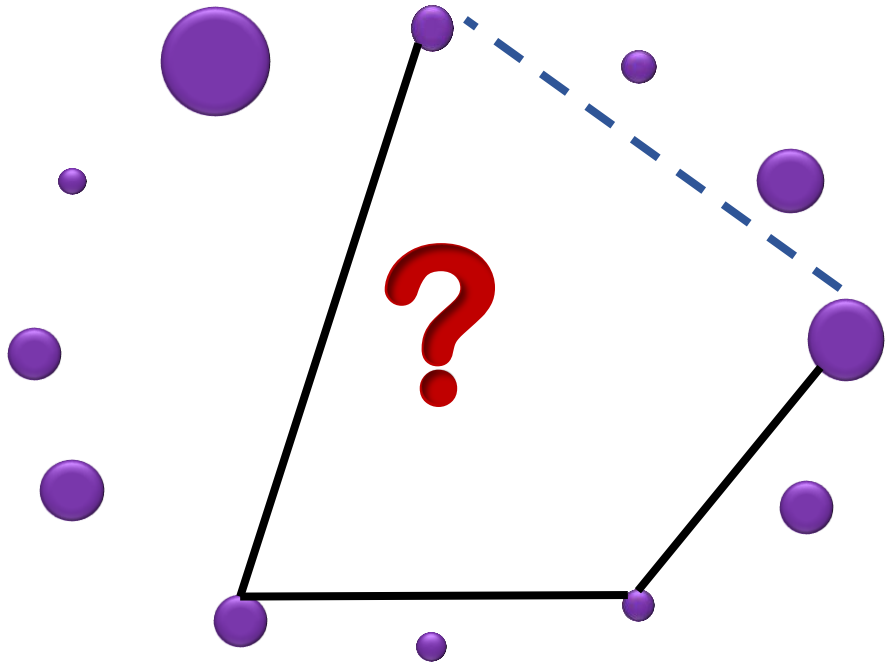
Network meta-analysis



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

direct evidence + indirect evidence → mixed evidence

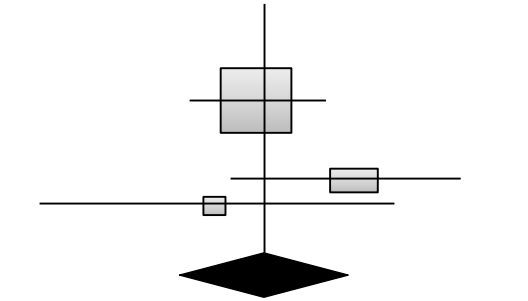
Network meta-analysis



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

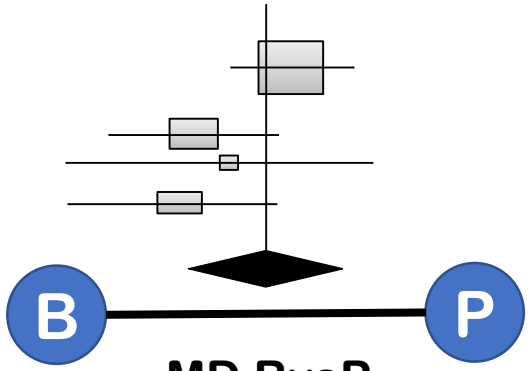
indirect evidence

Extending GRADE into NMA



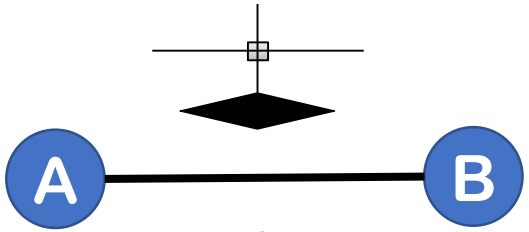
MD AvsP
0.37 (0.24,0.51)

⨁⨁⨁◯



MD BvsP
0.58 (0.39,0.77)

⨁⨁◯◯

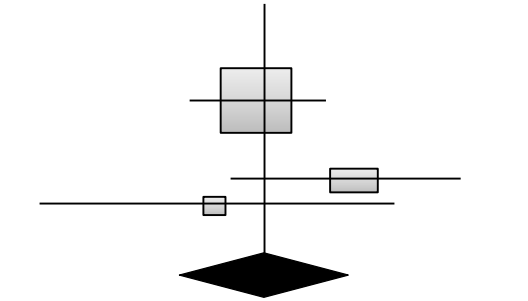


MD AvsB
-0.42 (-0.71,-0.14)

⨁◯◯◯

Background

confidence in network meta-analysis results



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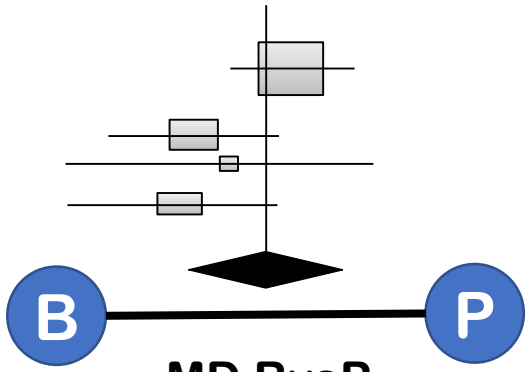
⊕⊕⊕◯



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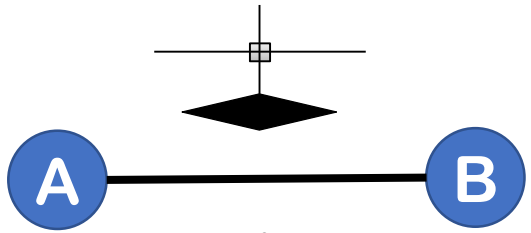
⊕⊕◯◯



MD AvsB
-0.42 (-0.71,-0.14)

⊕◯◯◯

Direct
+
Indirect
Confidence

Direct
+
Indirect
Evidence

Based on….

OPEN ACCESS Freely available online

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]*

1 Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece, **2** Statistics Unit, Department of Clinical and Diagnostic Medicine and Public Health, University of Modena and Reggio Emilia, Modena, Italy, **3** School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom, **4** Centre for Reviews and Dissemination, University of York, York, United Kingdom

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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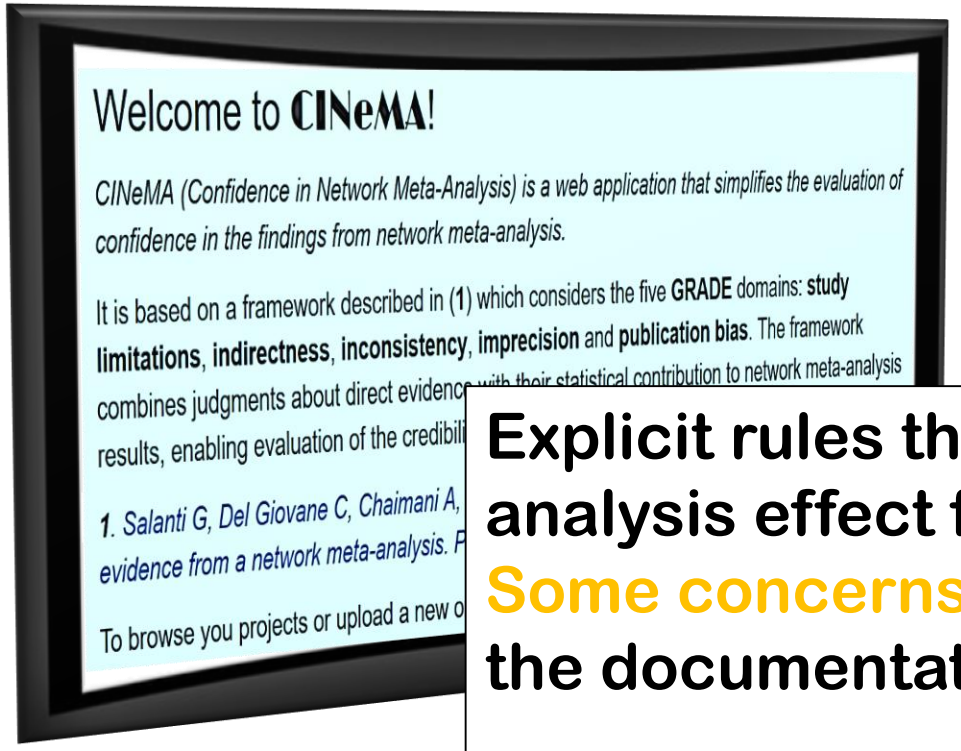
An alternative equivalent approach is presented in:

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, Rochwerg B5, Hazlewood GS6, Alhazzani W5, Mustafa RA7, Murad MH8, Puhan MA9, Schünemann HJ1, Guyatt GH10; GRADE Working Group.

