Statistical considerations in indirect comparisons and network meta-analysis

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Handout S10-L

Presenting and evaluating the evidence from network meta-analysis

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Reporting a network meta-analysis

- PRISMA items to report in meta-analysis

  Moher at al PLoS 2009
- Network meta-analysis needs more information
- Reporting in network meta-analysis is suboptimal

  See Donegan S et al. PLoS One 2010, Song F et al. BMJ 2009

Section/Topic	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or bo
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: backgr criteria, participants, and interventions; study appraisal and syr and implications of key findings; systematic review registratior
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is
Objectives	4	Provide an explicit statement of questions being addressed wi comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be acces registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) a language, publication status) used as criteria for eligibility, givi
Information sources	7	Describe all information sources (e.g., databases with dates of additional studies) in the search and date last searched.

Reporting a network meta-analysis (1)

- Describe a **clear rationale regarding the choice of interventions**, with respect to the condition and outcomes of interest.
  - Treatments need to be competing or alternative treatments for the condition of interest;
  - In principle, treatments should be '**jointly randomizable**'; meaning that a trial including all treatments would be clinically reasonable.
- Describe the inclusion criteria for patients and condition
- Report whether treatments will be included that are not of **direct interest but may provide useful indirect evidence** (as long as the risk of inconsistency and bias does not outweigh their value!)

Reporting a network meta-analysis (2)

- Report whether **transitivity** is likely to hold in the set of trials you expect to find
- Describe the intended **strategy to evaluate consistency** (including statistical and strategic approaches).
- Think about **possible sources of heterogeneity and inconsistency** by describing *a priori* any effect modifiers that may vary across studies and comparisons.
- Predefine whether network meta-analysis will be used to combine all identified studies (or whether planned for only on a subset of studies).
- Register the protocol?

Reporting a network meta-analysis (3)

- Identify and consider all studies that evaluate at least two of the treatments of interest. (report flow chart)
- **Report on heterogeneity** (e.g. calculate the heterogeneity variance, calculate I^2, derive predictive intervals, perform network meta-regression).
- **Report on inconsistency** (e.g. perform loop-based tests, implement inconsistency models, compare the fit of the models, perform network meta-regression).
- Report on estimation of the model fit of and the fit of alternative models, and check sensitivity to analysis assumptions.

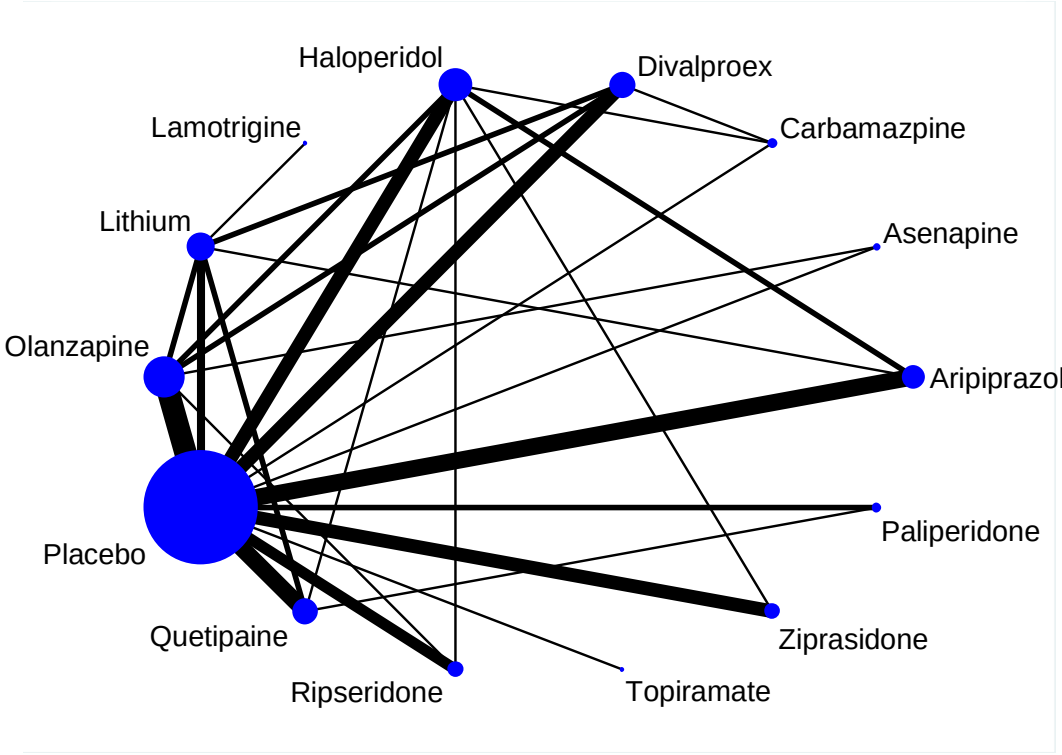
Reporting a network meta-analysis (4)

- Present **graphically the network** of trials (with information about number of studies informing each comparison).
- Provide (in an appendix if needed) individual **study data**.
- Present **estimates of direct and mixed effects** if possible and appropriate.
- Present the effect sizes for each treatment versus **a pre-defined reference treatment** as obtained from the network meta-analysis model.
- Explicitly **discuss issues of bias** and the validity of findings in the light of the presence/absence of consistency.

Graphical presentation of the network

STATA function `networkplot`

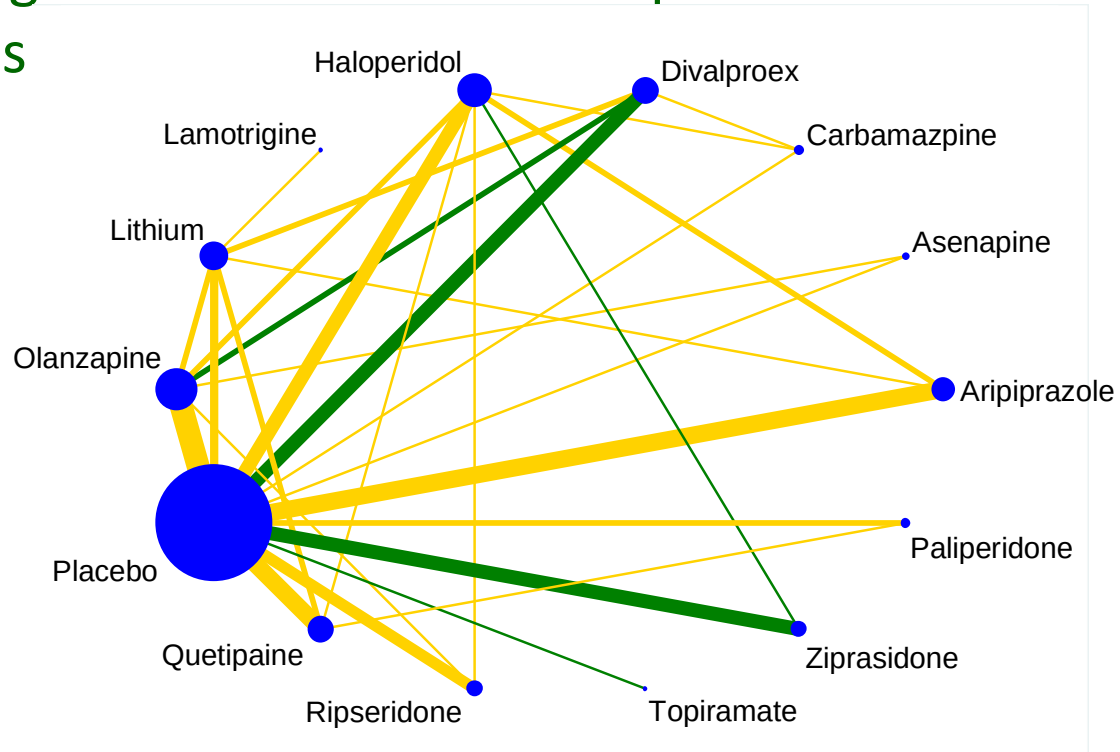
- Present the network with information on evidence characteristics
  - Nodes and edges: size can be proportional to number of studies, number of patients, mean age of participant in studies, price of the drug etc.



