LIFE SCIENCE ACADEMY

Fabrizio D'Ascenzo, MD Division of Cardiology
Prof. Fiorenzo Gaita, MD Division of Cardiology
Prof. Mauro Gasparini, Phd Politecnico di Torino

AIM OF THE COURSE

A critical appraisal of:

- Pairwise meta-analysis

- Network meta-analysis

TODAY'S PROGRAM: FIRST PART

1) Meta-analysis: general concepts
2) Statistics and Evidence-Based Medicine
3) Quick assessment of Meta-analysis
4) Critical assesment of Meta-analysis

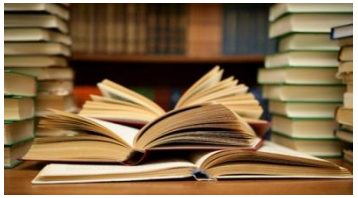
WHAT ARE WE TALKING ABOUT?

Meta analysis = pooling results from different studies

- ✓Head to head or Pairwise Metanalysis (PWMA) = several studies of the same intervention vs. the same control

- ✓Network Metanalysis (NMA)/Mixed Treatment Comparison (MTC) = different treatments againts one another, possibly with a common comparison.

SOME HISTORY



•1904 - Karl Pearson (UK): correlation between inoculation of vaccine for typhoid fever and mortality across apparently conflicting studies

•1931 – Leonard Tippet (UK): comparison of differences between and within farming techniques on agricultural yield adjusting for sample size across several studies

•1937 – William Cochran (UK): combination of effect sizes across different studies of medical treatments

•1970s – Robert Rosenthal and Gene Glass (USA), Archie Cochrane (UK): combination of effect sizes across different studies of, respectively, educational and psychological treatments

•1980 – Aspirin after myocardial infarction. Lancet 1980;1:1172–3

•1980s – Diffuse development/use of meta-analytic methods

STATISTICS AND EVIDENCE-BASED MEDICINE

PAIRWISE META-ANALYSIS

Direct comparison of the same intervention vs control.

We need some basic statistics:

- Relative measures of effect
- Confidence intervals (CI)
- P values
- Forest plots
- Regression = statistical dependence

RELATIVE MEASURES OF EFFECT

– For continuous variables:
  - Mean difference
  - Standardized mean difference

– For binary variables:
  - Odds Ratio
  - Relative Risk
  - Absolute Risk
  - Number Needed to Treat

- For times to events (e.g. Overall survival or disease free survival):
  - Hazard Ratio
  - Odds Ratio

RELATIVE RISKS of A vs. B

Relative risks (RR) are defined as the ratio of incidence rates

	Events yes	**Events no**
Group A	Z	Y
Group B	W	H

RR= [Z/(Z+W)]/[Y/(Y+H)]

- *RR=1* no difference in risk
- *RR<1* reduced risk in group 1 vs 2
- *RR>1* increased risk in group 1 vs 2

ODDS RATIOS

Odds ratios (OR) are defined as the ratio of the odds

	Events yes	**Events no**
Group A	Z	Y
Group B	W	H

OR= (Z/W)/(Y/H)

When prevalences are low, OR is a good approximation of RR.

RISK DIFFERENCES and NUMBER NEEDED TO TREAT/HARM

The risk difference (RD), ie absolute risk difference, is the difference between the incidence of events in the A vs. B groups.

The number to treat (NNT), defined as 1/RD, identifies the number of patients that we need to treat with the experimental therapy to avoid one event*

Rd and NNT change too much with disease prevalence.

**Numbers needed to harm (NNH) similarly express the number of patients that we have to treat with the experimental therapy to cause one adverse event*

RR, OR or RD/NNT?

	OR	RR	RD/NNT
Communication	-	+	++
Consistency	+	++	-
Mathematics	++	-	-

ICS VS PLACEBO: A FOREST PLOT

Effects of inhaled corticosteroids on airway inflammation in chronic obstructive pulmonary disease: a systematic review and meta-analysis

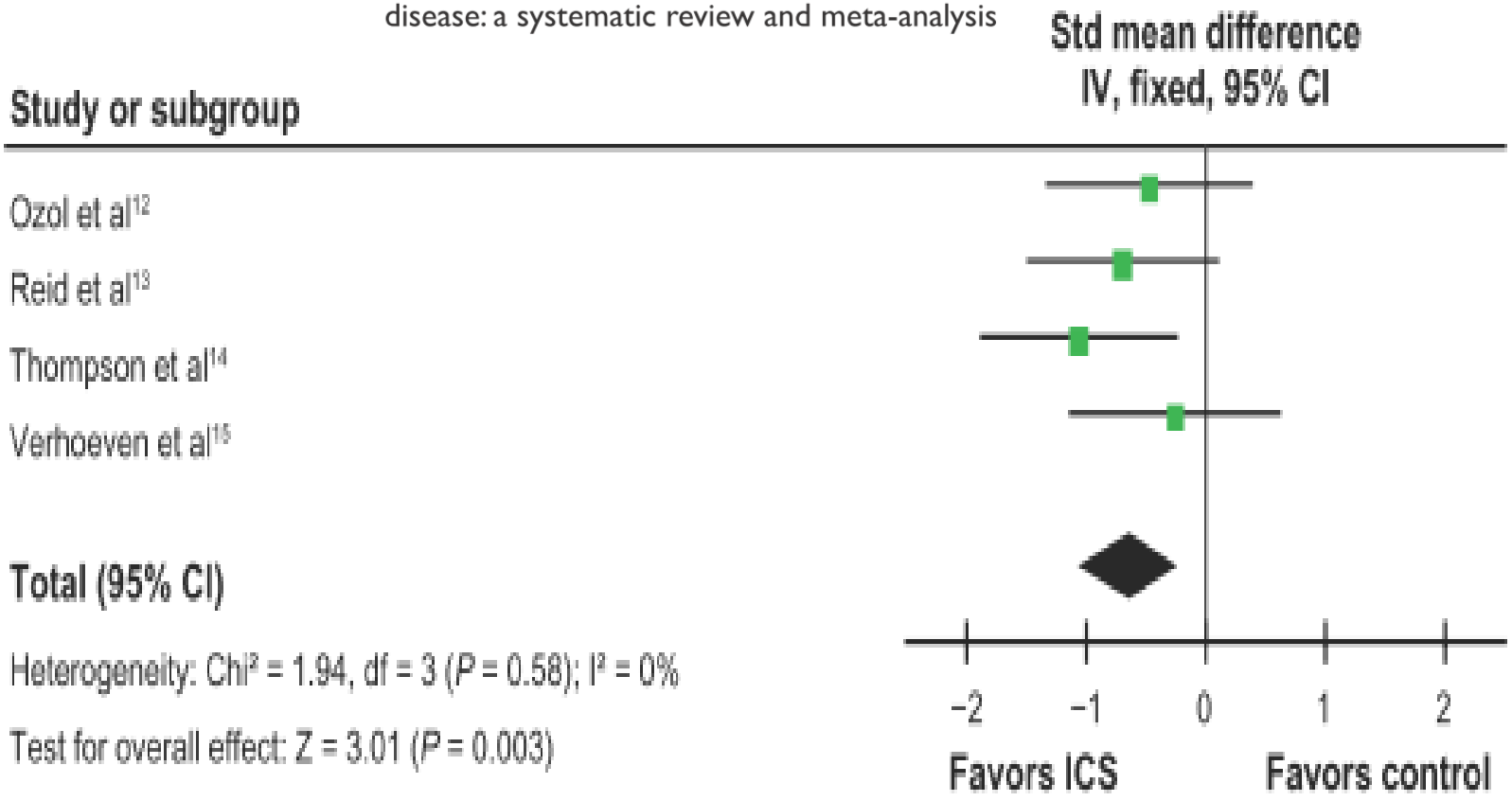


Figure 2 Effects of inhaled corticosteroids (ICS) on neutrophils in the bronchoalveolar levage (BAL) of stable chronic obstructive pulmonary disease (COPD) patients.
Abbreviations: CI, confidence interval; FP, fluticasone propionate; IV, intravenous; SFC, salmeterol-fluticasone combination; mon, months; Std, standard.

GRADING THE EVIDENCE (from NICE)

Level of evidence	Type of evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2^{++}	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

PRISMA

TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES

Home | News | The PRISMA Statement | History | Endorsing PRISMA

27 items to appraise quality of a meta-analysis.