Time for CINeMA

cinema.ispm.ch



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

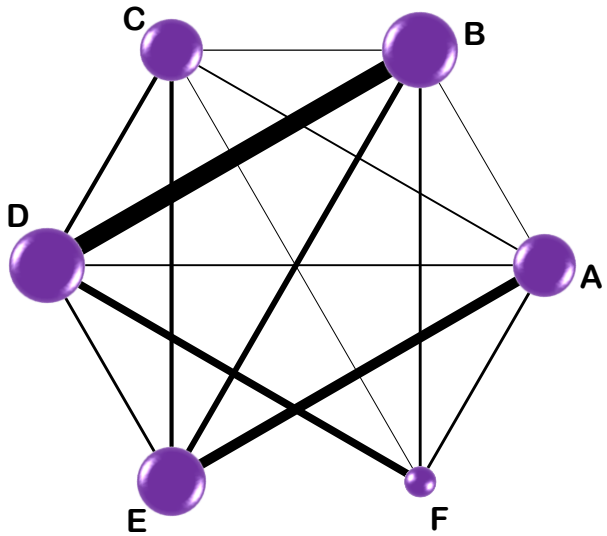
The rules can be overw

Advantages

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 143 153 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 Intitial 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 (ω=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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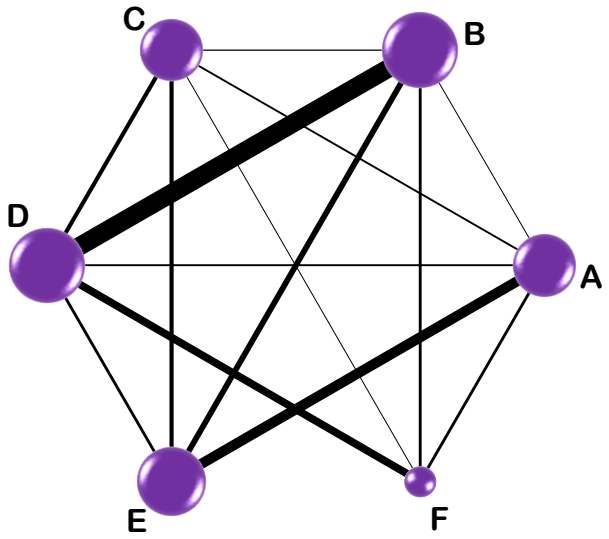
(Prof W J Elliott MD, P M Meyer PhD)

Correspondence to:
Prof William J Elliott
welliott@rush.edu

Example

antihypertensives & incidence of diabetes



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

1 LOW RoB
2 UNCLEAR RoB
3 HIGH RoB

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
EWPHE	9	Diuretic	29	416	2
EWPHE	9	Placebo	20	424	2
FEVER	10	CCB	177	4841	1
FEVER	10	Placebo	154	4870	1

Data upload

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

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.

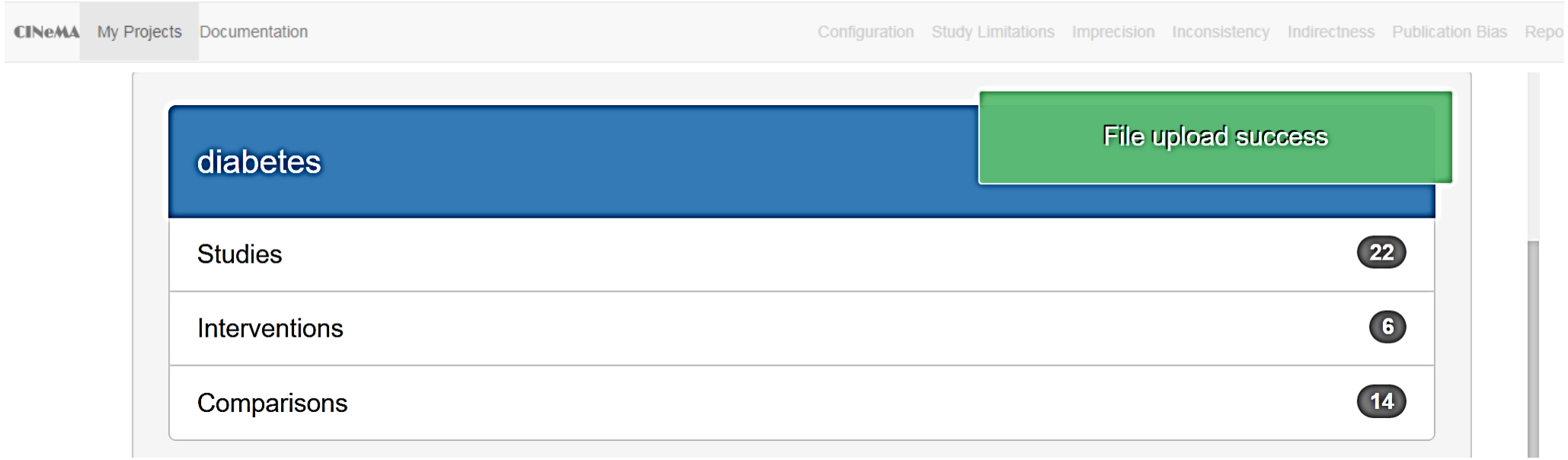
Example binary format 1:

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

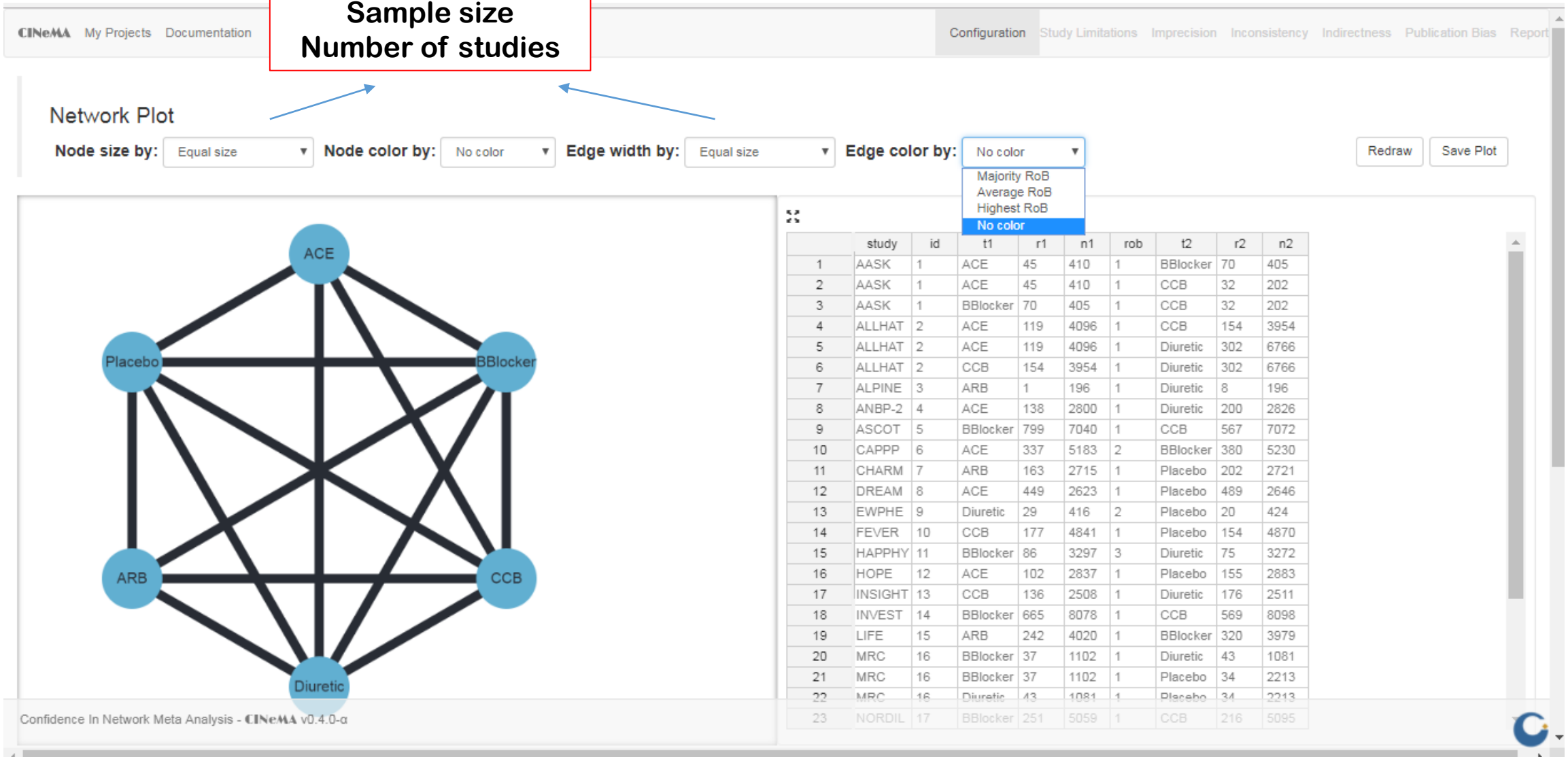
Data upload



…Evaluation starts!