Graphical presentation of the network

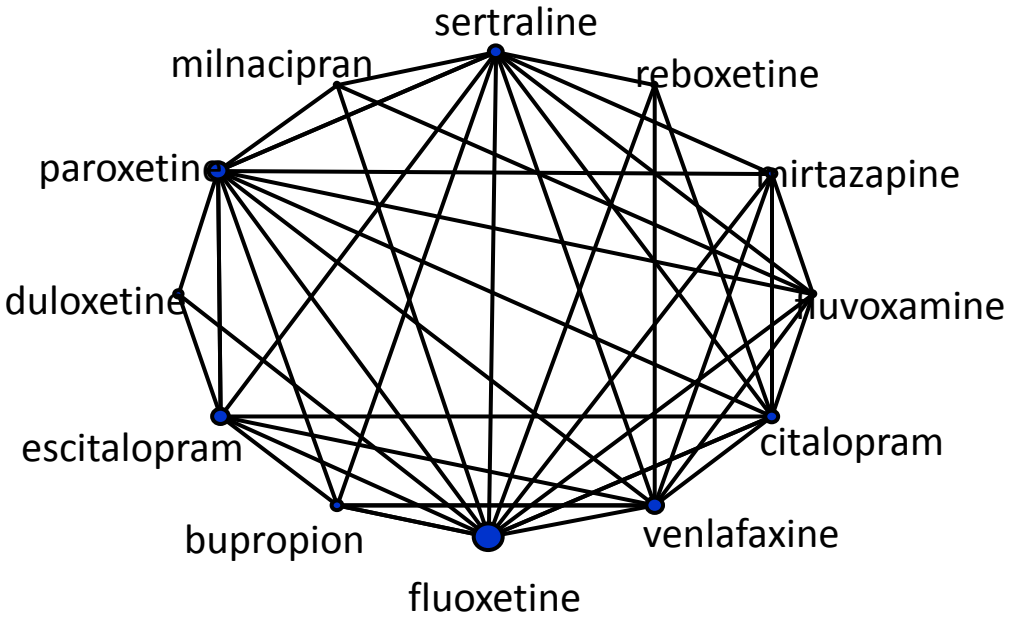
STATA function `networkplot`

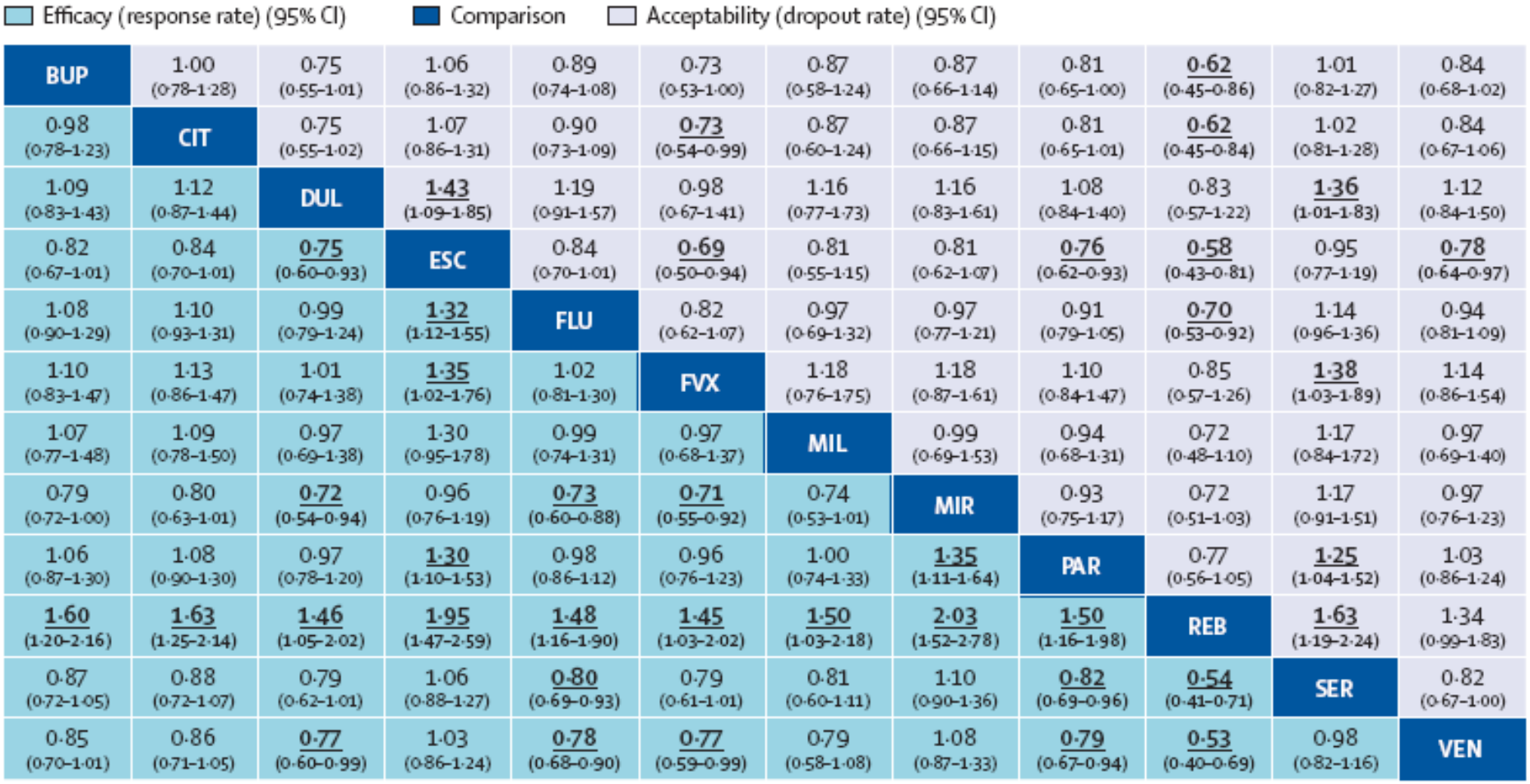
- Present the network with information on evidence characteristics
  - Nodes and edges: size can be proportional to number of studies, number of patients, mean age of participant in studies, price of the drug etc.
  - Nodes and edges color can be used to present risk of bias characteristics



Numerical presentation of results from network meta-analysis

- Typically effect sizes (and their uncertainty) for all pairwise comparisons are reported
- With many treatments judgments based on pairwise effect sizes are difficult to make
- Example: Antidepressants

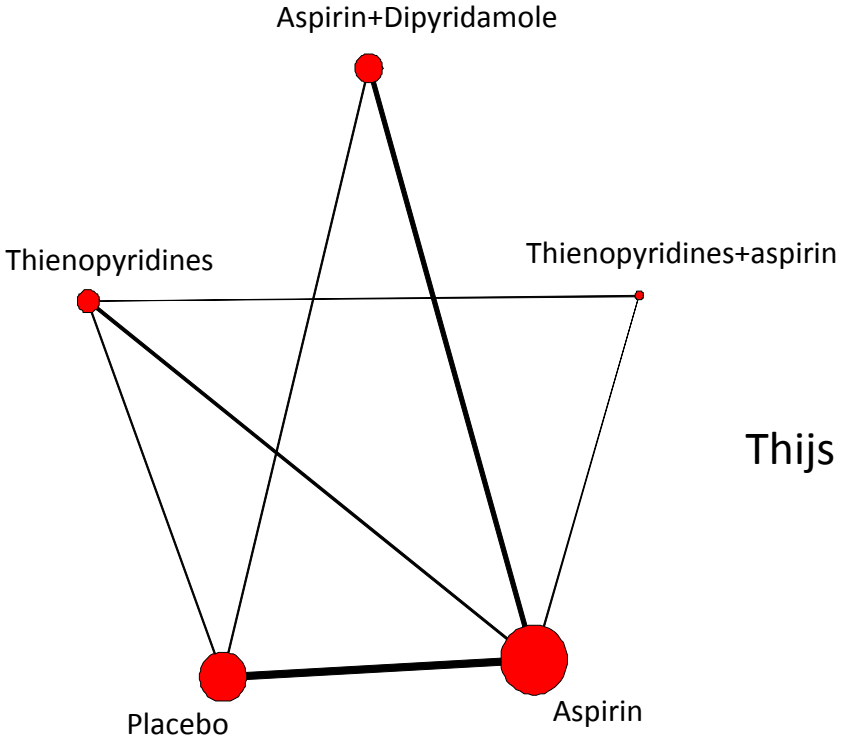




OR>1 means the treatment in top-left is better

Numerical and graphical presentation of results from network meta-analysis

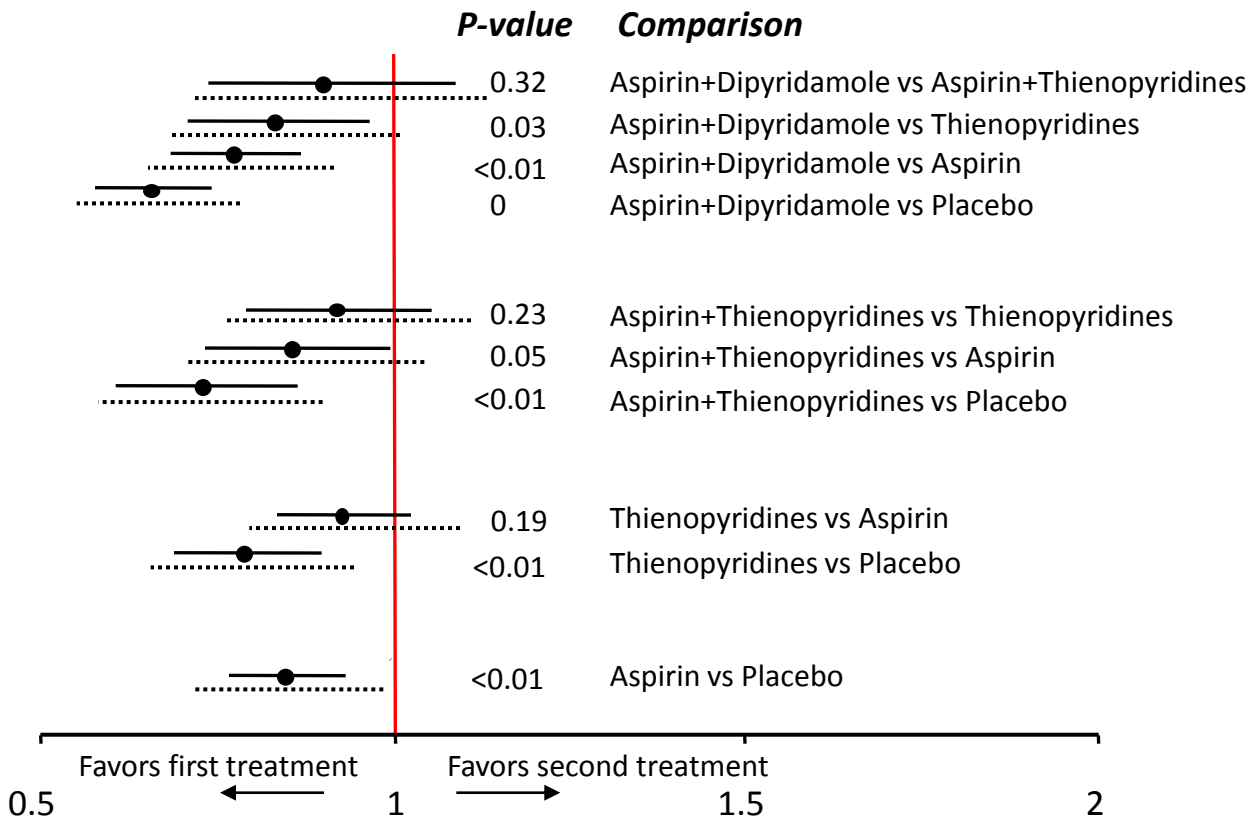
- With many treatments judgments based on pairwise effect sizes are difficult to make
- Example: Antidepressants
- Example: Antiplatelet regimens for serious vascular events