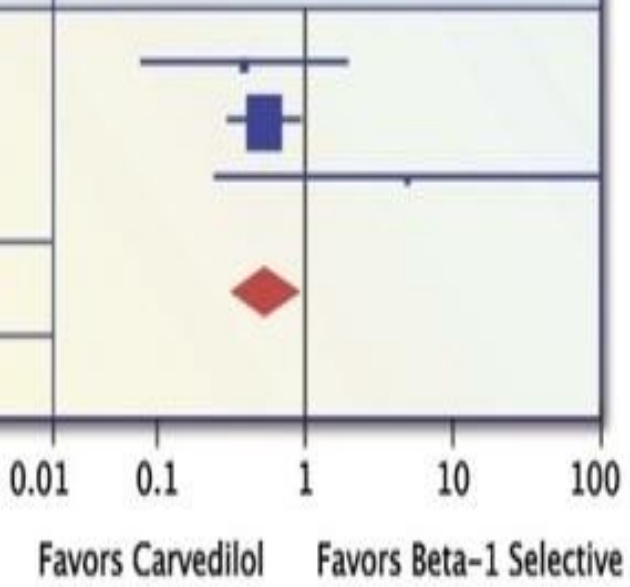
Too many? Only boring theory?

Meta-Analysis of *Carvedilol* Versus Beta 1 Selective Beta-Blockers (*Atenolol, Bisoprolol, Metoprolol,* and *Nebivolol*)

www.ajconline.org

James J. DiNicolantonio, PharmD[a,*], Carl J. Lavie, MD[b,c], Hassan Fares, MD[b], Arthur R. Menezes, MD[b], and James H. O'Keefe, MD[d]

Study or Subgroup	Carvedilol Events	Carvedilol Total	Beta-1 Selective Events	Beta-1 Selective Total	Weight	Risk Ratio IV, Fixed, 95% CI
Jonsson 2005	2	118	5	114	11.1%	0.39 [0.08, 1.95]
Mrdovic 2007	15	155	29	158	85.7%	0.53 [0.29, 0.94]
Tolg 2006	2	50	0	49	3.2%	4.90 [0.24, 99.57]
Total (95% CI)		**323**		**321**	**100.0%**	**0.55 [0.32, 0.94]**
Total events	19		34			



Heterogeneity: $Chi^2 = 2.23$, $df = 2$ ($P = 0.33$); $I^2 = 10\%$

Test for overall effect: $Z = 2.19$ ($P = 0.03$)

Figure 3. Forest plot of relative risk for all-cause mortality in patients with AMIs.

Ok! I will give carvedilol to my patients, and they will die less after 5 years…

…or maybe not?

Study or Subgroup	Carvedilol Events	Carvedilol Total	Beta-1 Selective Events	Beta-1 Selective Total	Weight	Risk Ratio IV, Random, 95% CI
Jonsson 05	2	118	5	114	16.4%	0.39 [0.08, 1.95]
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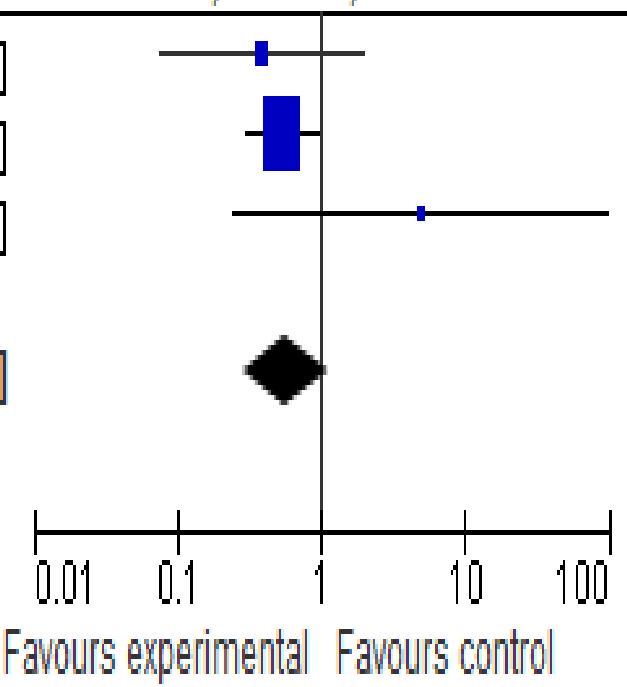
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 2.23$, df = 2 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 1.64 (P = 0.10)



Find the difference…

DIFFERENT LEVELS OF INTERPRETATION

FIRST LEVEL:

quick assesment of meta-analysis accuracy.

DIFFERENT LEVELS OF INTERPRETATION

SECOND LEVEL:

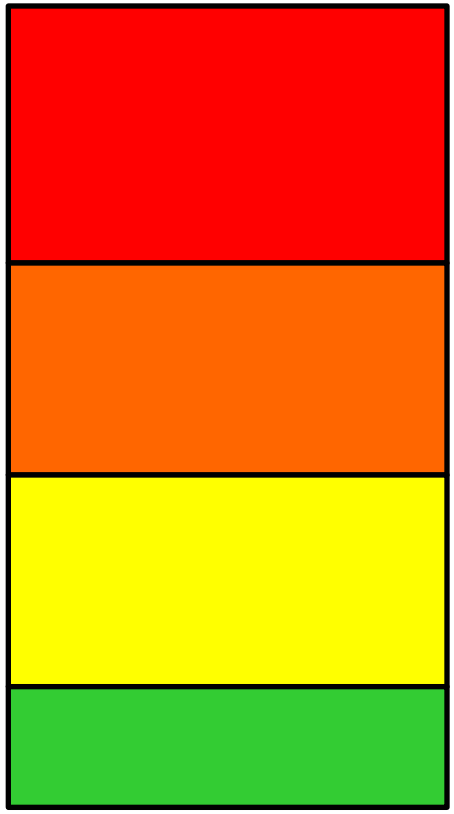
critical assessment of meta-analysis accuracy.

QUICK ASSESSMENT

QUICK ASSESSMENT

Heterogeneity probably represents the most important feature to assess in a meta-analysis.

COMPONENTS OF HETEROGENEITY



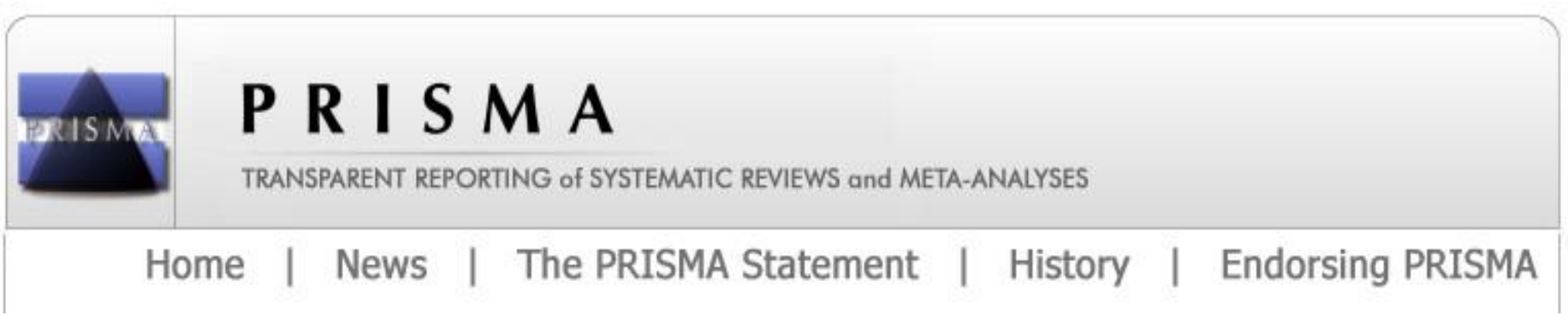
CLINICAL HETEROGENEITY

METHODOLOGICAL HETEROGENEITY

STATISTICAL HETEROGENEITY

PLAY OF CHANCE

CLINICAL and METHODOLOGICAL HETEROGENEITY



- ✓ Inclusion/exclusion criteria of studies
- ✓ Definition of endpoints (primary,secondary)