Configuration – network plot

Sample size
Number of studies

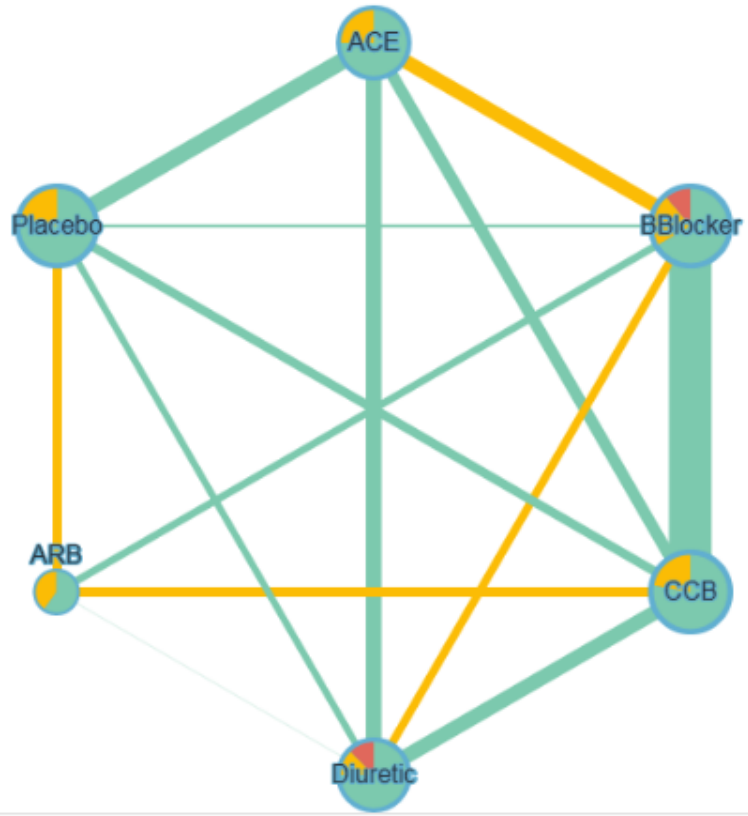


	study	id	t1	r1	n1	rob	t2	r2	n2
1	AASK	1	ACE	45	410	1	BBlocker	70	405
2	AASK	1	ACE	45	410	1	CCB	32	202
3	AASK	1	BBlocker	70	405	1	CCB	32	202
4	ALLHAT	2	ACE	119	4096	1	CCB	154	3954
5	ALLHAT	2	ACE	119	4096	1	Diuretic	302	6766
6	ALLHAT	2	CCB	154	3954	1	Diuretic	302	6766
7	ALPINE	3	ARB	1	196	1	Diuretic	8	196
8	ANBP-2	4	ACE	138	2800	1	Diuretic	200	2826
9	ASCOT	5	BBlocker	799	7040	1	CCB	567	7072
10	CAPPP	6	ACE	337	5183	2	BBlocker	380	5230
11	CHARM	7	ARB	163	2715	1	Placebo	202	2721
12	DREAM	8	ACE	449	2623	1	Placebo	489	2646
13	EWPHE	9	Diuretic	29	416	2	Placebo	20	424
14	FEVER	10	CCB	177	4841	1	Placebo	154	4870
15	HAPPHY	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

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
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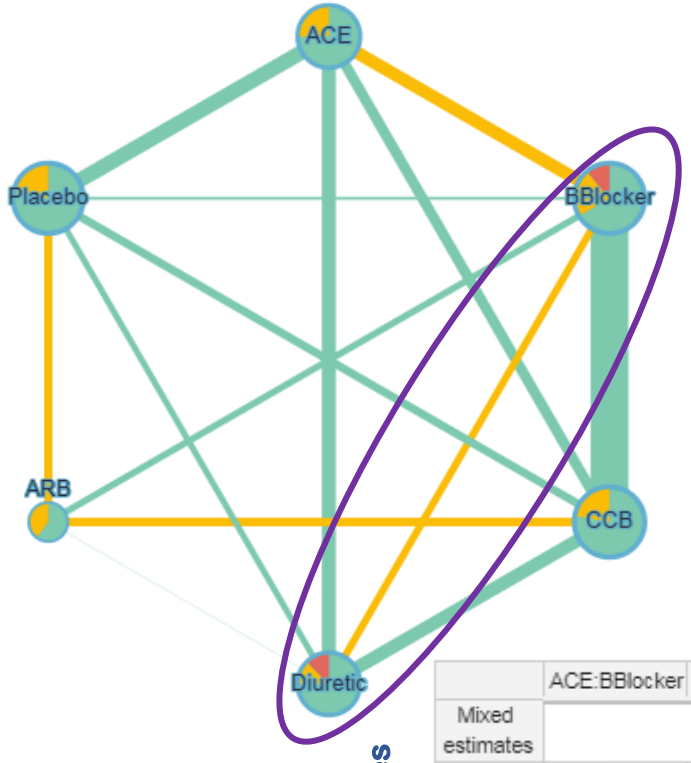
23	NORDIL	17	BBlocker	251	5059	1	CCB	216	5095

ıfidence In Network Meta Analysis - CINeMA v0.4.0-g

Setting up the evaluation



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:BBloc	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:Diure	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:Place	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:BBloc	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:Diure	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:Place	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:C	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:D	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:P	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:Diure	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:Place	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:Pla	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

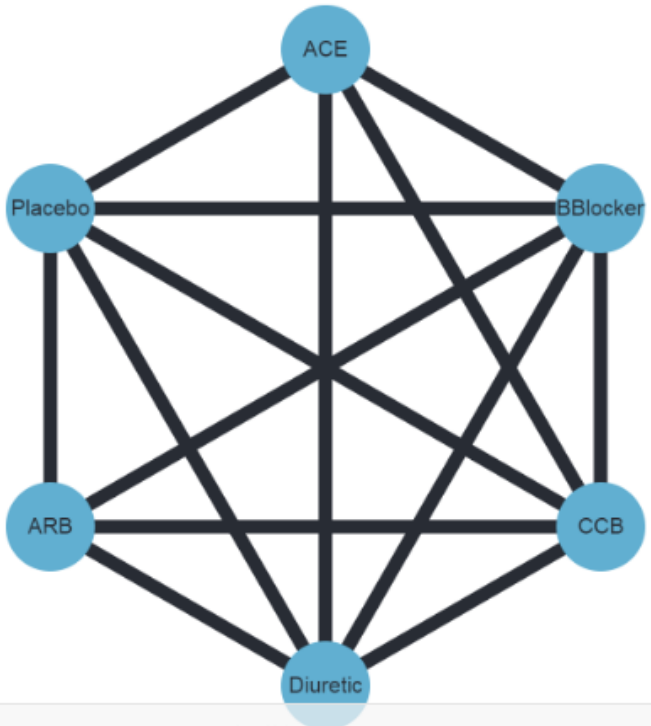
Configuration | Study Limitations | Imprecision | Inconsistency | Indirectness | Publication Bias | Report

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

Majority RoB
Average RoB
Highest RoB
No color



	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
9	ASCOT	5	BBlocker	799	7040	1	CCB	567	7072
10	CAPPP	6	ACE	337	5183	2	BBlocker	380	5230
11	CHARM	7	ARB	163	2715	1	Placebo	202	2721
12	DREAM	8	ACE	449	2623	1	Placebo	489	2646
13	EWPHE	9	Diuretic	29	416	2	Placebo	20	424
14	FEVER	10	CCB	177	4841	1	Placebo	154	4870
15	HAPPHY	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

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

Comparison:	ACE:BBlocker
Number of studies:	3
Sample size:	15158
Majority RoB:	moderate
Average RoB:	moderate
Highest RoB:	moderate
Direct RoB:	moderate

Comparison:	ACE:CCB
Number of studies:	3
Sample size:	12597
Majority RoB:	low
Average RoB:	low
Highest RoB:	moderate
Direct RoB:	low

Comparison:	ACE:Diuretic
Number of studies:	2
Sample size:	16488
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

Comparison:	ACE:Placebo
Number of studies:	3
Sample size:	17893
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

Comparison:	ARB:BBlocker
Number of studies:	1
Sample size:	7999
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

Comparison:	ARB:CCB
Number of studies:	1
Sample size:	10161
Majority RoB:	moderate
Average RoB:	moderate
Highest RoB:	moderate
Direct RoB:	moderate

Comparison:	ARB:Diuretic
Number of studies:	1
Sample size:	392
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

Comparison:	ARB:Placebo
Number of studies:	2
Sample size:	9778
Majority RoB:	moderate
Average RoB:	moderate
Highest RoB:	moderate
Direct RoB:	moderate

Comparison:	BBlocker:CCB
Number of studies:	5
Sample size:	44974
Majority RoB:	low
Average RoB:	low
Highest RoB:	moderate
Direct RoB:	low

Comparison:	BBlocker:Diuretic
Number of studies:	2
Sample size:	8752
Majority RoB:	high
Average RoB:	moderate
Highest RoB:	high
Direct RoB:	moderate

Comparison:	BBlocker:Placebo
Number of studies:	1
Sample size:	3315
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