Thijs et al Eur Heart J 2008

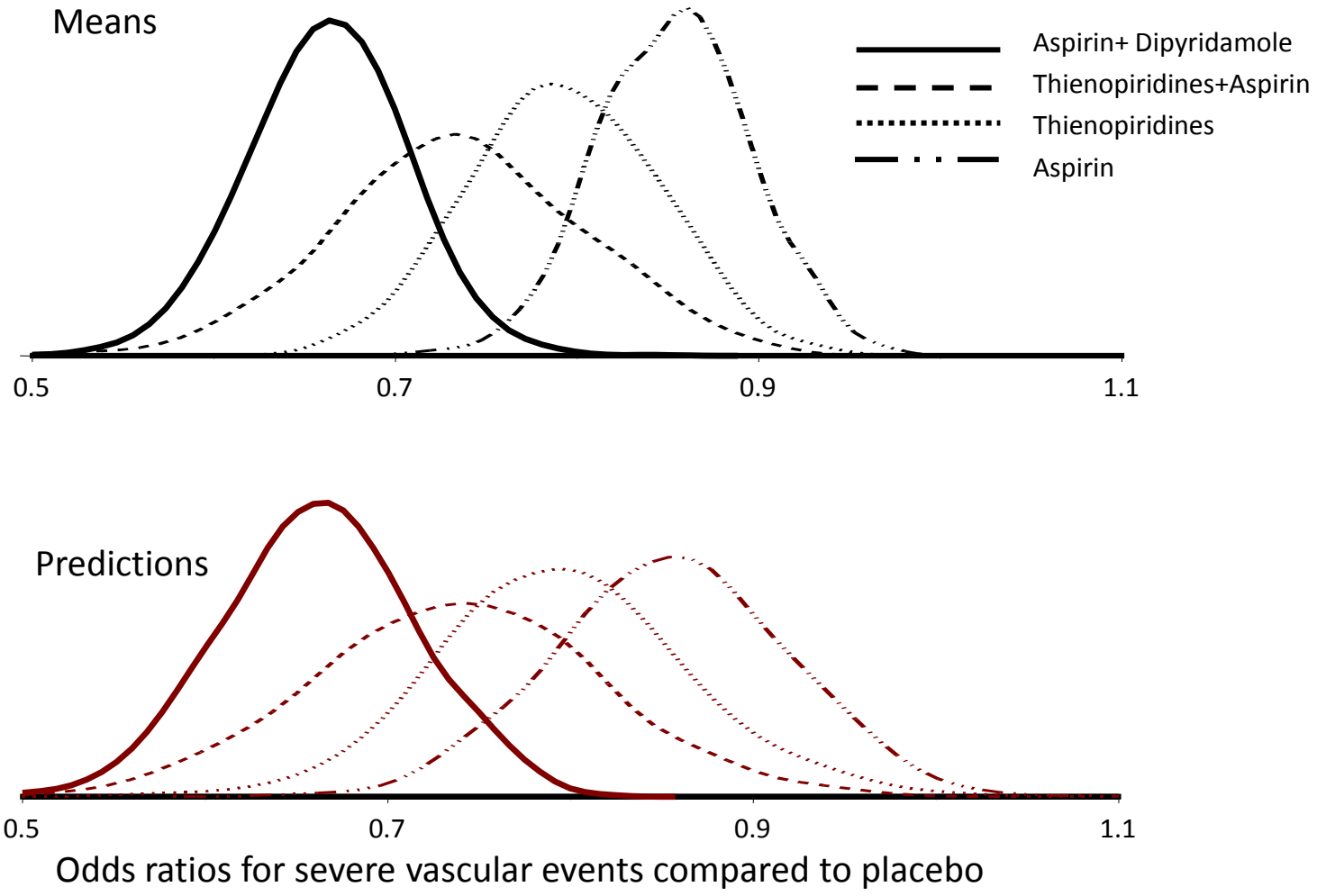
Serious vascular events with antiplatelet regimens: Network pairwise estimates

STATA function `intervalplot`



Odds Ratio for serious vascular event

Odds-ratios for serious vascular events with antiplatelet treatments compared to placebo

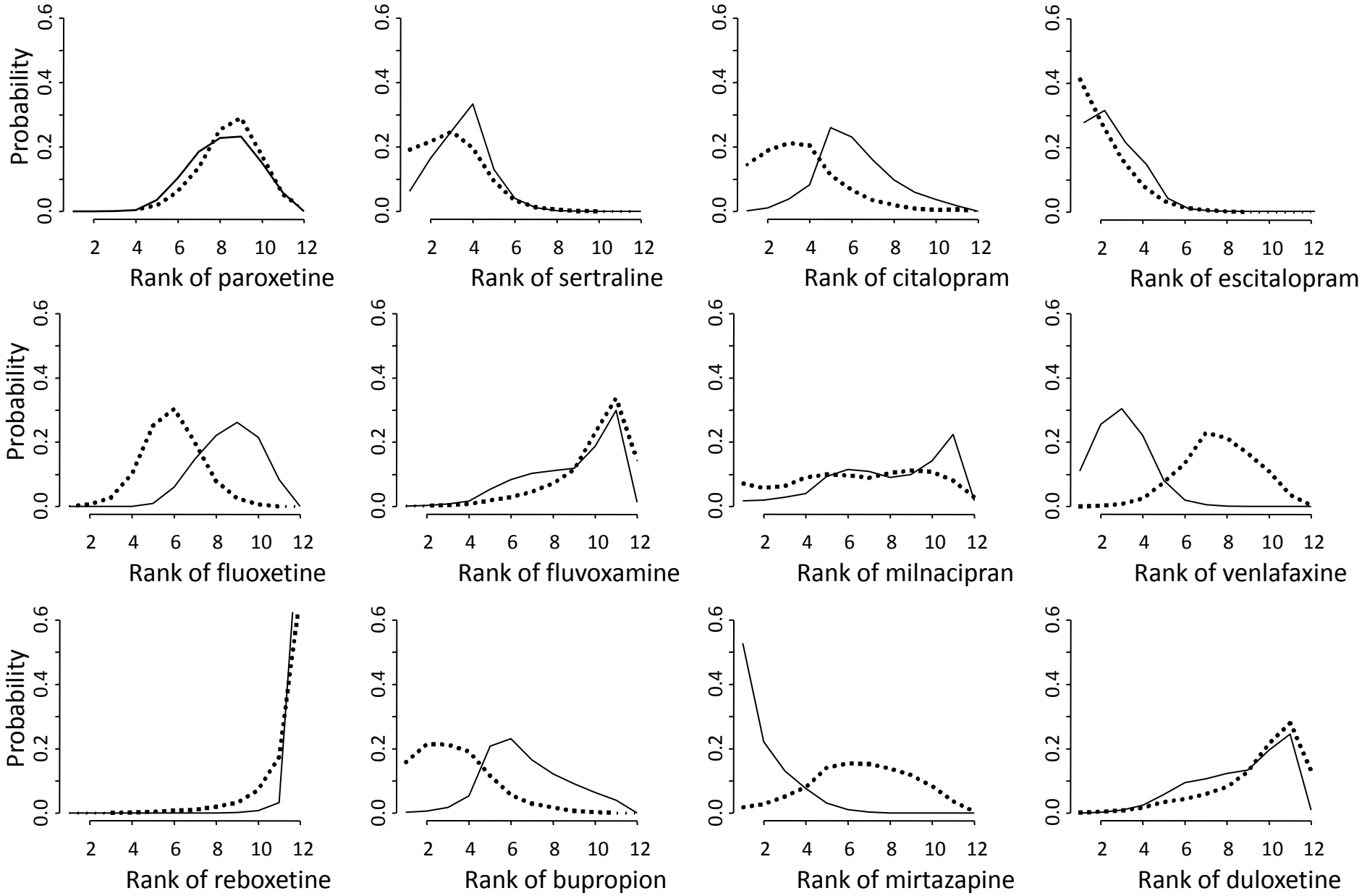


Salanti et al JCE 2011

Probabilities

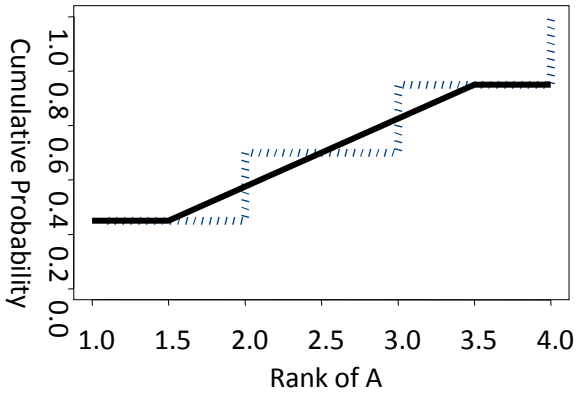
- Estimate for each treatment **the probability of being the best**
- This is straightforward within a Bayesian framework and fairly easy in frequentist setting (use re-sampling techniques)
  - Use the (posterior) distributions for all relative treatment effects
  - 'Draw' many random samples
  - Find which intervention outperforms in each sample
  - The number of times that an intervention ranks first out of the total number of random samples gives the P(best).