SELECTION OF STUDIES

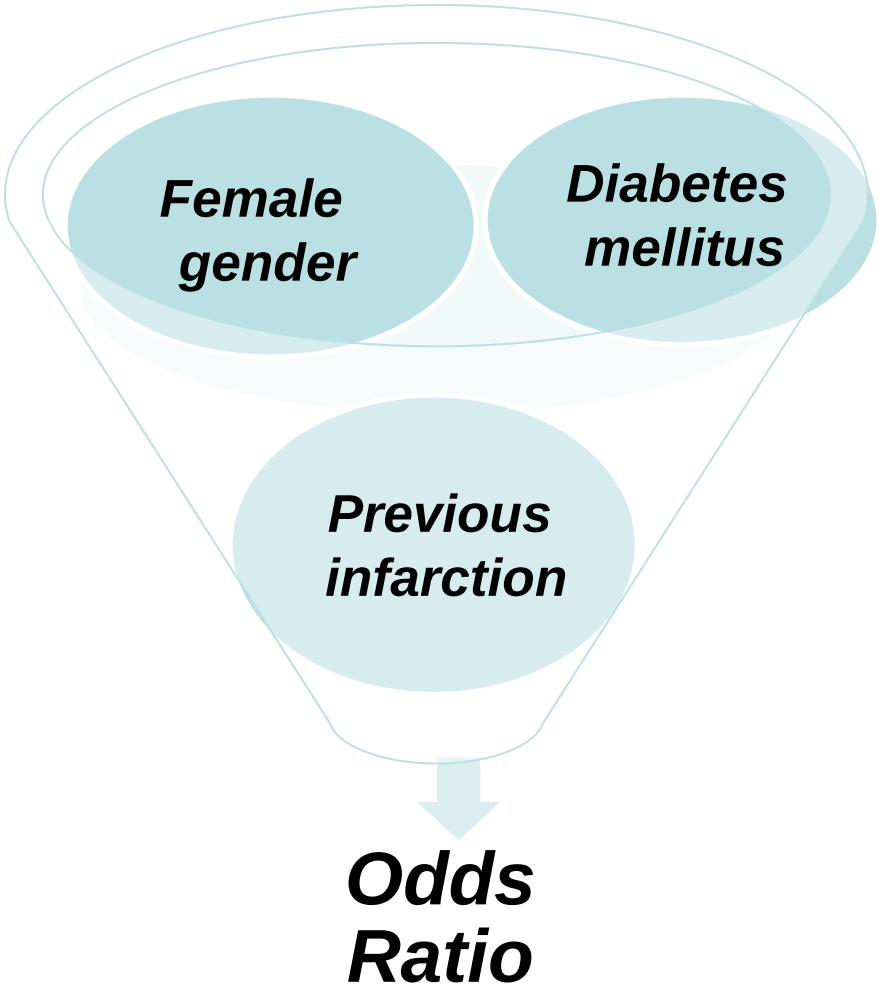
Were the inclusion criteria accurate and precise for the clinical question?

Were the endpoints of a clinical relevance?

(hard end point like death, or surrogate like improvement in instrumental data?)

METAREGRESSION

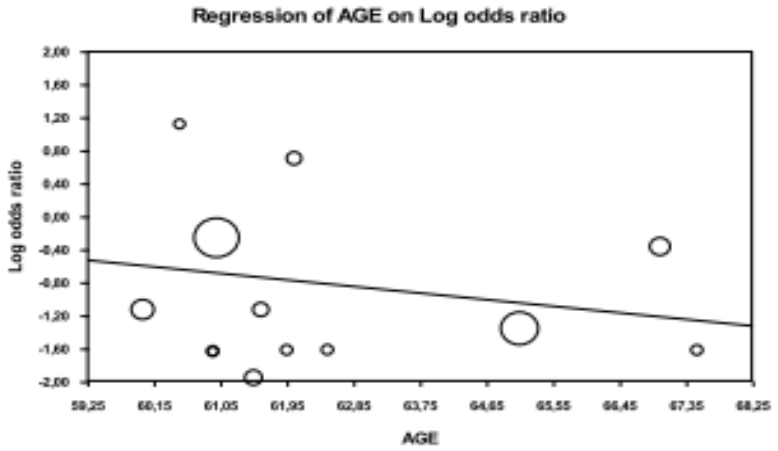
It quantitatively explores interactions between a given effect (eg the risk of an event in patients treated with A vs B, as expressed with odds ratios) and a moderator or covariate of interest
(eg prevalence of female gender in each study

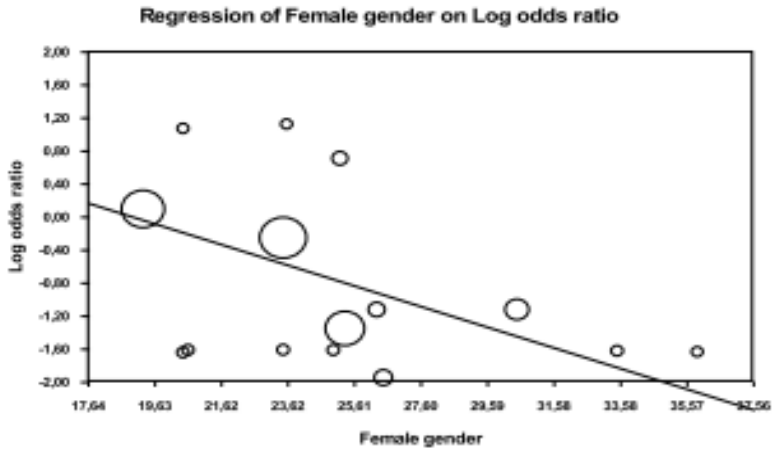


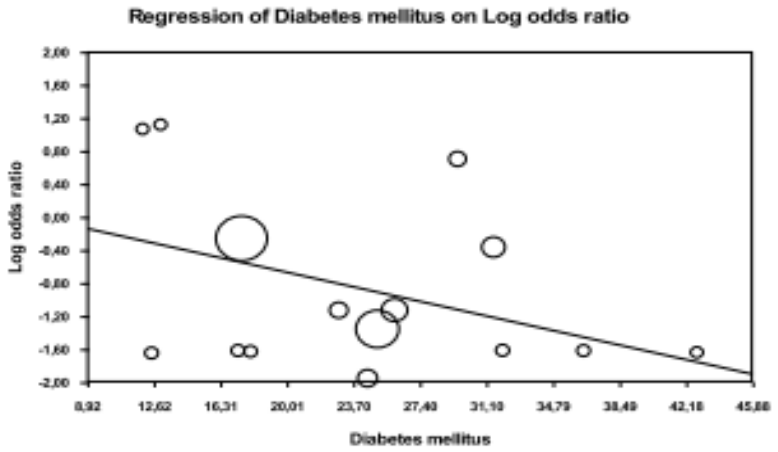
METAREGRESSION

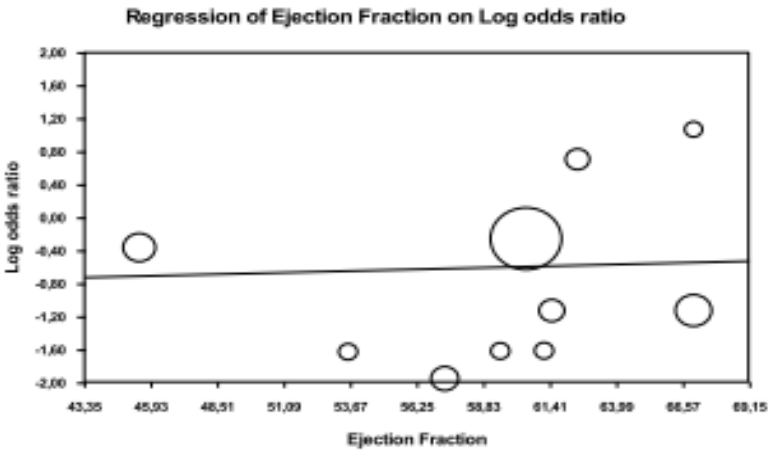
The key aspect of meta-regression is that each single study is given a specific weight which corresponds to its precision and/or size (when performing a weighted least squares [WLS] linear regression).

PCI REDUCED STROKE VS CABG (OR 0.59;0.38-0.93) BUT IN WHICH PATIENTS?









Meta regression of risk ok stroke at follow up on several clinical variables

D'Ascenzo et al, under review.