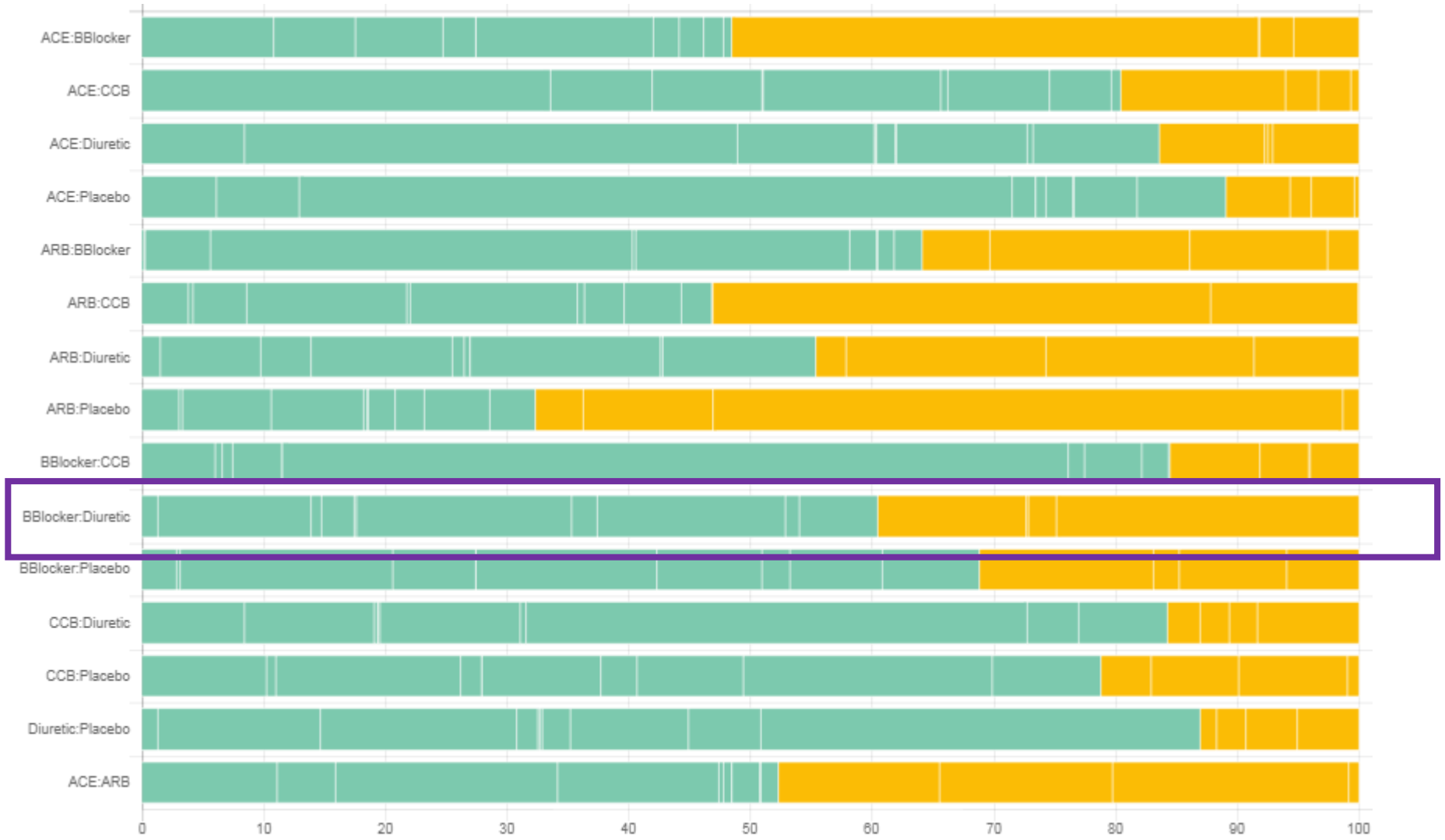
Comparison:	CCB:Diuretic
Number of studies:	2
Sample size:	15739
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

Comparison:	CCB:Placebo
Number of studies:	1
Sample size:	9711
Majority RoB:	low
Average RoB:	low
Highest RoB:	low
Direct RoB:	low

Comparison:	Diuretic:Placebo
Number of studies:	3
Sample size:	7343
Majority RoB:	low
Average RoB:	low
Highest RoB:	moderate
Direct RoB:	low