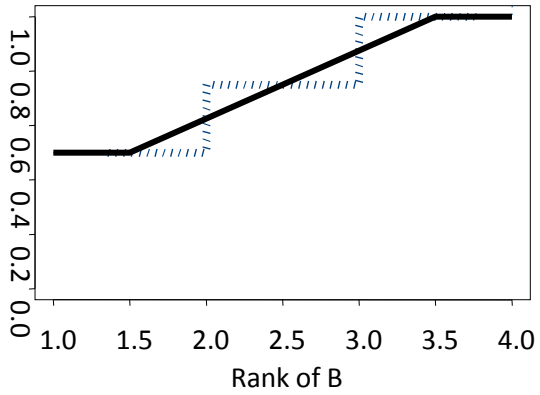
% probability	A	B	C	D
Best	0.25	0.50	0.25	0.00
Second	0.25	0.25	0.50	0.00
Third	0.25	0.25	0.25	0.25
Last	0.25	0	0	0.75

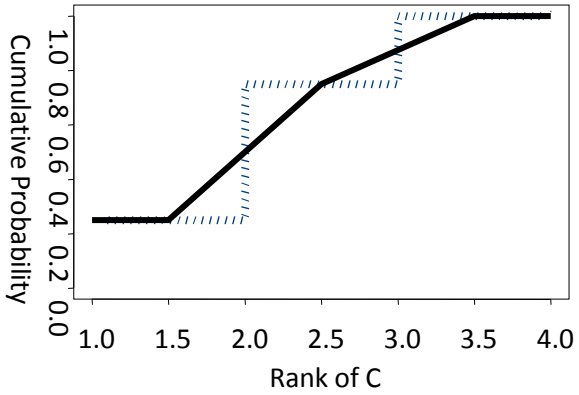


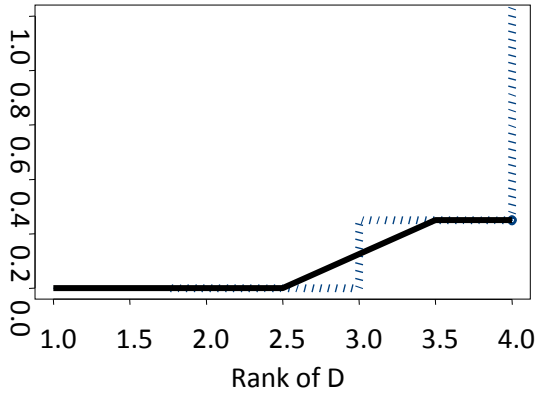
Ranking for efficacy (solid line) and acceptability (dotted line). Ranking: probability to be the best treatment, to be the second best, the third best and so on, among the 12 comparisons).

% probability	A	B	C	D
Best	0.25	0.50	0.25	0.00
Second	0.50	0.75	0.75	0.00
Third	0.75	1.00	1.00	0.25
Last	1.00	1.00	1.00	1.00









The areas under the cumulative curves for the four treatments of the example above are

A=0.5

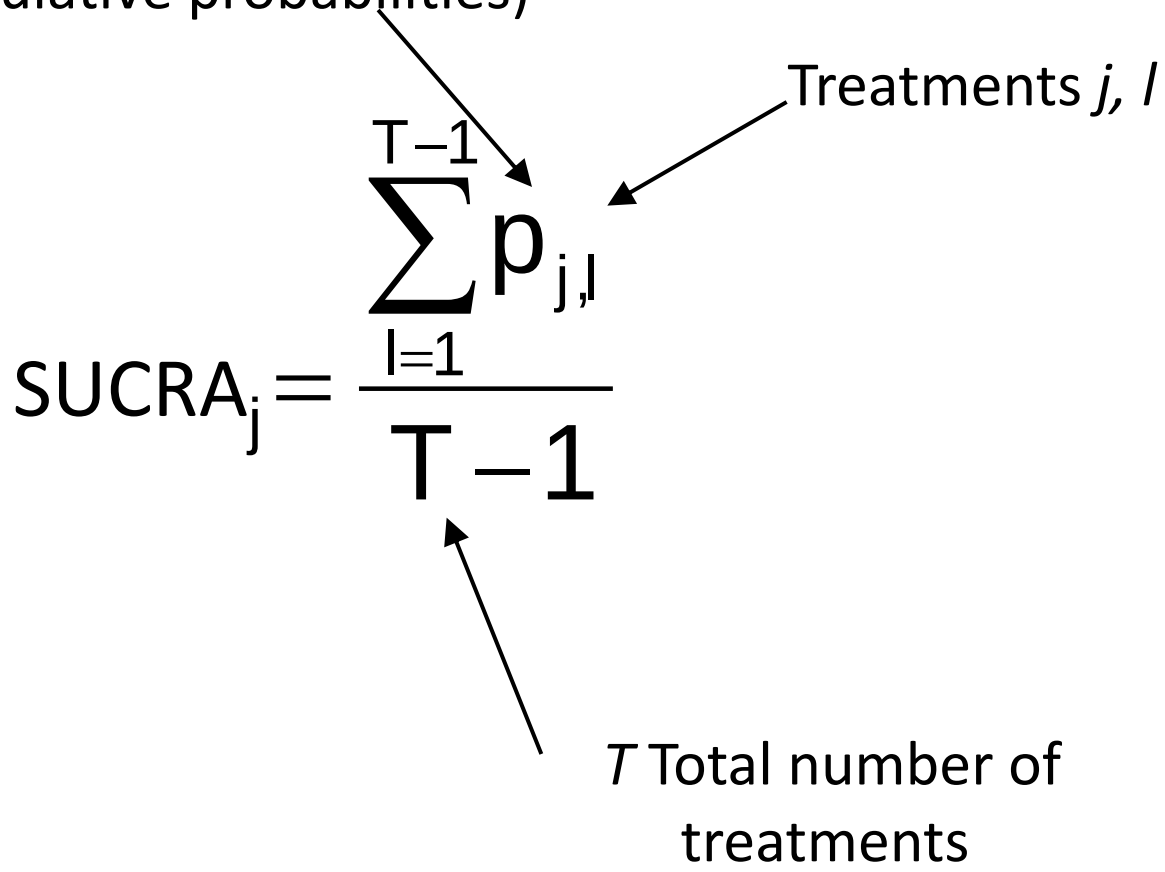
B=0.75

C=0.67

D=0.08

Surface Under the Cumulative RAnking curve (SUCRA)

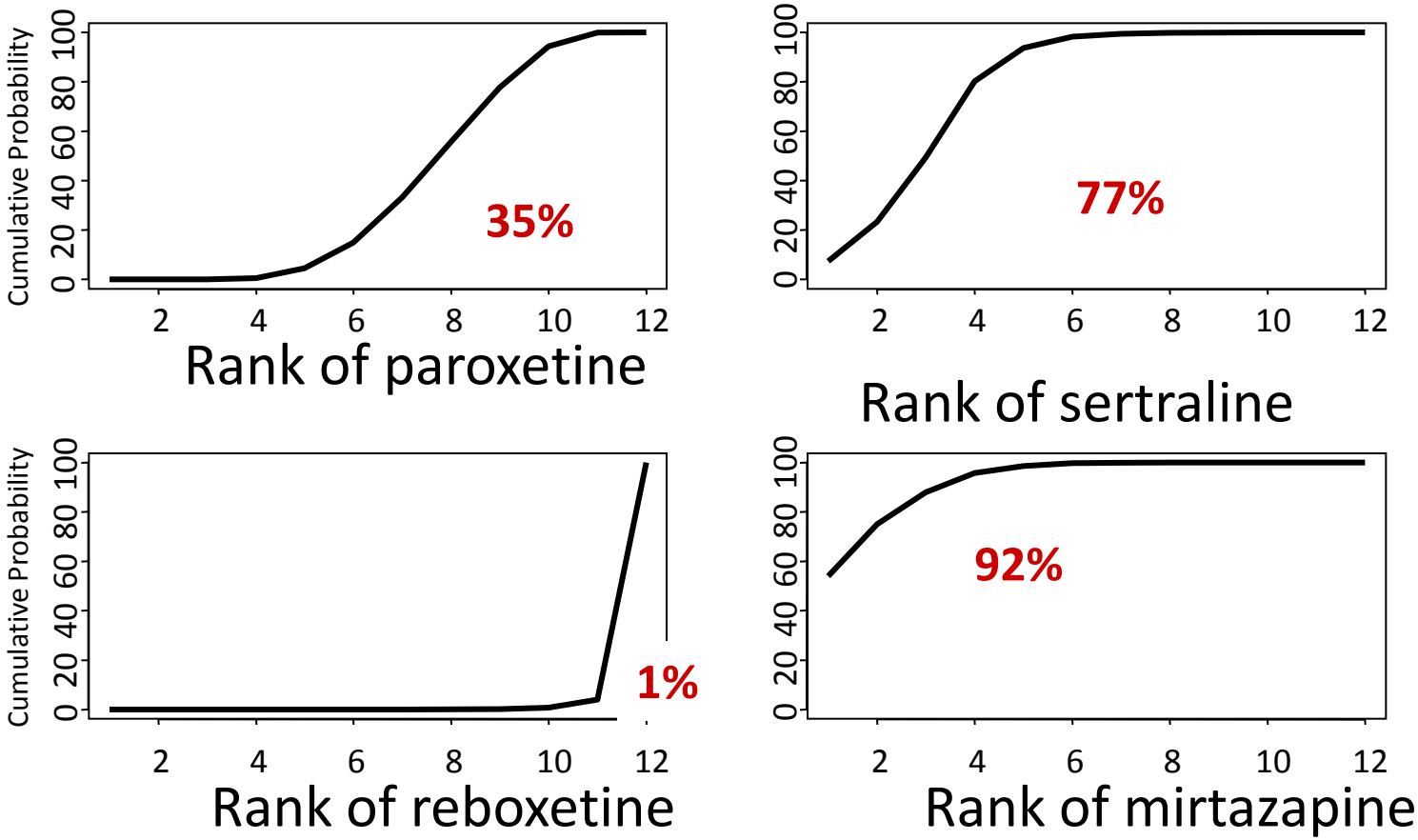
Use <u>posterior probabilities</u> for each treatment to be among the *n* - best options (cumulative probabilities)