In our example, we can conclude that we found *a* *significant effect of female gender (beta=-0.12, p=0.003) on the Odds Ratio (in log scale) of PCI vs CABG.*

Thus *PCI becomes significantly more beneficial than CABG in female patients.*

STATISTICAL HETEROGENEITY

The variation among the results of individual trials beyond that expected from chance.

A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect.

Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses

Eric A. Engels, Christopher H. Schmid, Norma Terrin, Ingram Olkin, and Joseph Lau

HOW TO ASSESS HETEROGENEITY?

The usual test statistic (Cochran's Q) is computed by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution.

Measuring inconsistency in meta-analyses

Julian P T Higgins, Simon G Thompson, Jonathan J Deeks, Douglas G Altman

Cochrane Reviews have recently started including the quantity I^2 to help readers assess the consistency of the results of studies in meta-analyses. What does this new quantity mean, and why is assessment of heterogeneity so important to clinical practice?

$$Q = \sum w(E - E_C)^2, \text{where } E_C = \frac{\sum wE}{\sum w}$$

and w is the weight & E is the effect size of the individual study

INCONSISTENCY

The statistic I2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance.

$$I^2 = \begin{cases} (Q-(k-1))/Q \times 100\% & for\ Q > (k-1) \\ 0 & for\ Q \le (k-1) \end{cases}$$

and Q is the statistic from Cochrane Q test; (k-1) is the degree of freedom

HOW TO DEAL WITH HETEROGENEITY?

Fixed effect?

Random effect?

FIXED EFFECT META-ANALYISIS.

It is based on the assumption of a true effect size common to all studies.

It detects easily a significant statistical difference
but
is at risk of a reduced accuracy of the model, not conservative enough.

RANDOM EFFECT

Individual studies are estimating different treatment effects

and

to make some sense of the different effects we assume they come from the same distribution with some central value and some degree of variability.

ADVICES OF COCHRANE COLLABORATION

Cochrane recommends

to analize your review in both ways

and see how the results vary.

ADVICES OF COCHRANE COLLABORATION

If fixed effect and random effect meta-analyses give identical results

then

it is unlikely that there is important statistical heterogeneity.

ADVICES OF COCHRANE

If your results vary a little

you will need to decide
which is the better method

usually the most conservative,
usually the random effect model.

BACK TO CARVEDILOL…

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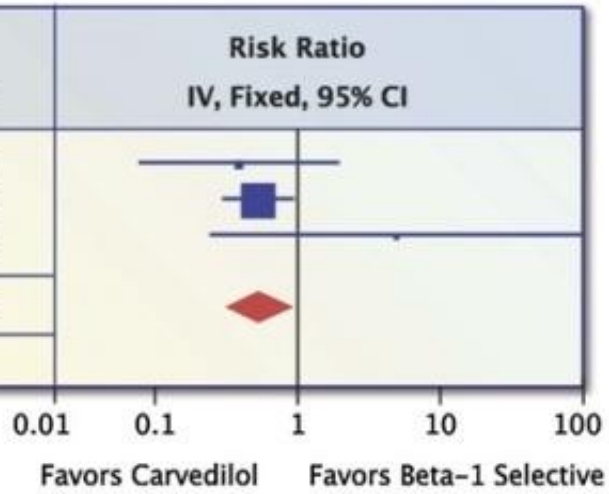

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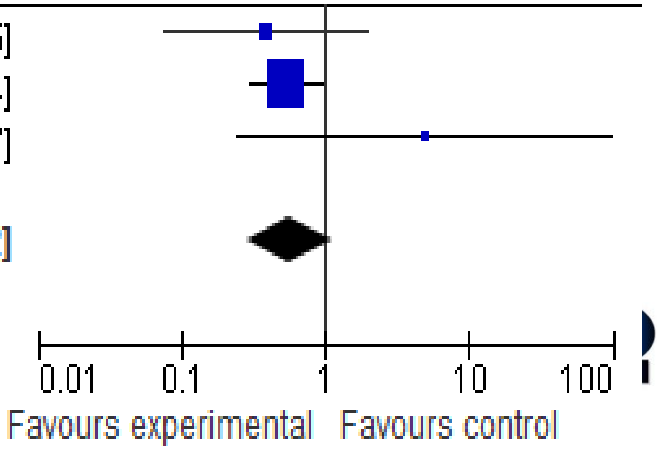


CRITICAL ASSESSMENT

PICO APPROACH

- **P**opulation of interest

eg elderly male >2 weeks after myocardial infarction)

- **I**ntervention (or exposure)

eg intracoronary infusion of progenitor blood cells

- **C**omparison

eg patients treated with progenitor cells vs standard therapy

- **O**utcome(s)

eg change in echocardiographic left ventricular ejection fraction from discharge to 6-month control

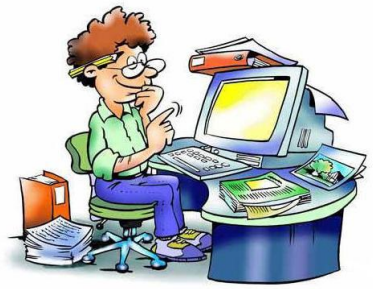
Biondi-Zoccai et al, Ital Heart J 2004

METHODS

Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched

Eg:Pubmed, Embase, Cochrane were searched for…

State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).



The authors of the paper e-mailed all corresponding authors of selected studies

Incidence and predictors of coronary stent thrombosis: Evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses

Fabrizio D'Ascenzo [a,1], Mario Bollati [a], Fabrizio Clementi [b], Davide Castagno [a], Bo Lagerqvist [c], Jose M. de la Torre Hernandez [d], Juriën M. ten Berg [e], Bruce R. Brodie [f], Philip Urban [g], Lisette Okkels Jensen [h], Gabriel Sardi [i], Ron Waksman [i], John M. Lasala [j], Stefanie Schulz [k], Gregg W. Stone [l], Flavio Airoldi [m], Antonio Colombo [n], Gilles Lemesle [o], Robert J. Applegate [p], Piergiovanni Buonamici [q], Ajay J. Kirtane [l], Anetta Undas [r], Imad Sheiban [a], Fiorenzo Gaita [a], Giuseppe Sangiorgi [b], Maria Grazia Modena [s], Giacomo Frati [t], Giuseppe Biondi-Zoccai [t,*,1]

International Journal of Cardiology

Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate)
and
any processes for obtaining and confirming data from investigators.

RISK OF BIAS

- ✓ methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level)

- ✓ and how this information is to be used in any data synthesis.

CLASSIFICATION SCHEME

Type of bias	Description	Relevant domains in the Collaboration's 'Risk of bias' tool
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation; • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants, personnel and outcome assessors; • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data; • Blinding of participants, personnel and outcome assessors.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of participants, personnel and outcome assessors; • Other potential threats to validity.
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting; • (see also Chapter 10).