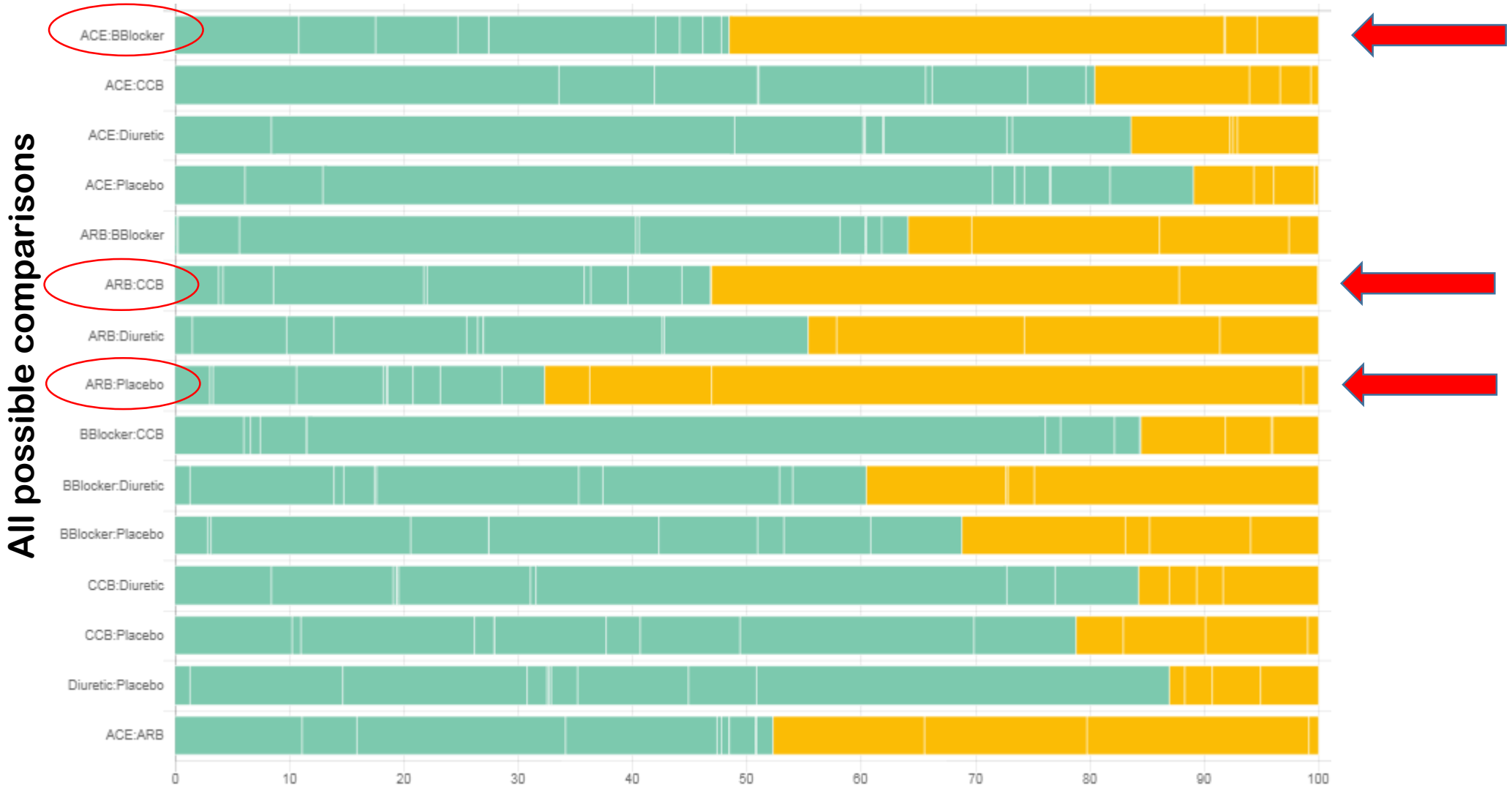
Risk of Bias bar chart

All possible comparisons



Inference for study limitations

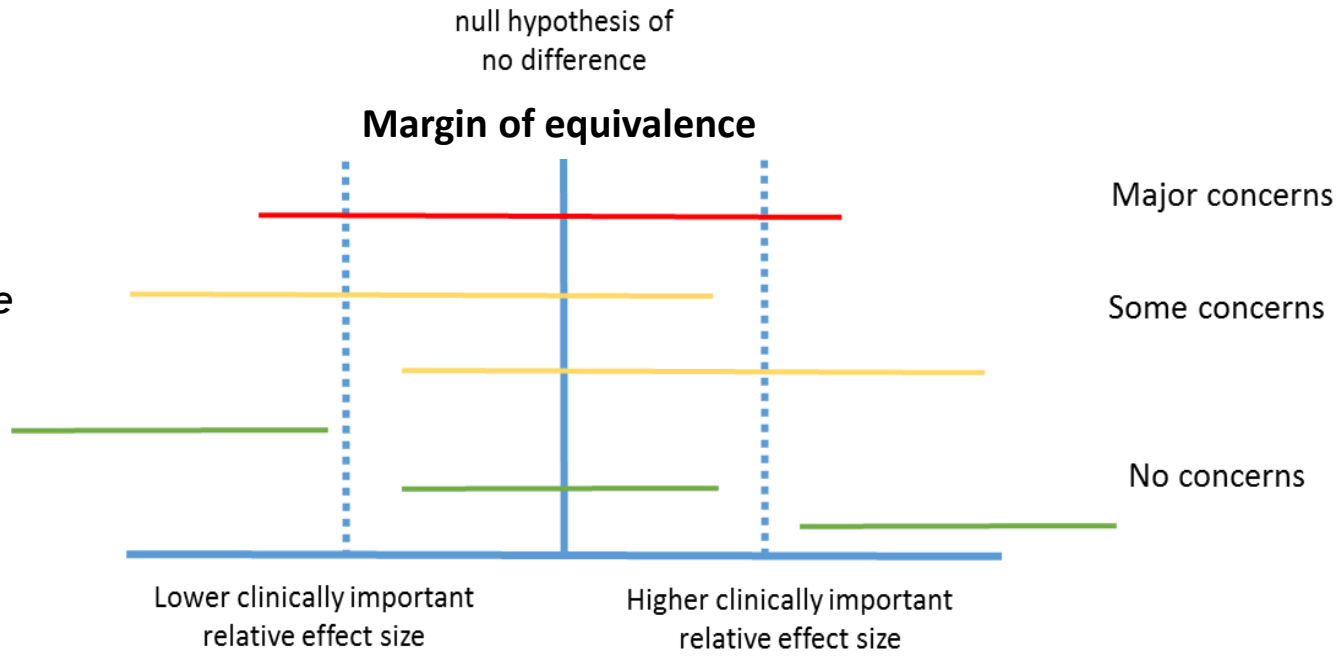
Risk of Bias bar chart



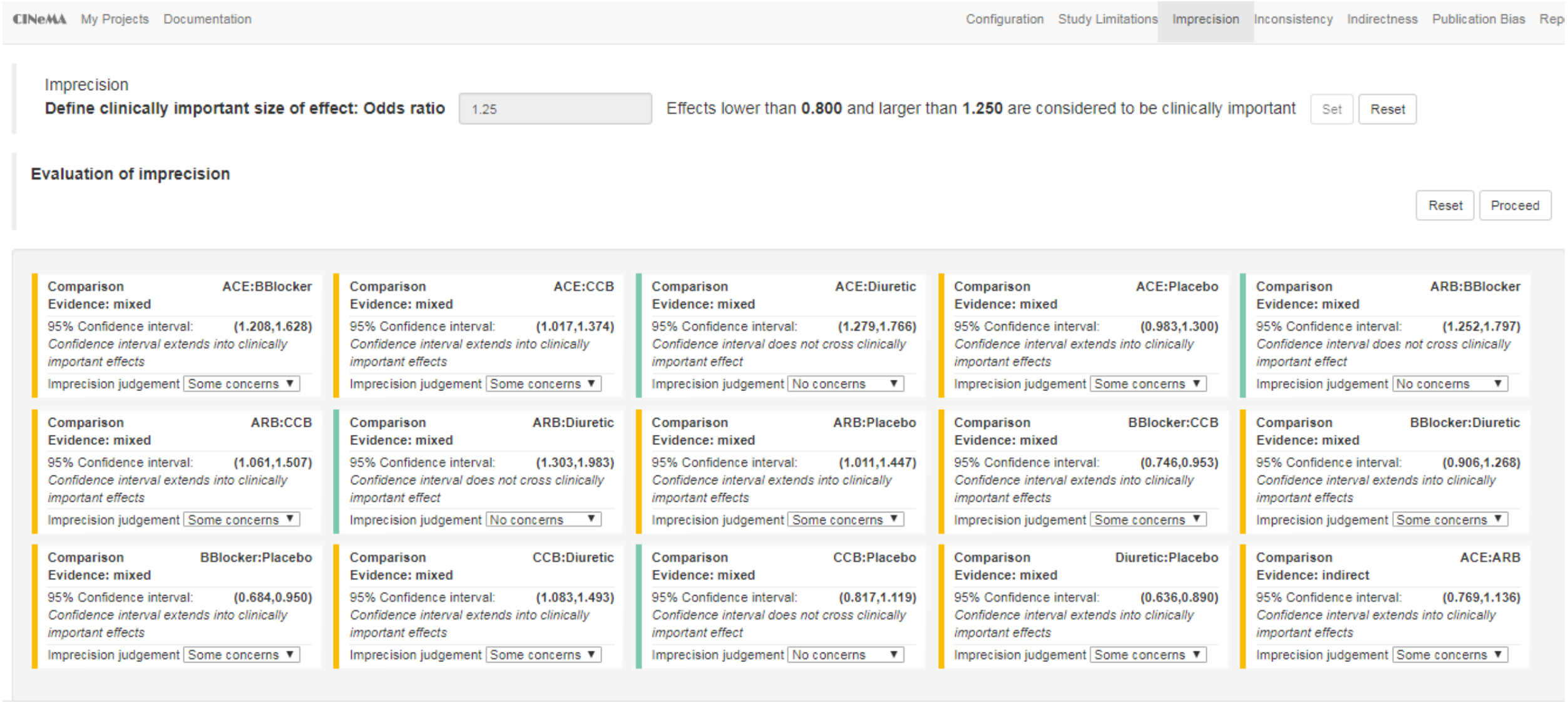
Imprecision

- 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)

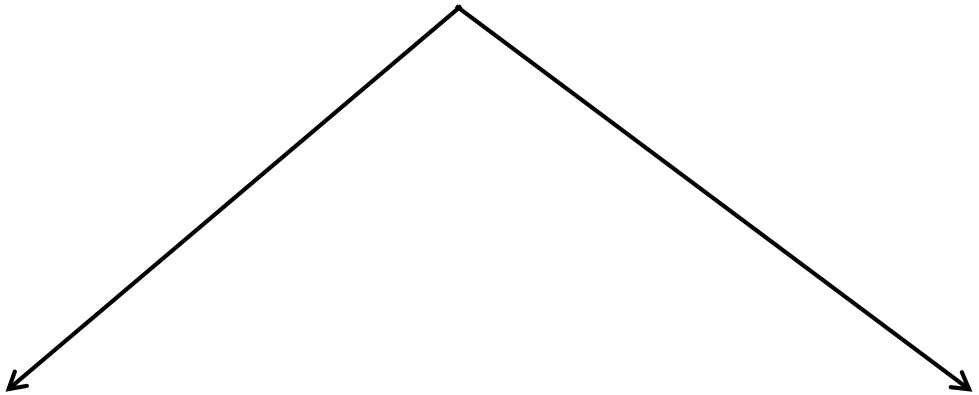
Rules implemented in the software



Inference for imprecision



Inconsistency



Heterogeneity
between-study variance
within a comparison

Incoherence
disagreement between
different sources of evidence

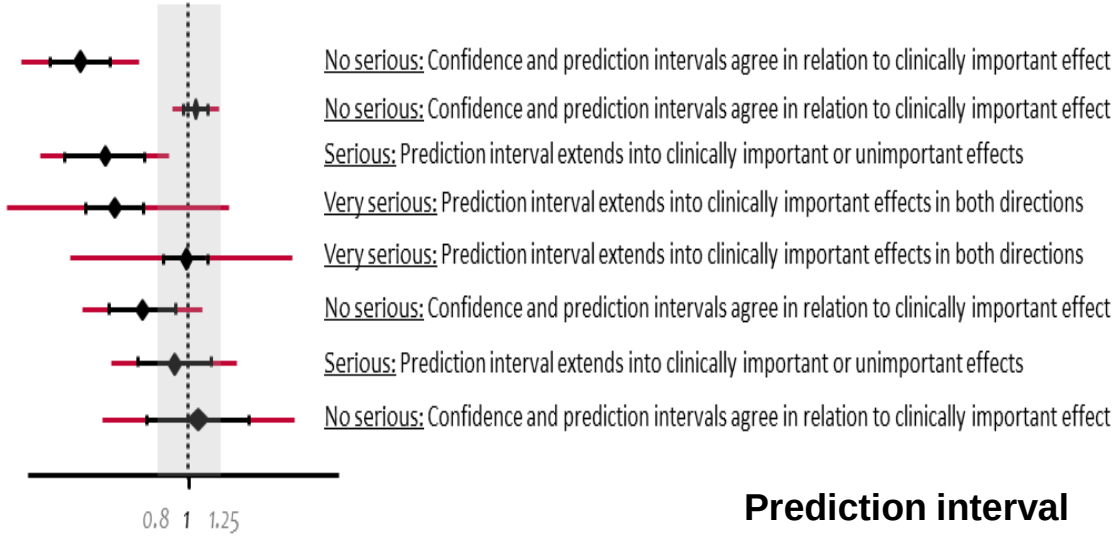
Heterogeneity

- The major driver in judging heterogeneity is whether <u>it impacts on clinical decisions</u>
- 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



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

Prediction interval
Confidence interval

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 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
- The common heterogeneity variance (τ^2) estimated in the entire network is also reported in the software

Inference for heterogeneity

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

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	

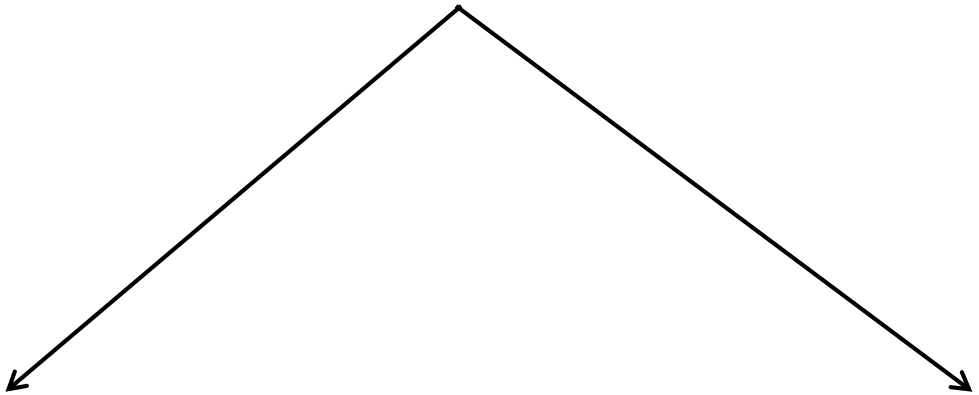
Comparison	ACE:Diuretic
Evidence: mixed	
Between-study heterogeneity for each direct comparison	
I^2:	0.0%
Estimated τ^2:	0.000
Reference Values for τ^2	
first quantile:	0.004
median:	0.040
third quantile:	0.429
95% intervals for NMA estimate	
Confidence interval:	(1.279,1.766)
Prediction interval:	(1.096,2.061)
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