Salanti et al JCE 2011

Surface Under the Cumulative RAnking curve

STATA function `sucra`



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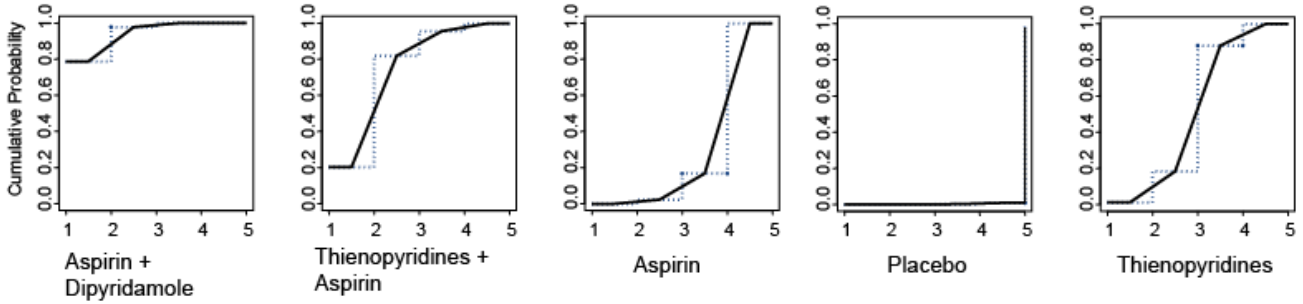
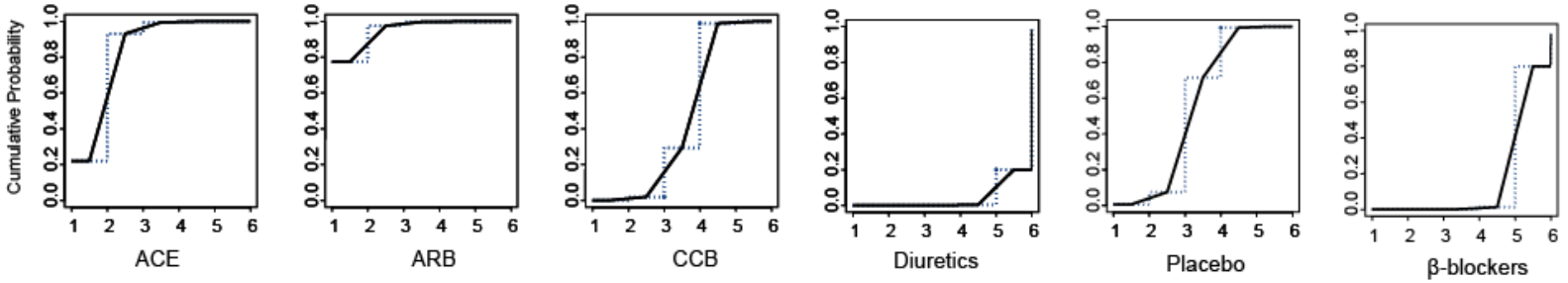
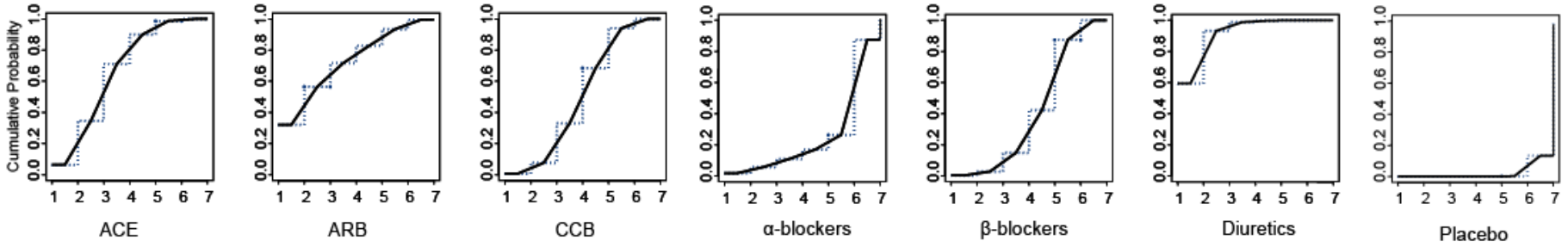
Serious vascular events with antiplatelet regimens



Incident diabetes with antihypertensive drugs



Serious cardiovascular event with antihypertensive drugs



Salanti et al JCE 2011

Ranking based on probabilities – caution is needed

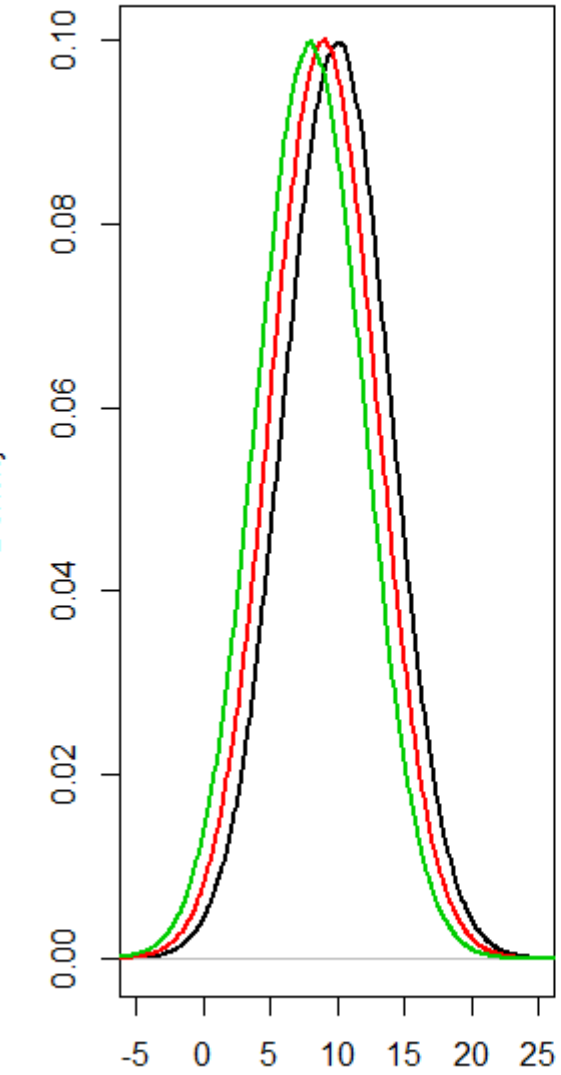
- Using P(best) to rank treatments can be misleading!
- Ranking based on SUCRAs accounts better for the uncertainty in the estimated treatment effects
- SUCRAs are conditional on the set of treatments being compared
  - This means SUCRAs and possibly the ranking will change if a subset of the treatments are compared
- Ranking measures are not a substitute for relative treatment effects!
  - They cannot be interpreted clinically

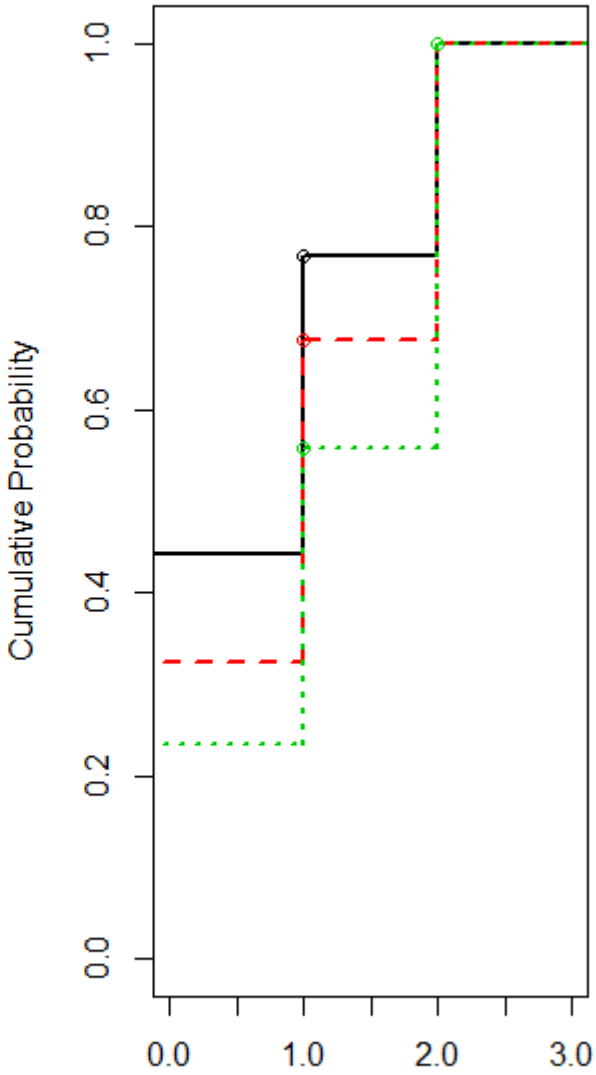
x~ N(10, 4)

y~ N(9, 4)

z~ N(8, 4)

	x	y	z
P(best)	0.44	0.33	0.23
P(sec)	0.33	0.35	0.32
P(third)	0.22	0.32	0.44
Sucras	***0.60***	***0.50***	***0.40***