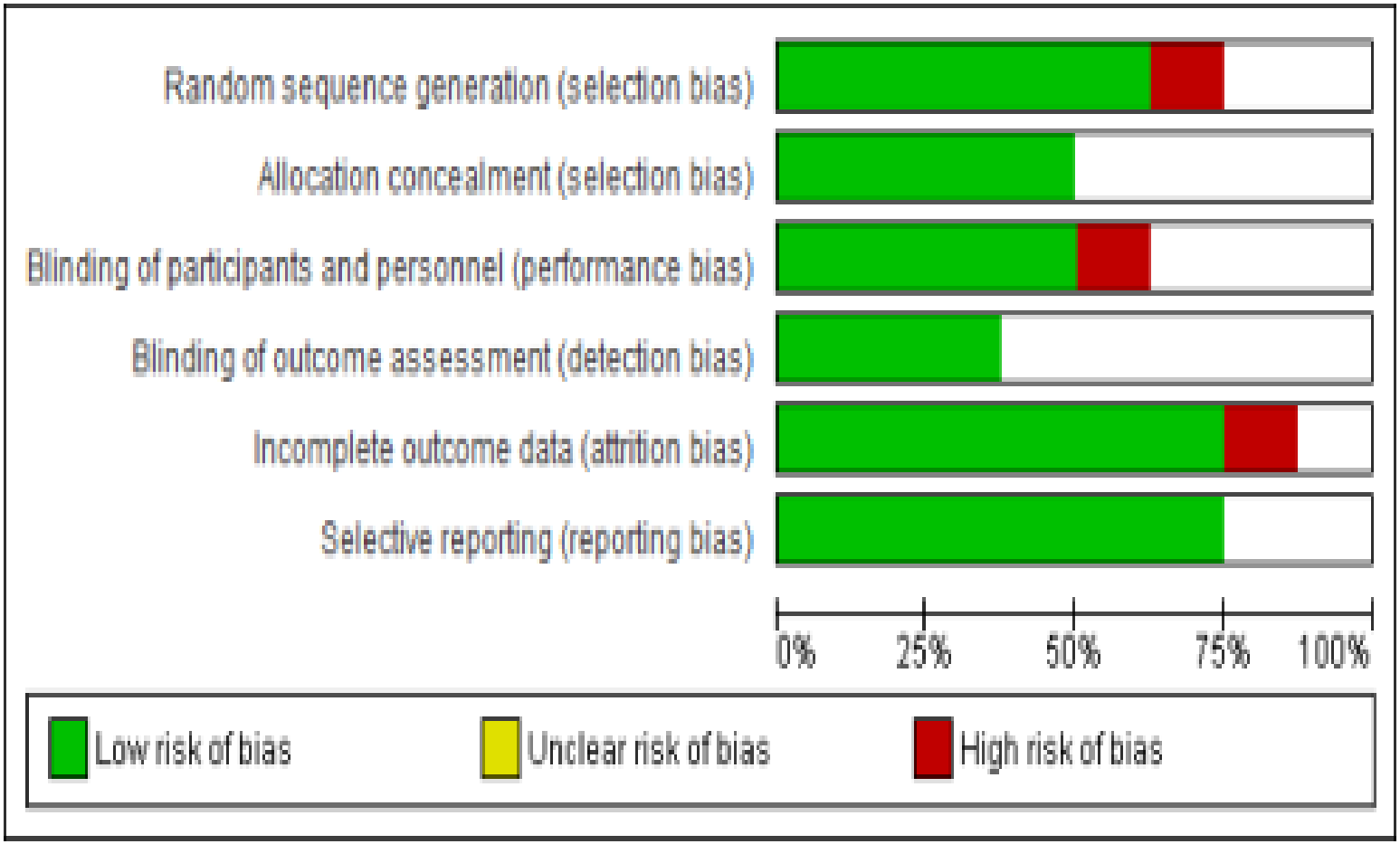


Figure A.(web only)Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

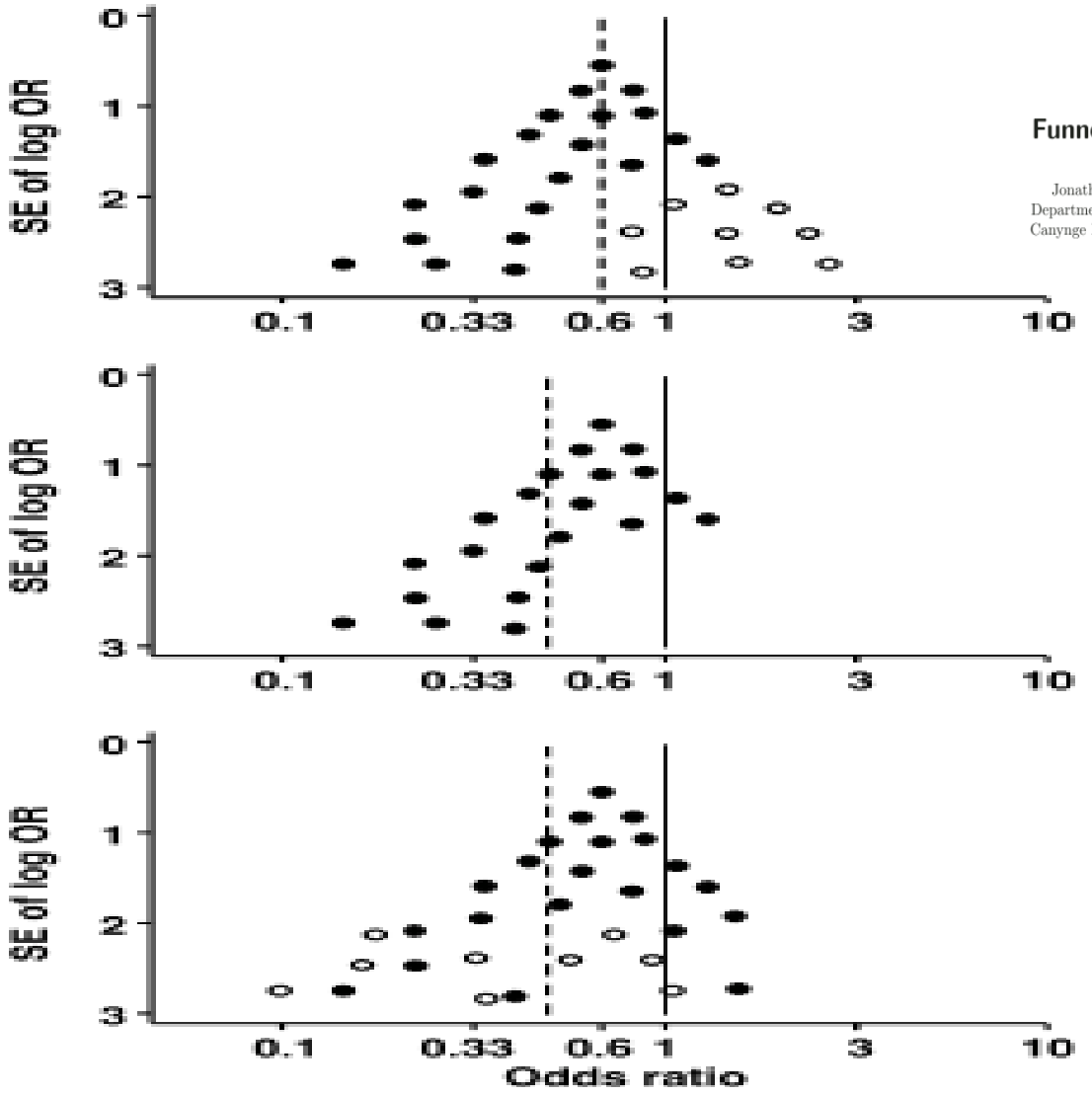
Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis

Fabrizio D'Ascenzo,[1,2] Erika Cavallero,[1] Claudio Moretti,[1,2] Pierluigi Omedè,[1]
Heart 2012;**98**:1267–1271. doi:10.1136/heartjnl-2011-301551
eon Yunseok,[4]
Robert Wagner, Tomas Freiberger, Gudrun Kunst, Michael S Marber,[7]
Matthias Thielmann,[8] Bingyang Ji,[9] Yasser M Amr,[10] Maria Grazia Modena,[11]
Giuseppe Biondi Zoccai,[2,11] Imad Sheiban,[1] Fiorenzo Gaita[1]

BUT MOST CHALLENGING

Publication bias results in being easier to find studies with a 'positive' result.

WAS PUBLICATION BIAS CORRECTLY APPRAISED?



Funnel plots in meta-analysis

Jonathan A. C. Sterne and Roger M. Harbord
Department of Social Medicine, University of Bristol
Canynge Hall, Whiteladies Road, Bristol BS8 2PR UK

EASY TO OBTAIN?

Publication, availability, and selection biases are a potential concern for meta-analyses of individual participant data, but many reviewers neglect to examine or discuss them.

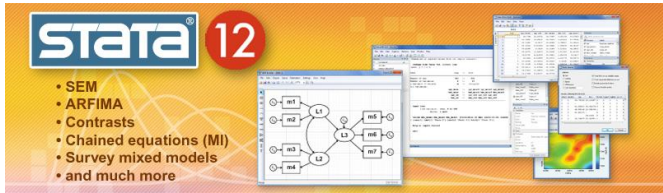
Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey

OPEN ACCESS

Ikhlaaq Ahmed *postgraduate student*[1], Alexander J Sutton *professor of medical statistics*[2], Richard D Riley *senior lecturer in medical statistics*[3]

SOFTWARES

- Rev Man (http://ims.cochrane.org/revman)
- STATA (http://www.stata.com/)
- Comprehensive meta analysis (http://www.meta-analysis.com/)



LIFE SCIENCE ACADEMY

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Prof. Fiorenzo Gaita. MD Division of Cardiology
Prof. Mauro Gasparini, Phd, Politecnico di Torino

Is pairwise meta-analysis all Biostatistics

can give?