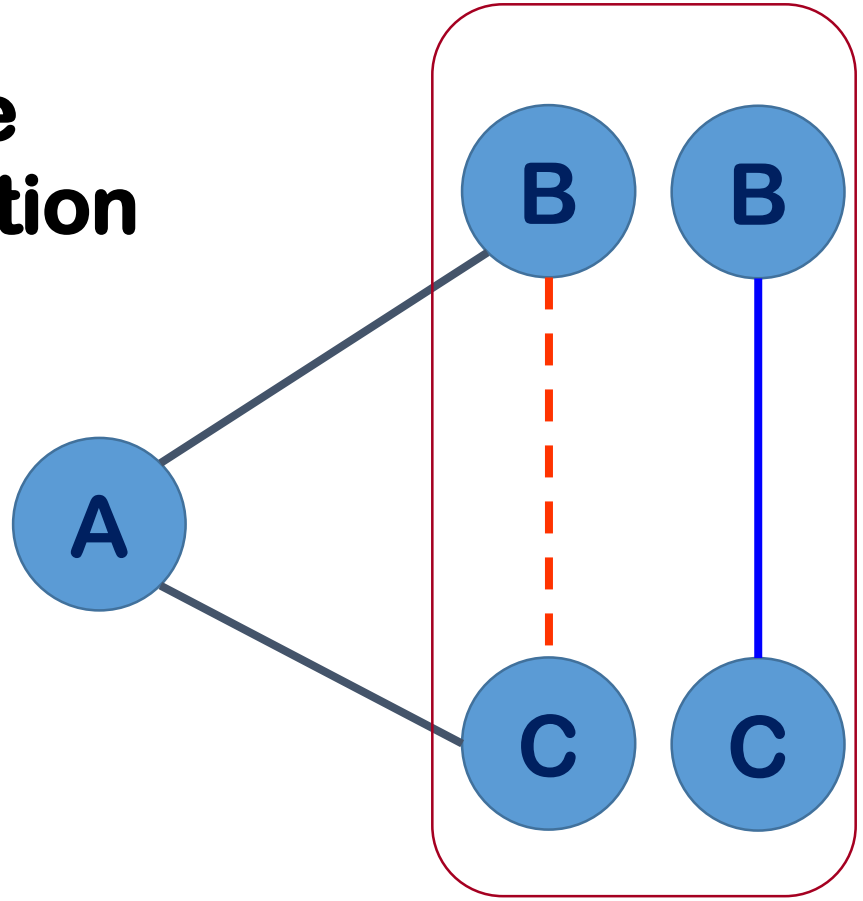


Heterogeneity
between-study variance
within a comparison

Incoherence
disagreement between
different sources of evidence

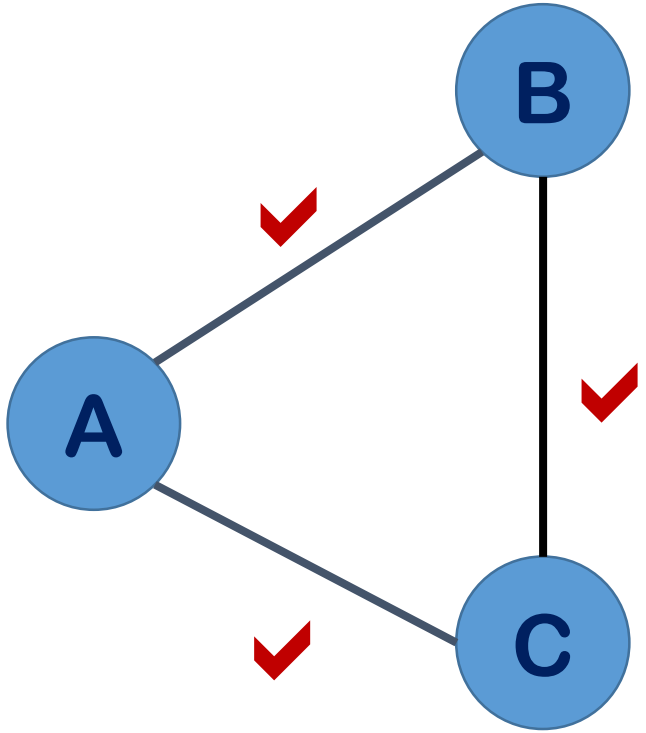
Coherence

Testable assumption



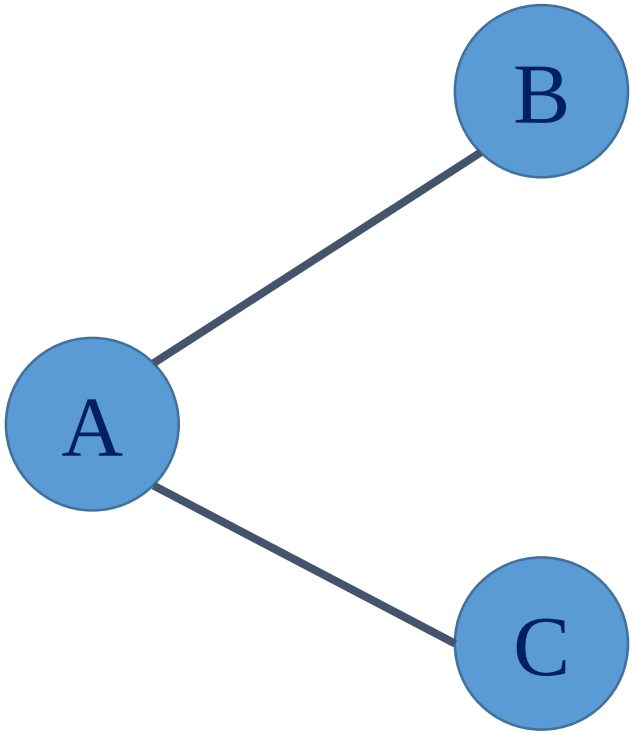
Direct and indirect evidence are in agreement

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 <u>network estimates</u> informed by less than 90% from direct evidence**

		Design by treatment interaction model		
		p-value>0.1	***0.01<p-value<0.1***	***p-value<0.01***
SIDE	***p-value>0.1***	No concerns	No concerns	Some concerns
	0.01<p-value<0.1	Some concerns	Some concerns	Major concerns
	p-value<0.01	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	ACE:CCB	ACE:Diuretic	ACE:Placebo	ARB:BBlocker
Evidence: mixed					
NMA odds ratio:	1.402(1.208,1.628)	1.182(1.017,1.374)	1.503(1.279,1.766)	1.130(0.983,1.300)	1.500(1.252,1.797)
Direct odds ratio:	1.194(0.970,1.471)	1.249(0.989,1.577)	1.515(1.199,1.916)	1.230(1.030,1.469)	1.365(1.009,1.848)
Indirect odds ratio:	1.662(1.341,2.059)	1.137(0.934,1.383)	1.492(1.194,1.864)	0.983(0.783,1.235)	1.580(1.261,1.978)
Direct contribution:	51.4	41.5%	47.4%	62.2%	35.5%
Inconsistency measures		ures			
Ratio of odds ratios:	0.719(0.533,0.969)	1.099(0.810,1.490)	1.015(0.735,1.403)	1.251(0.938,1.669)	0.864(0.593,1.260)
P value:	0.030	0.545	0.926	0.128	0.449
Incoherence judgement	Some concerns	No concerns	No concerns	No concerns	No concerns

SIDE test

Comparison	ARB:CCB	ARB:Diuretic	ARB:Placebo	BBlocker:CCB	BBlocker:Diuretic
Evidence: mixed					
NMA odds ratio:	1.264(1.061,1.507)	1.608(1.303,1.983)	1.209(1.011,1.447)	0.843(0.746,0.953)	1.072(0.906,1.268)
Direct odds ratio:	1.273(0.971,1.670)	8.298(1.013,67.979)	1.251(0.978,1.601)	0.816(0.706,0.943)	0.985(0.718,1.349)
Indirect odds ratio:	1.258(1.000,1.583)	1.581(1.281,1.953)	1.164(0.896,1.511)	0.916(0.728,1.155)	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