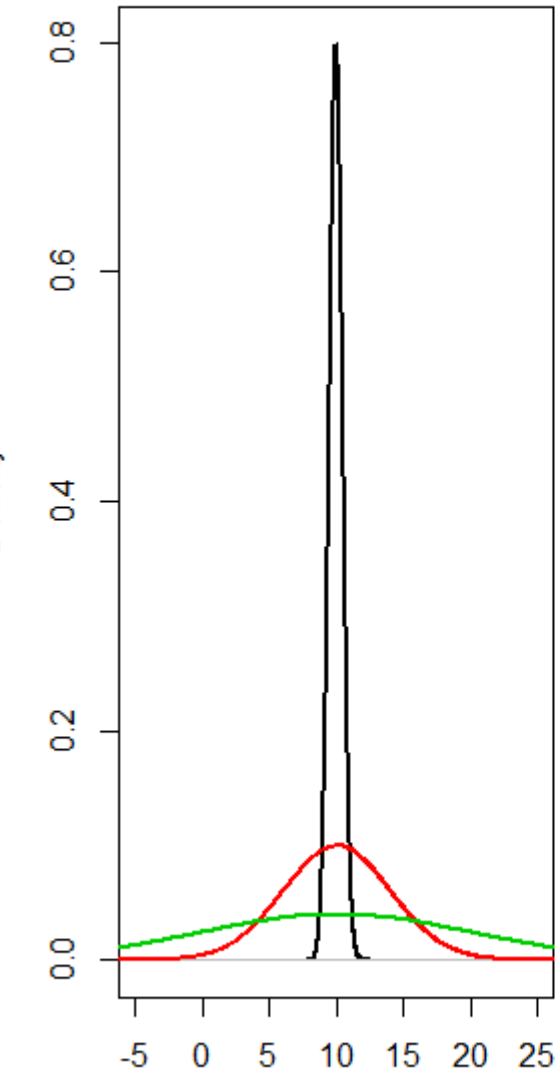


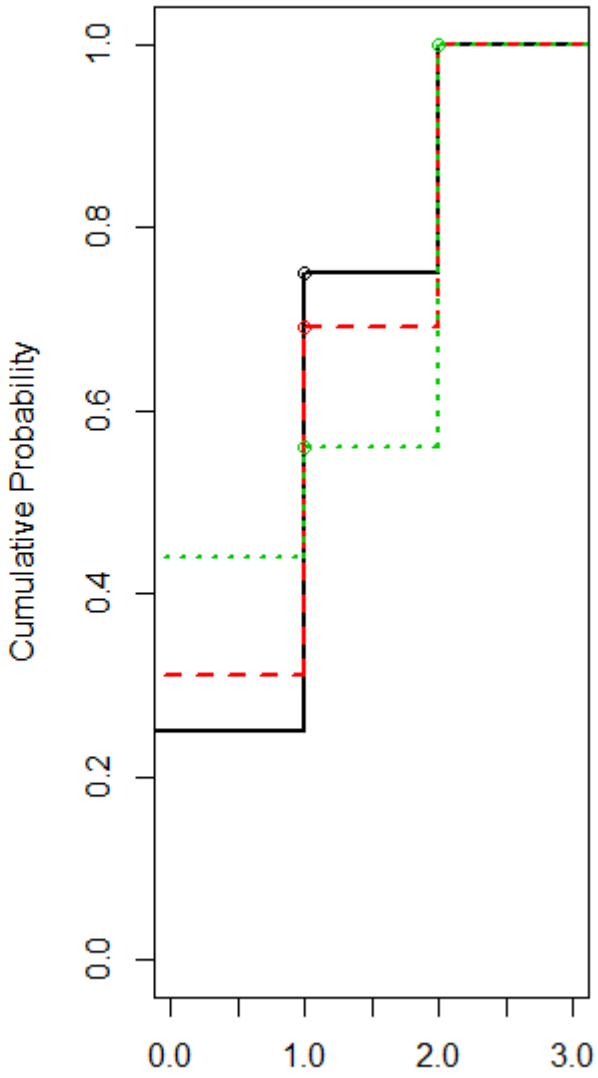
x~ N(10.0,5)

y~ N(10,4)

z~ N(10,10)

	x	y	z
P(best)	0.25	0.31	0.44
P(sec)	0.50	0.38	0.12
P(third)	0.25	0.31	0.44
Sucras	***0.50***	***0.50***	***0.50***



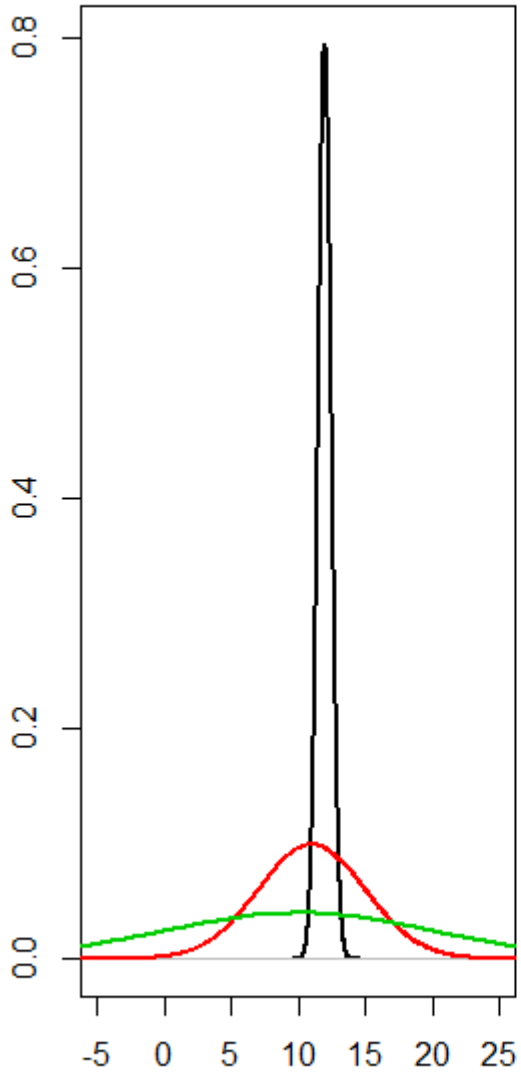


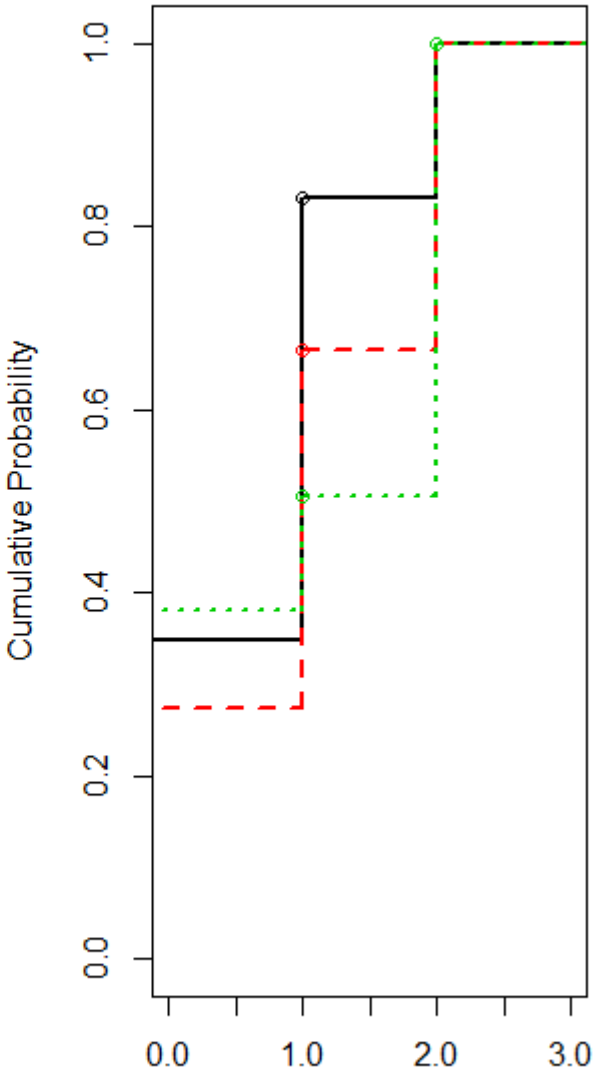
x~ N(12,0.5)

y~ N(11,4)

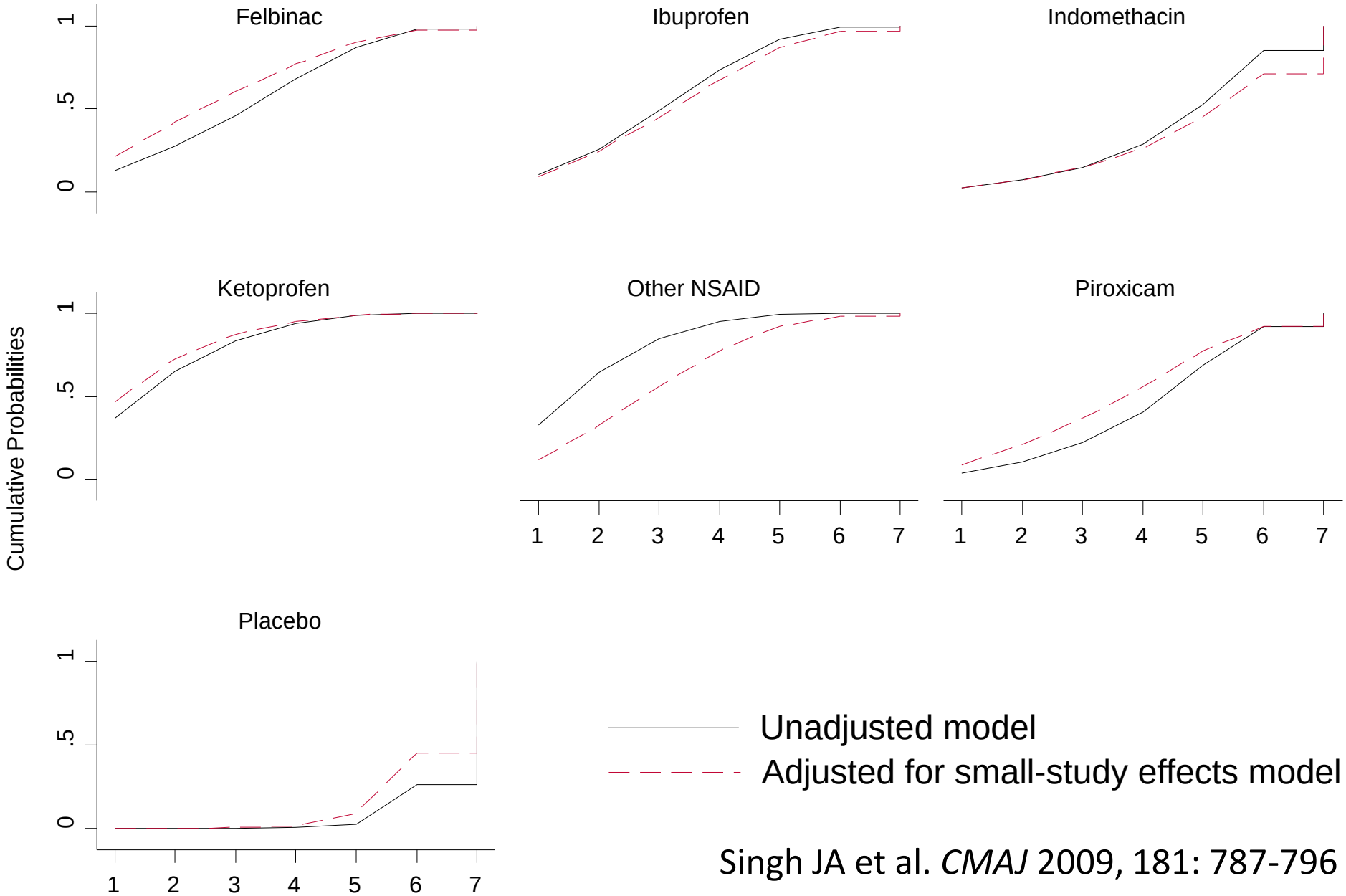
z~ N(10,10)

	x	y	z
P(best)	0.35	0.27	0.38
P(sec)	0.48	0.39	0.13
P(third)	0.17	0.34	0.50
Sucras	***0.60***	***0.47***	***0.44***