TODAY'S PROGRAM: SECOND PART

1) Network Meta-analysis: general concepts
2) Points in common with PWMA
3) Only for NMA/MTC

GENERAL CONCEPTS

LACK OF RANDOMIZED DIRECT COMPARISON

New drugs/techologies may not be directly compared due to:

- ✓Fear of negative results
- ✓Marketing strategies
- ✓Lack of financial resources
- ✓Underreporting of non-significant or negative data

BUT IF I HAVE A PATIENT

and many different options for him/her,

but not directly compared in the literature,

What should I do?

REALISTIC, BUT INCOHERENT

- ✓ Juventus-Inter; 4-2
- ✓ Inter-Milan; 3-1
- ✓ Milan-Juventus; 1-0

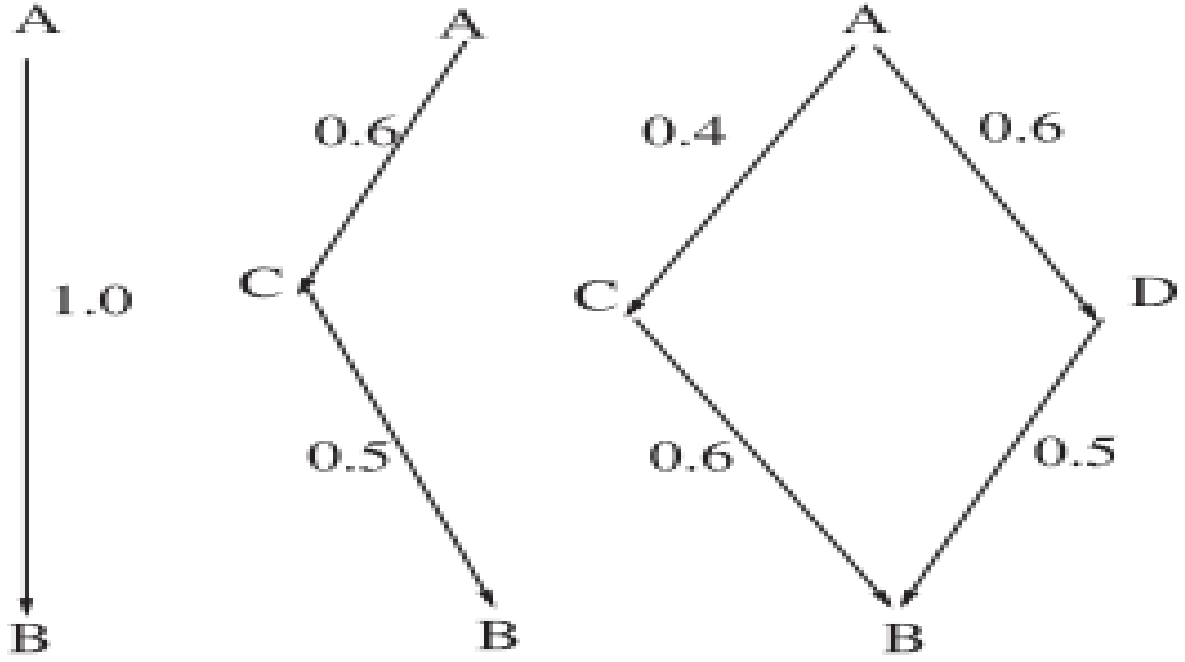


Figure 1. Simple networks of comparisons.

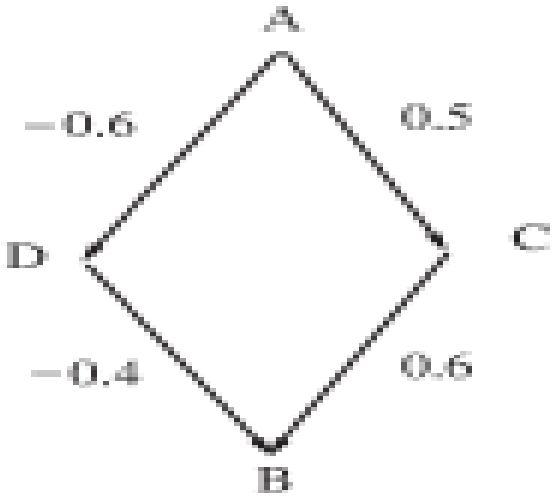


Figure 2. An incoherent network of comparisons.

Thomas Lumley*,†

Department of Biostatistics, University of Washington, Box 357232, Seattle, WA 98195-7232, U.S.A.

SOLUTION

Network meta-analysis (NMA)/ Mixed treatment comparator (MTC): it indirectly compares different interventions from many trials and suitably combines such estimates.

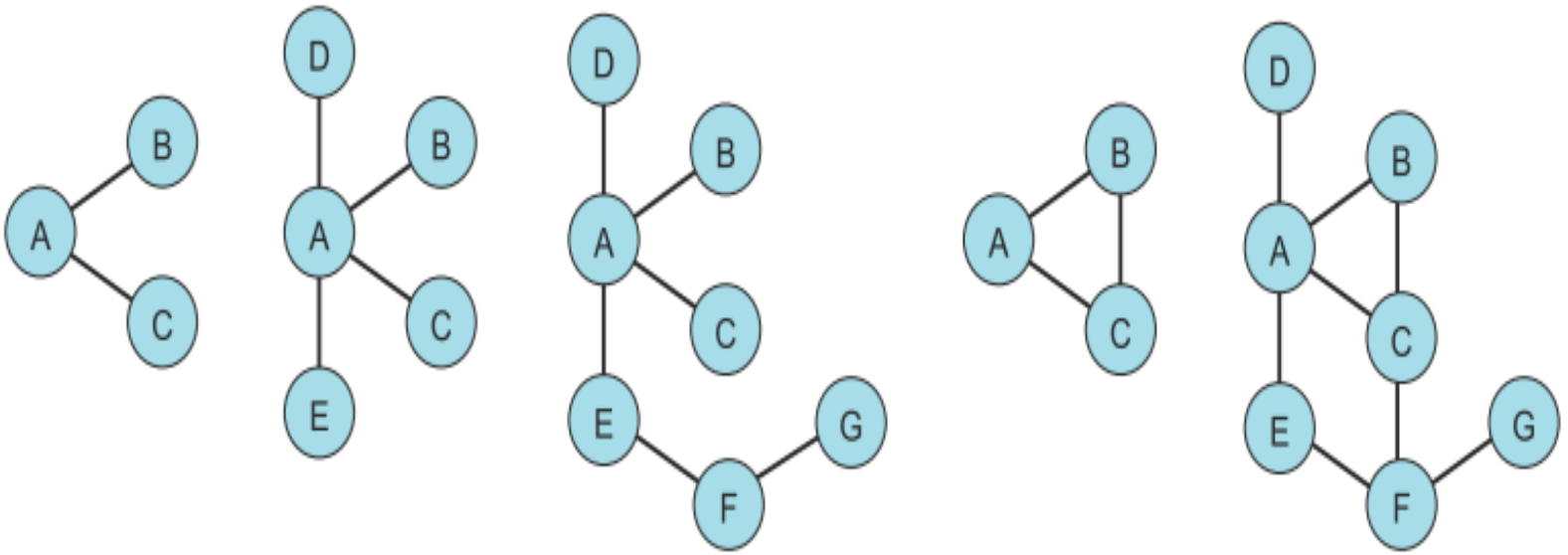
SOME GLOSSARY

✓Indirect treatment comparisons (ITC) investigate the effects of intervention B versus intervention C given a common comparator A.

✓Network Meta analysis (NMA) is ITC performed on trials comparing two different interventions, directly or not or both.

✓Mixed treatment comparator (MTC) is ITC performed on trials comparing more than two different interventions, directly or not or both.

Networks of evidence



Closed loops in network: combination of direct and indirect evidence

Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1

Jeroen P. Jansen, PhD[1,], Rachael Fleurence, PhD[2], Beth Devine, PharmD, MBA, PhD[3], Robbin Itzler, PhD[4], Annabel Barrett, BSc[5], Neil Hawkins, PhD[6], Karen Lee, MA[7], Cornelis Boersma, PhD, MSc[8], Lieven Annemans, PhD[9], Joseph C. Cappelleri, PhD, MPH[10]*

SHOULD WE TRUST NMA/MTC?