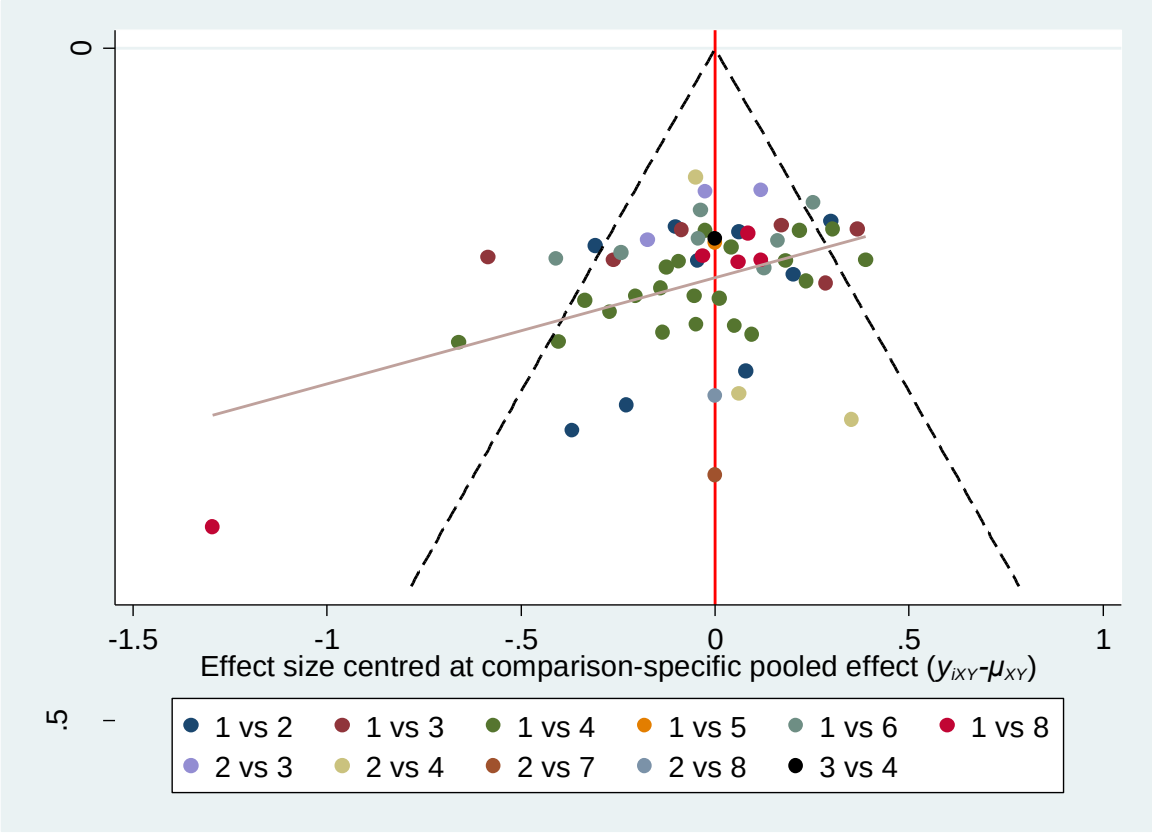
Selected rule: Average

Reset | Proceed

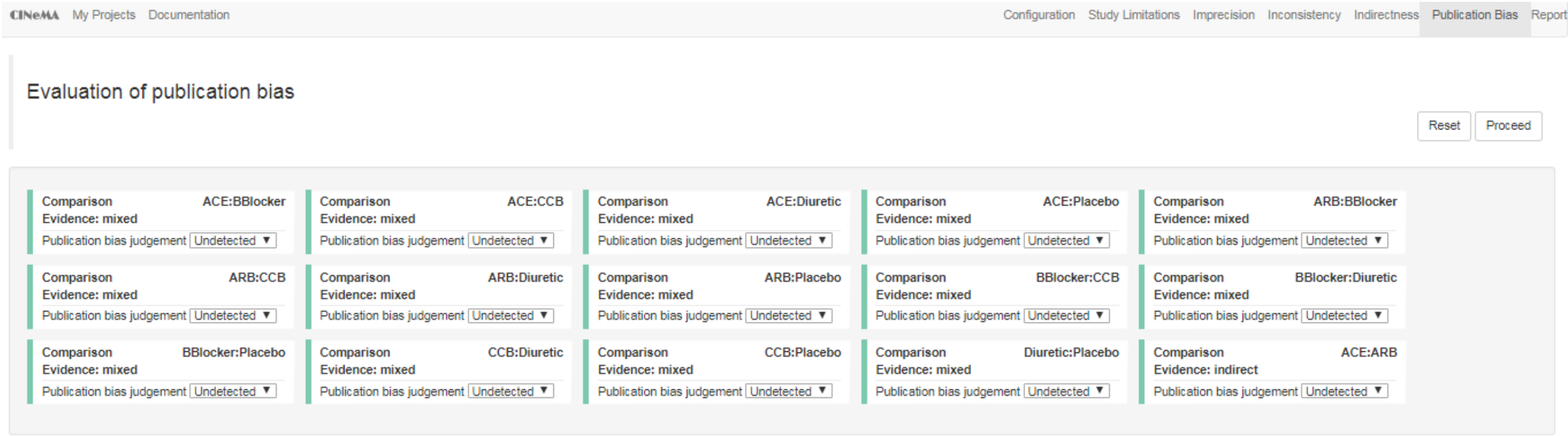
Comparison ACE:BBlocker **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** ACE:CCB **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** ACE:Diuretic **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** ACE:Placebo **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** ARB:BBlocker **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns
Comparison ARB:CCB **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** ARB:Diuretic **Evidence: mixed** Majority: No concerns Average: **Some concerns** Highest: Major concerns NMA judgement: Some concerns	**Comparison** ARB:Placebo **Evidence: mixed** Majority: Some concerns Average: **Some concerns** Highest: Major concerns NMA judgement: Some concerns	**Comparison** BBlocker:CCB **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** BBlocker:Diuretic **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns
Comparison BBlocker:Placebo **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** CCB:Diuretic **Evidence: mixed** Majority: No concerns Average: **Some concerns** Highest: Major concerns NMA judgement: Some concerns	**Comparison** CCB:Placebo **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** Diuretic:Placebo **Evidence: mixed** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns	**Comparison** ACE:ARB **Evidence: indirect** Majority: No concerns Average: **No concerns** Highest: Major concerns NMA judgement: No concerns

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



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

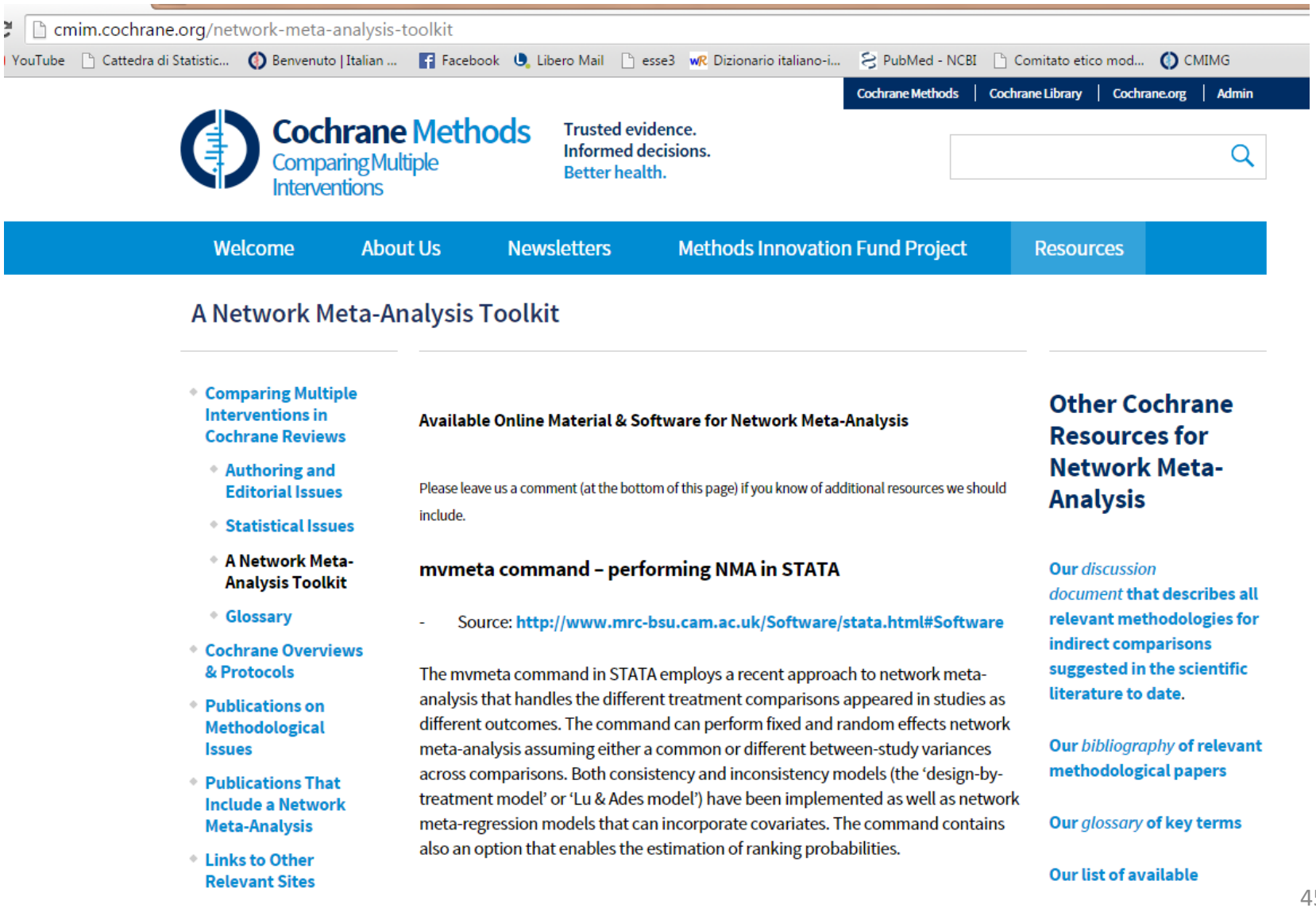
- ✓ The final rating of confidence is not necessarily obtained by aggregating the domain-specific judgements and may be different from the degree of downgrading suggested by the separate considerations for each domain.
- ✓ Imprecision, inconsistency and indirectness are related
- ✓ Intransitivity could 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