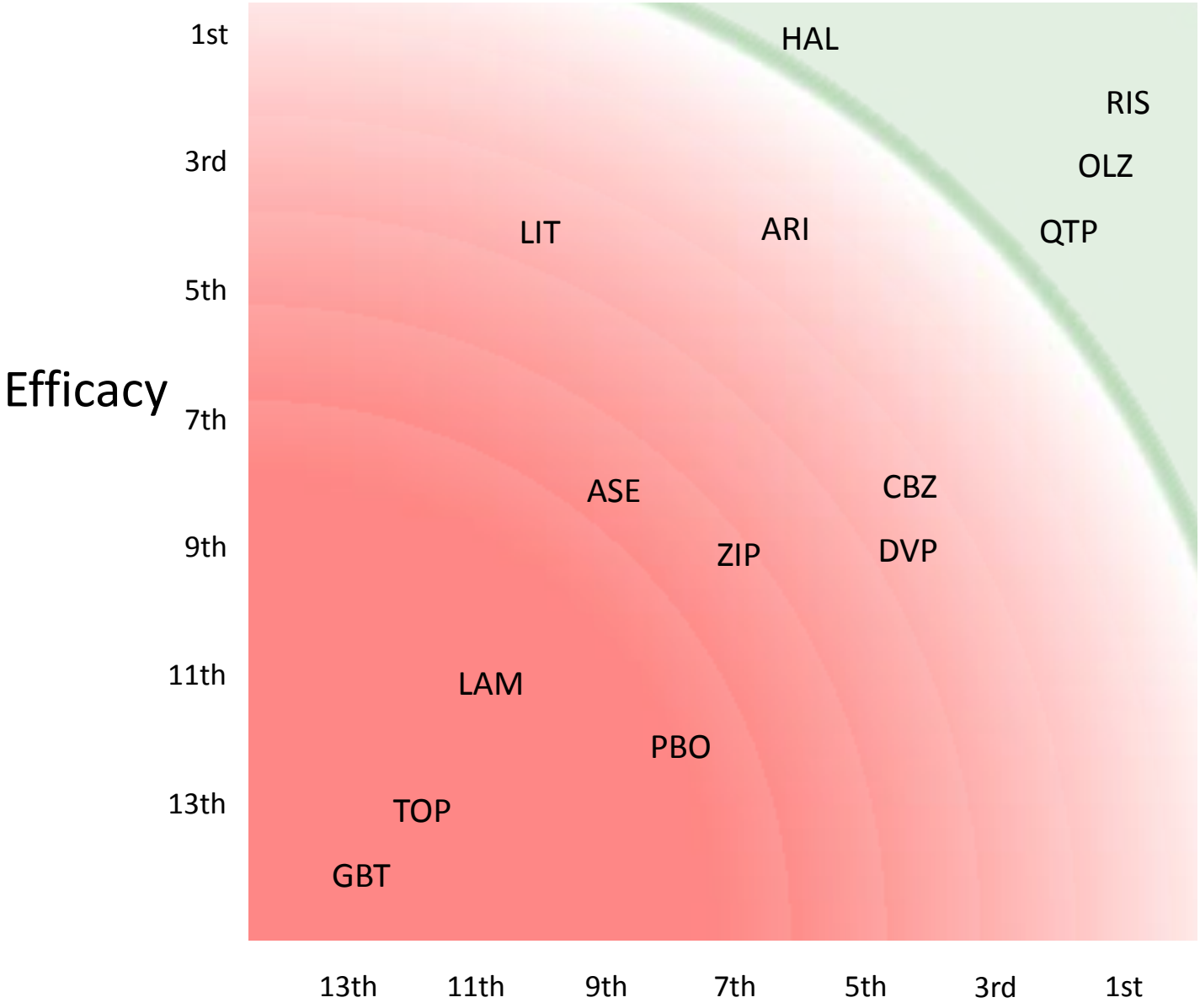


SUCRAs can be used to examine the impact of different models on ranking: ranking of treatments for RA



Singh JA et al. *CMAJ* 2009, 181: 787-796

Present ranking of treatments for two outcomes



(Cipriani et al Lancet 2011)

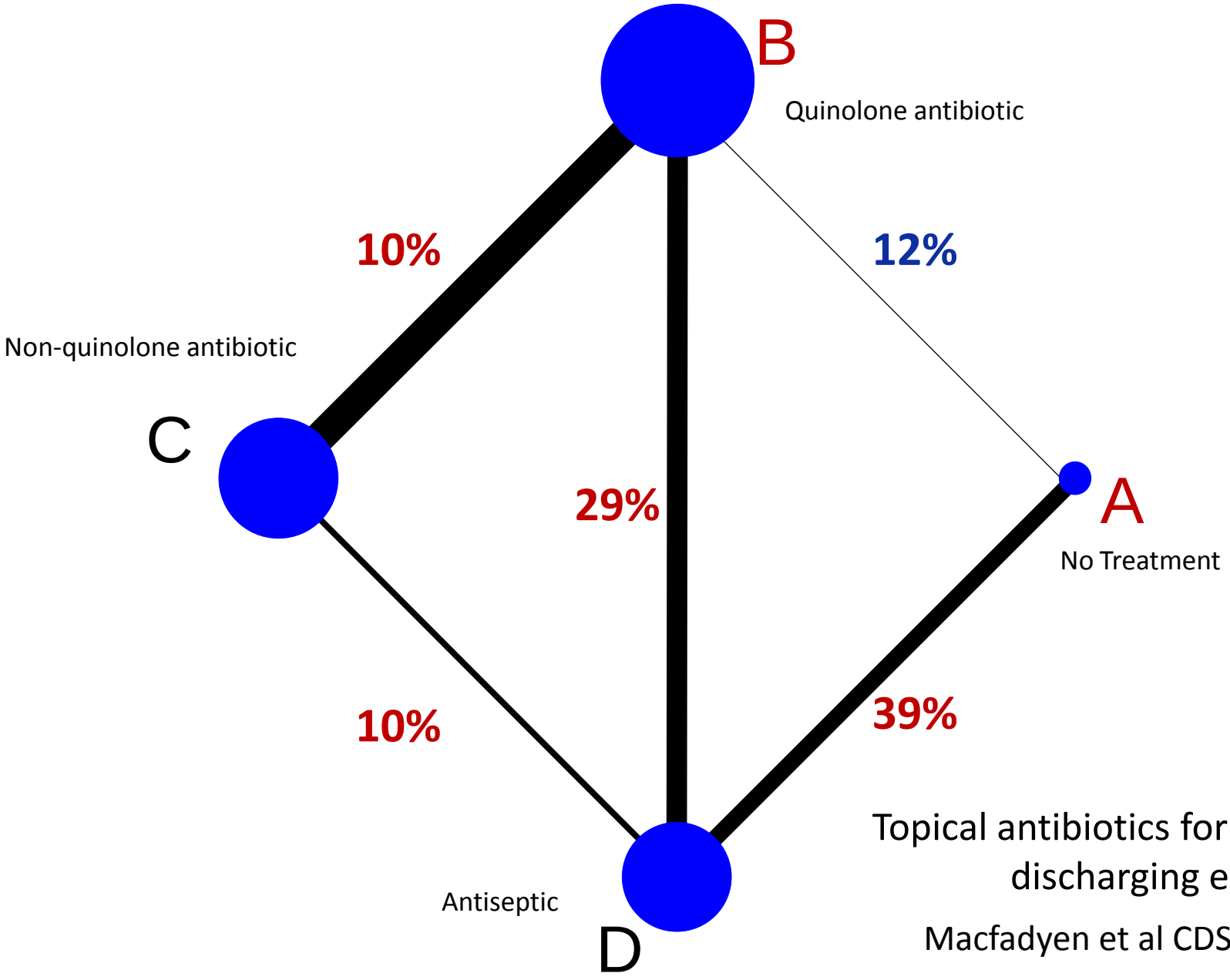
Grading the evidence from a network

- A network has two outputs: Pairwise network estimates and ranking
- We need to grade the evidence of each output separately
  - Grading each pairwise network estimate
  - Grade the ranking
- GRADE:
  - Study limitations
  - Indirectness
  - Inconsistency
  - Imprecision
  - Publication bias
- **All this is still work in progress!!**

Interpret the evidence from a network: principals

- Pieces of direct evidence contribute to the network relative treatment effects and the ranking
- The contribution of each piece of direct evidence is different
  - Precise direct comparisons (e.g. comparisons with many, large studies) contribute more
  - "Central" comparisons contribute more
- The **exact contribution** of each piece of evidence can be derived mathematically (using a fixed effects network meta-analysis model)
  - Koenig J et al., 33rd Annual Conference of the International Society for Clinical Biostatistics