Methods of comparison and number of significant findings* in 44 meta-analyses of competing interventions. Weighted κ 0.53 for agreement between direct and adjusted indirect estimate

	Adjusted indirect estimate		
Direct estimate	**Significant effect (–) (n=6)**	**Non-significant effect (n=33)**	**Significant effect (+) (n=5)**
Significant effect (–) (n=8)	5	3	0
Non-significant effect (n=25)	1	23	1
Significant effect (+) (n=11)	0	7	4

*Non-significant effect: difference between intervention groups is non-significant (P>0.05); significant effect (P≤0.05) is separated according to whether intervention A is less (–) or more effective (+) than intervention B.

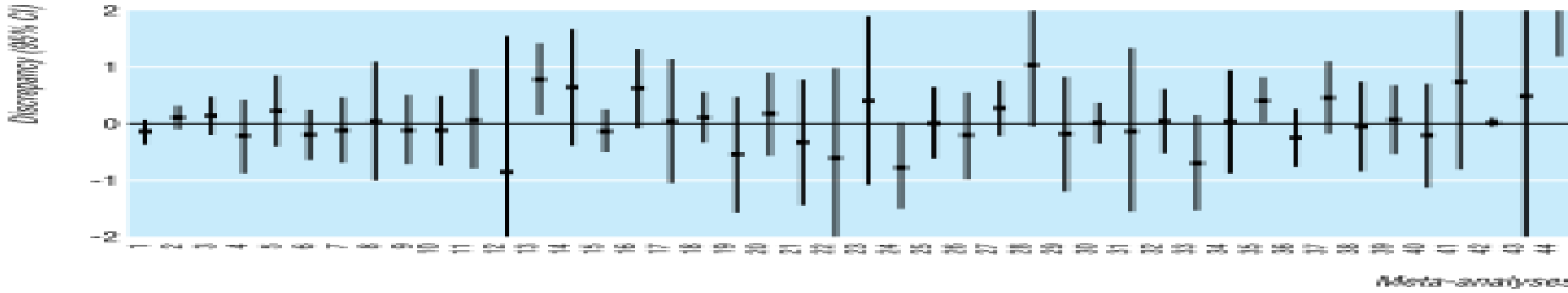


Fig 1 Discrepancy between direct and adjusted indirect comparison defined as difference in estimated log relative risk (meta-analyses 1-39) or difference in estimated standardised mean difference (meta-analysis 40) or difference in estimated mean difference (meta-analyses 41–44): empirical evidence from 44 published meta-analyses (see webextra table A)

Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses

Fujian Song, Douglas G Altman, Anne-Marie Glenny, Jonathan J Deeks

Comparisons in Meta-Analysis of Randomized Controlled Trials

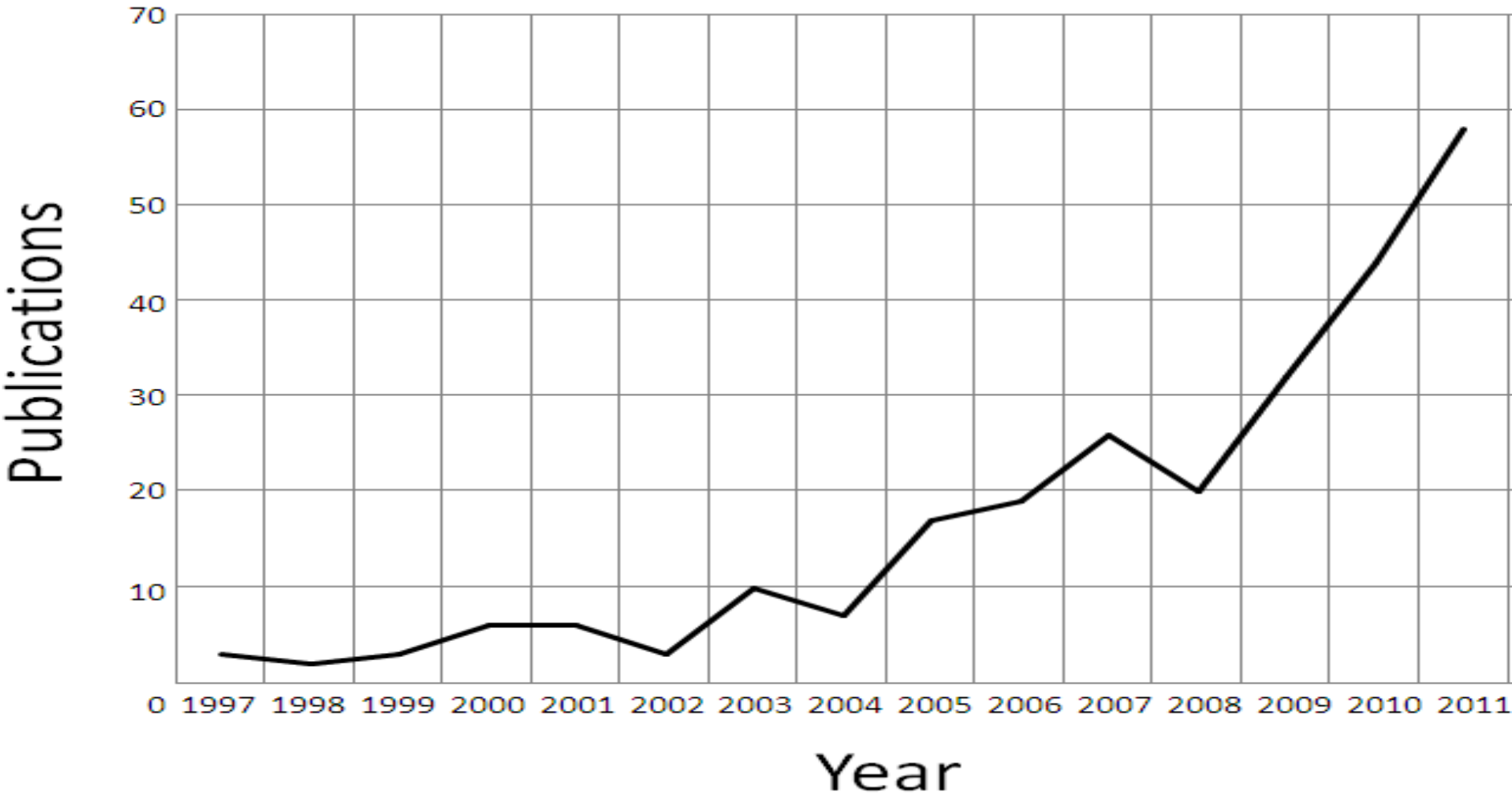
Heiner C. Bucher, Gordon H. Guyatt, Lauren E. Griffith, and Stephen D. Walter*
Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada, L8N 3Z5

NICE does make funding decisions taking into account the results of an NMA/MTC

but

evidence from head-to-head randomized controlled trials is still considered to be the most valuable.

AN INCREASING INTEREST*



comparison*) OR (network NEAR (metaanalys* OR meta-analys*)) OR (indirect AND comparison AND (metaanalys* OR meta-analys*)))

POINTS IN COMMON WITH PWMA

POINTS IN COMMON WITH PWMA

Heterogeneity

- ✓ if and how it was evaluated
- ✓ correct pooling was performed according to it (fixed vs random effect)

Table III. Parameter estimates for models (1), 3(b) and 4(b).