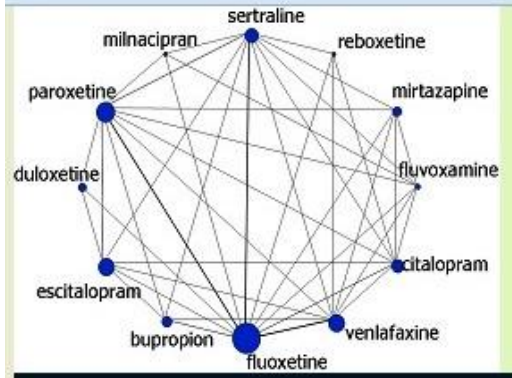
- ✓ Applications of network meta-analysis surge in medical literature
- ✓ Critical appraisal of results should become every-day practice in the field
- ✓ A user-friendly and freely available tool is necessary to facilitate the evaluation process and force researchers to incorporate such considerations 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



www.mtm.uoi.gr



Multiple-Treatments Meta-Analysis

A Framework for Evaluating and Ranking Multiple Healthcare Technologie

You are here: Home

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- 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)

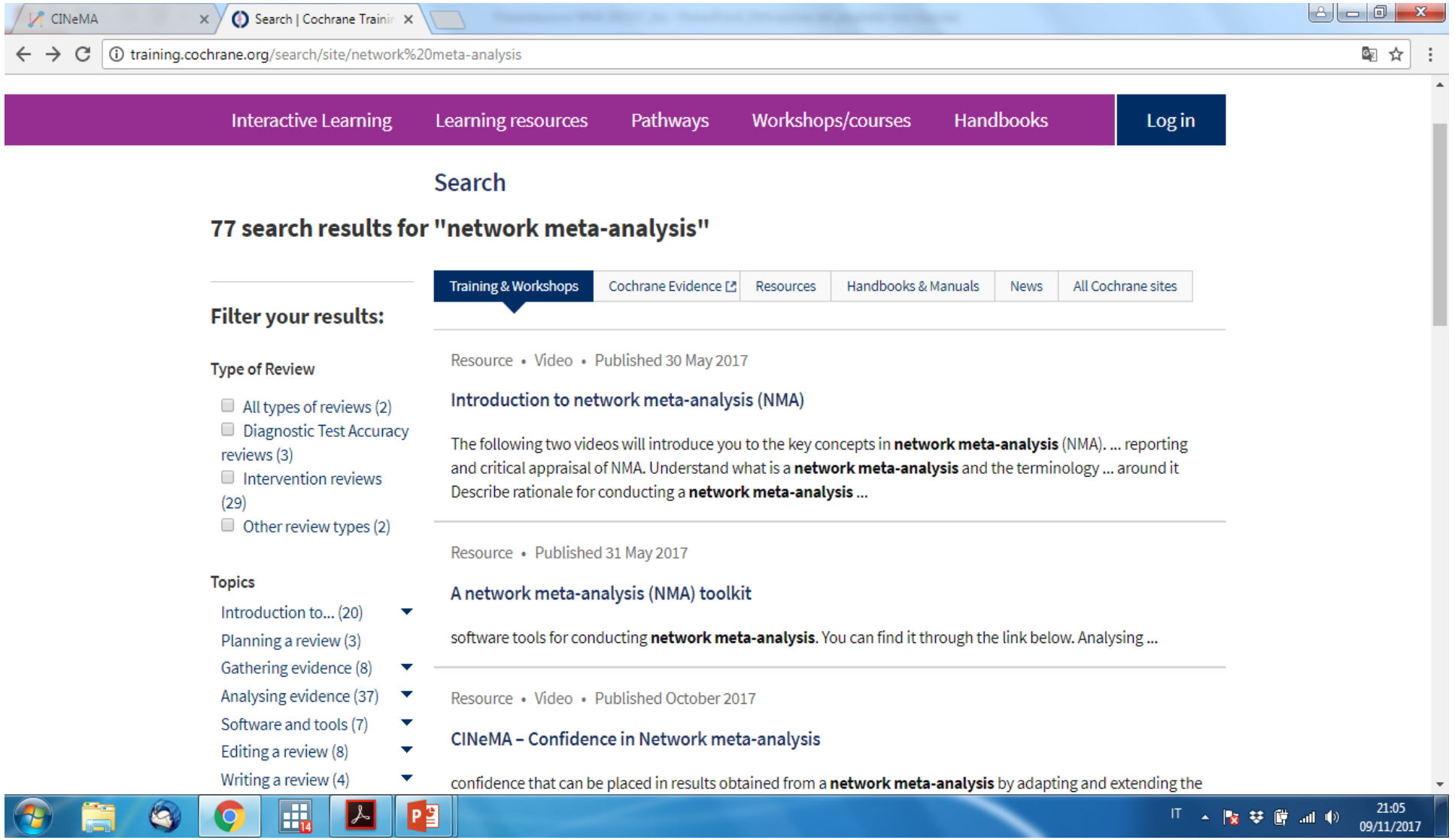
Meta-analysis is the statistical technique used to synthesize evidence from experiments addressing the same research question. It is often used to combine data from clinical trials regarding the relative effectiveness of two interventions in order, for example, to infer about whether antihypertensives 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**

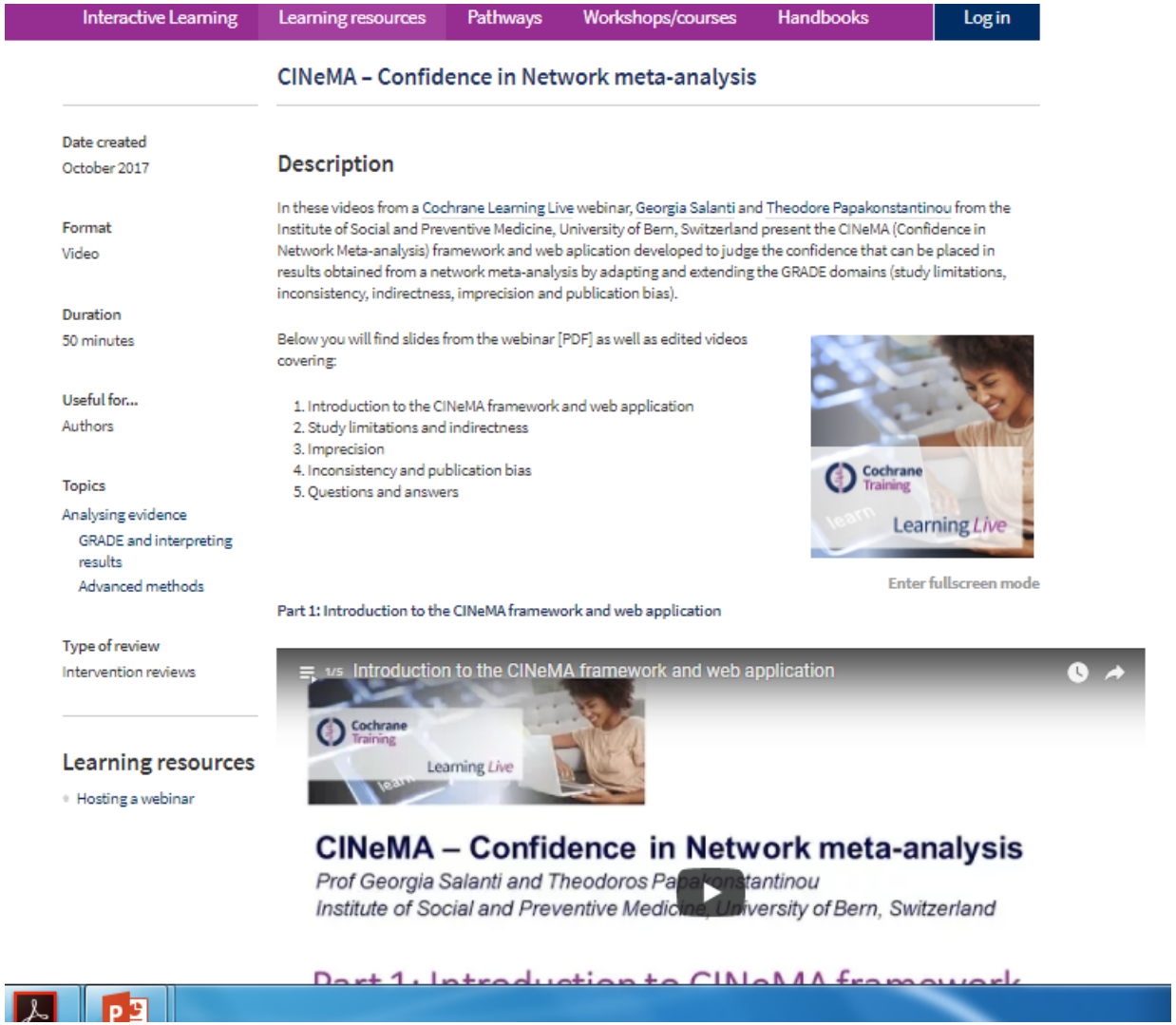
Cochrane Training on NMA

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



CINeMA

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



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