Percentage contribution of each direct estimate to the network AB estimate



Topical antibiotics for chronically discharging ears

Macfadyen et al CDSR 2005

Direct Comparisons in the Network

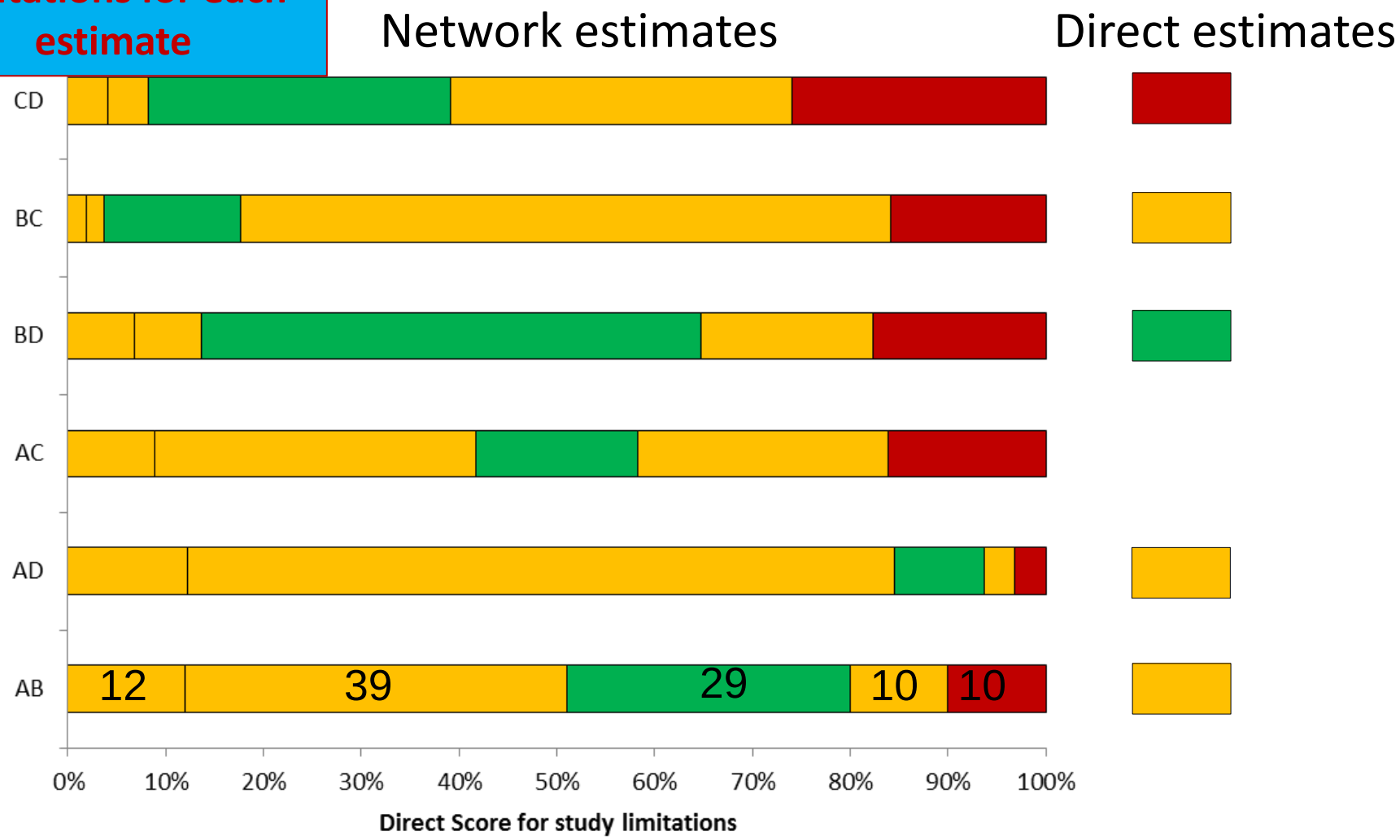
Network Meta-Analysis Estimates	AB	AD	BC	BD	CD
Mixed Estimates					
AB	12.0	39.0	10.0	29.0	10.0
AD					
BC					
BD					
CD					
Indirect Estimates					
AC	8.9	32.8	25.5	16.7	16.1

Percentage contribution of each direct estimate
STATA function `netweight`

		Direct Comparisons in the Network				
		AB	AD	BC	BD	CD
Network Meta-Analysis Estimates	Mixed Estimates					
	AB	12.0	39.0	10.0	29.0	10.0
	AD	12.3	72.3	3.1	9.1	3.2
	BC	1.9	1.9	66.6	13.9	15.8
	BD	6.8	6.8	17.6	51.2	17.6
	CD	4.1	4.1	35.0	30.9	25.9
	Indirect Estimates					
	AC	8.9	32.8	25.5	16.7	16.1
Entire Network		8.0	26.6	25.3	25.0	15.1
Included Studies		2	1	7	5	4

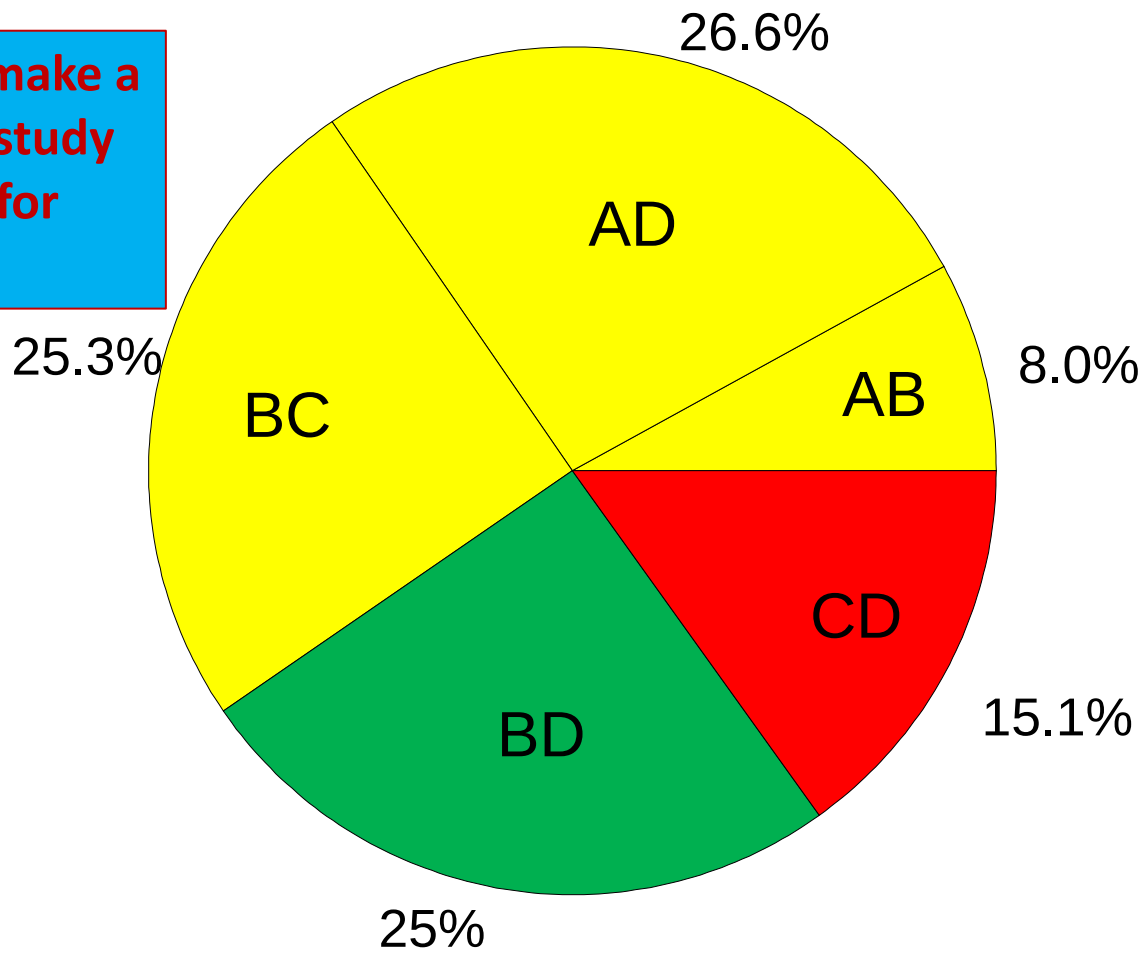
Evaluating Risk of Bias in the network estimates

Summarize to make a judgment for study limitations for each estimate



Evaluating Risk of Bias in the ranking

Summarize to make a judgment for study limitations for ranking



Evaluating inconsistency (1)

- **Inconsistency:** heterogeneity and network inconsistency
- Heterogeneity for each network estimate: as usual, plus consider the common τ^2
- Heterogeneity for ranking: consider the common τ^2
- How large is a large τ^2? Compare it to its empirical distribution

Empirical distributions for the heterogeneity variance (τ^2) across different categories of (dichotomous) outcome and intervention comparison

Outcome type	Pharmacological vs. Placebo	Pharmacological vs. Pharmacological	Non-Pharmacological (Any)
	50% quantile 75% quantile	50% quantile 75% quantile	25% quantile 50% quantile
All-cause mortality	0.007 1.017	0.005 1.014	0.007 1.02
Semi-Objective	0.014 1.05	0.011 1.04	0.016 1.058
Subjective	0.34 1.12	1.10 3.28	0.045 1.14

Turner et al Int J Epidemiol 2012

Evaluating inconsistency (2)

- **Inconsistency for each network estimate:** Evaluate inconsistency placing emphasis on how much each piece of direct evidence fits together with the indirect evidence
  - apply node splitting or the loop-specific approach
- **Inconsistency for ranking:** Evaluate the assumption of consistency as a whole
  - Lu& Ades model
  - Design by treatment model
- Do NOT rely on statistical tests: Evaluate the transitivity assumption!

Our STATA functions

- You can get the functions by typing in STATA

```
net from http://www.mtm.uoi.gr
```

```
intervalplot      Predictive intervals plot
ifplot            Inconsistency plot
netfunnel         Comparison-adjusted funnel plot
netweight         Contribution plot
networkplot       Network plot
sucra             Ranking plots for a single outcome using probabilities
```

Please cite our site www.mtm.uoi.gr and acknowledge **Anna Chaimani**, Dimitris Mavridis, Julian Higgins, Georgia Salanti

(we hope our paper will be submitted soon….)

References (Methods)

- Donegan S, Williamson P, Gamble C, Tudur-Smith C: Indirect comparisons: a review of reporting and methodological quality. *PLoS One* 2010, 5: e11054.
- Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG: Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009, 338: b1147.
- Salanti G, Ades AE, Ioannidis JP. 2011 Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 64(2):163-71
- Koenig J, Krahn U, Binder H: Adapting Cochran's Q for Network Meta-Analysis. Edited by Edited by 33rd Annual Conference of the International Society for Clinical Biostatistics: Bergen, Norway; 2012:44.
- 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.

References (Applications)

- Cipriani A, Furukawa TA, Salanti G, et al 2009 Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 373(9665):746-58.
- Cipriani A, Barbui C, Salanti G et al. 2011 Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011 Oct 8;378(9799):1306-15.
- Thijs V, Lemmens R, Fieuws S. 2008. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. *Eur Heart J* 29(9): 1086-1092.
- Macfadyen CA, Acuin JM, Gamble C. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. Cochrane Database Syst Rev 2005;CD004618
- Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA *et al*.: A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ* 2009, 181: 787-796.