Description			Model (1) No covariates	Model 3(b) Exchangeable treatment x covariate effects by class	Model 4(b) Same treatment x covariate effects by class
LogOR vs Placebo	Anti-coagulant (low)	d_2	−1.08 (−1.77 to −0.37)	−1.18 (−1.86 to −0.48)	−1.20 (−1.89 to −0.54)
	Anti-coagulant (standard)	d_3	−0.76 (−1.16 to −0.36)	−0.80 (−1.15 to −0.42)	−0.77 (−1.14 to −0.38)
	Warfarin (fixed)	d_4	0.18 (−0.73 to 1.06)	−0.36 (−1.89 to 0.77)	−0.11 (−0.90 to 0.72)
	Aspirin (low)	d_5	−0.15 (−0.56 to 0.27)	−0.12 (−0.49 to 0.25)	−0.08 (−0.47 to 0.30)
	Aspirin (medium)	d_6	−0.37 (−0.83 to 0.07)	−0.50 (−0.91*to*−0.09)	−0.45 (−0.87 to −0.03)
	Aspirin (high)	d_7	−0.25 (−1.72 to 1.23)	−0.59 (−4.12 to 2.98)	−0.39 (−1.86 to 1.11)
	Aspirin (alternate days)	d_8	−1.67 (−4.54 to 0.41)	−1.72 (−5.31 to 0.79)	−1.74 (−5.16 to 0.48)
	Ximelagatran	d_9	−0.84 (−1.50 to −0.18)	−0.95 (−1.64 to −0.33)	−0.86 (−1.42 to −0.27)
	Triflusal	d_{10}	−0.11 (−1.35 to 1.20)	−0.04 (−1.92–1.52)	0.13 (−1.05 to 1.38)
	Indobufen	d_{11}	−0.52 (−1.47 to 0.47)	−1.38 (−5.72 to 2.09)	−1.21 (−2.26*to*−0.13)
	Dipyridamole	d_{12}	−0.18 (−1.02 to 0.66)	−0.13 (−4.25 to −0.18)	−0.21 (−1.01 to 0.58)
	Warfarin (fixed) + Aspirin (low)	d_{13}	−0.29 (−1.09 to 0.51)	0.59 (−1.46 to 2.88)	0.54 (−0.80 to 1.85)
	Warfarin (fixed) + Aspirin (medium)	d_{14}	0.13 (−0.60 to 0.83)	0.09 (−0.53 to 0.74)	0.12 (−0.53 to 0.80)
	Acenocoumarol (low) + Triflusal	d_{15}	−1.56 (−3.31 to 0.06)	−0.55 (−3.03 to 2.00)	−0.534 (−2.67 to 1.38)
	Aspirin (low) + Copidogrel	d_{16}	−0.24 (−1.06 to 0.57)	−0.17 (−1.01 to 0.75)	−0.14 (−0.82 to 0.53)
	Aspirin (low) + Dipyridamole	d_{17}	−0.49 (−1.38 to 0.38)	−0.72 (−4.09 to 2.89)	−0.53 (−1.38 to 0.30)
Between-study variation		*sd*	0.28 (0.02–0.57)	0.16 (0.01–0.46)	0.19 (0.01–0.48)
Regression coefficients	Anti-coagulant (low)	β_2		−0.58 (−2.63 to 1.44)	
	Anti-coagulant (standard)	β_3		−0.54 (−1.44 to 0.39)	
	Warfarin (fixed)	β_4		−1.64 (−9.91 to 2.13)	
	Aspirin (low)	β_5		−0.09 (−1.04 to 0.78)	
	Aspirin (medium)	β_6		0.50 (−0.28 to 1.33)	
	Aspirin (high)	β_7		0.52 (−4.20 to 5.54)	
	Aspirin (alternate days)	β_8		0.18 (−5.61 to 6.20)	
	Ximelagatran	β_9		−1.80 (−10.47 to 1.95)	
	Triflusal	β_{10}		0.02 (−6.01 to 4.25)	
	Indobufen	β_{11}		0.56 (−4.29 to 6.97)	
	Dipyridamole	β_{12}		−0.06 (−5.24 to 5.13)	
	Warfarin (fixed) + Aspirin (low)	β_{13}		3.23 (−3.98 to 11.45)	
	Warfarin (fixed) + Aspirin (medium)	β_{14}		3.41 (−0.86 to 7.53)	

treatments in individuals with non-rheumatic atrial fibrillation

Nicola J. Cooper[1,*,†,‡], Alex J. Sutton[1,§], Danielle Morris[2],
A. E. Ades[3,¶] and Nicky J. Welton[3,‖]

POINTS IN COMMON WITH PWMA

Literature search

- ✓accurate and comprehensive, including at least two databases
- ✓performed by two or more blinded authors
- ✓explicited strategy of search

POINTS IN COMMON WITH PWMA

Outcomes

- ✓pre-defined outcomes
- ✓evaluation of different definitions of outcomes among included studies

POINTS IN COMMON WITH PWMA

Methodological assessment

✓performed according to Cochrane and reported in the paper

✓reported in the discussion and in the conclusion, with influence of presentation of the results

ONLY FOR NMA/MTC

ONLY FOR NMA/MTC

Statistics stuff

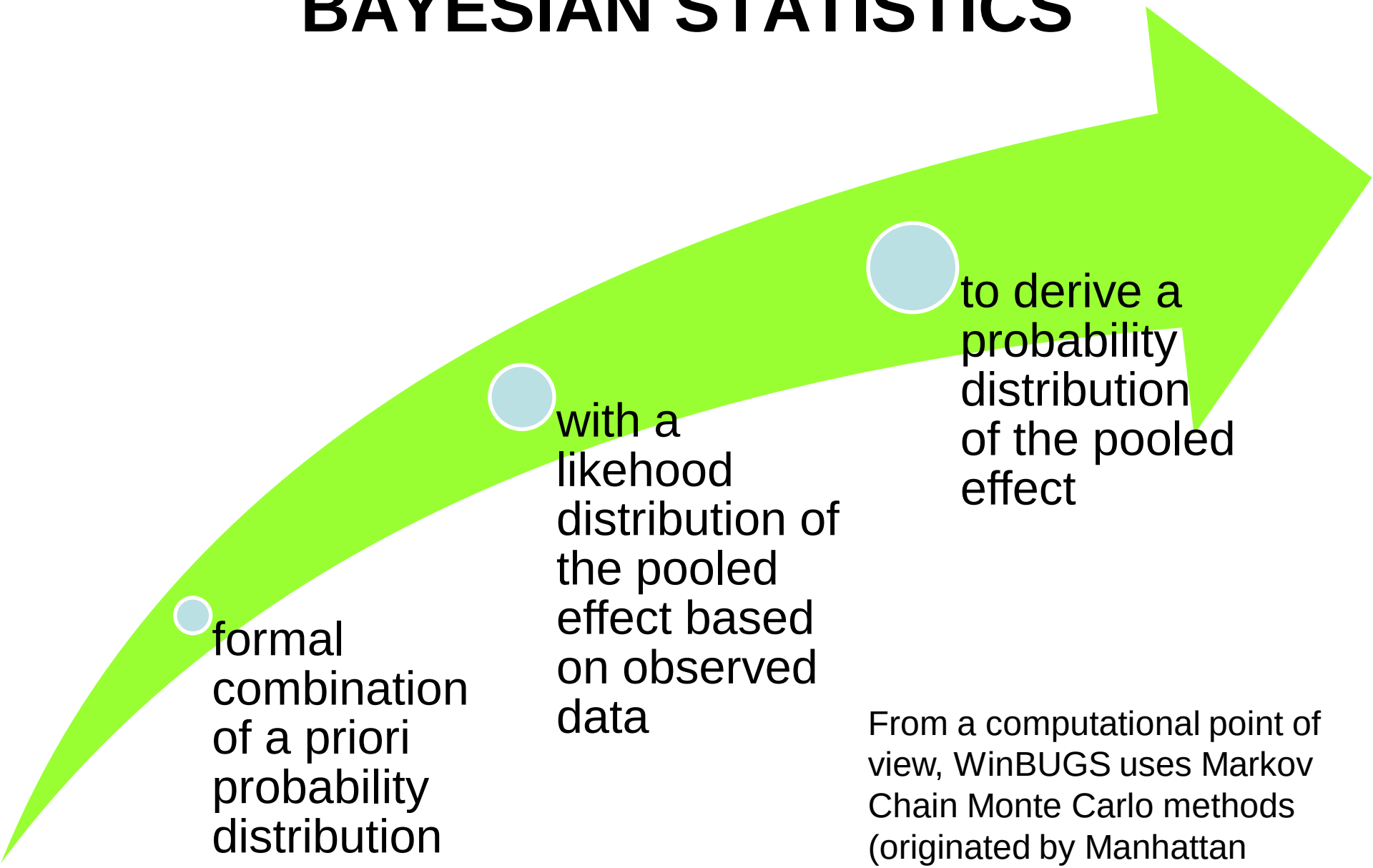
The most developed methods for NMA are Bayesian.

Software used is for example WinBUGS

http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml

You should be assisted by a professional statistician.

BAYESIAN STATISTICS



From a computational point of view, WinBUGS uses Markov Chain Monte Carlo methods (originated by Manhattan Project)

ONLY FOR NMA/MTC

Report of the results

- ✓ network diagrams and how to read them
- ✓ coherence

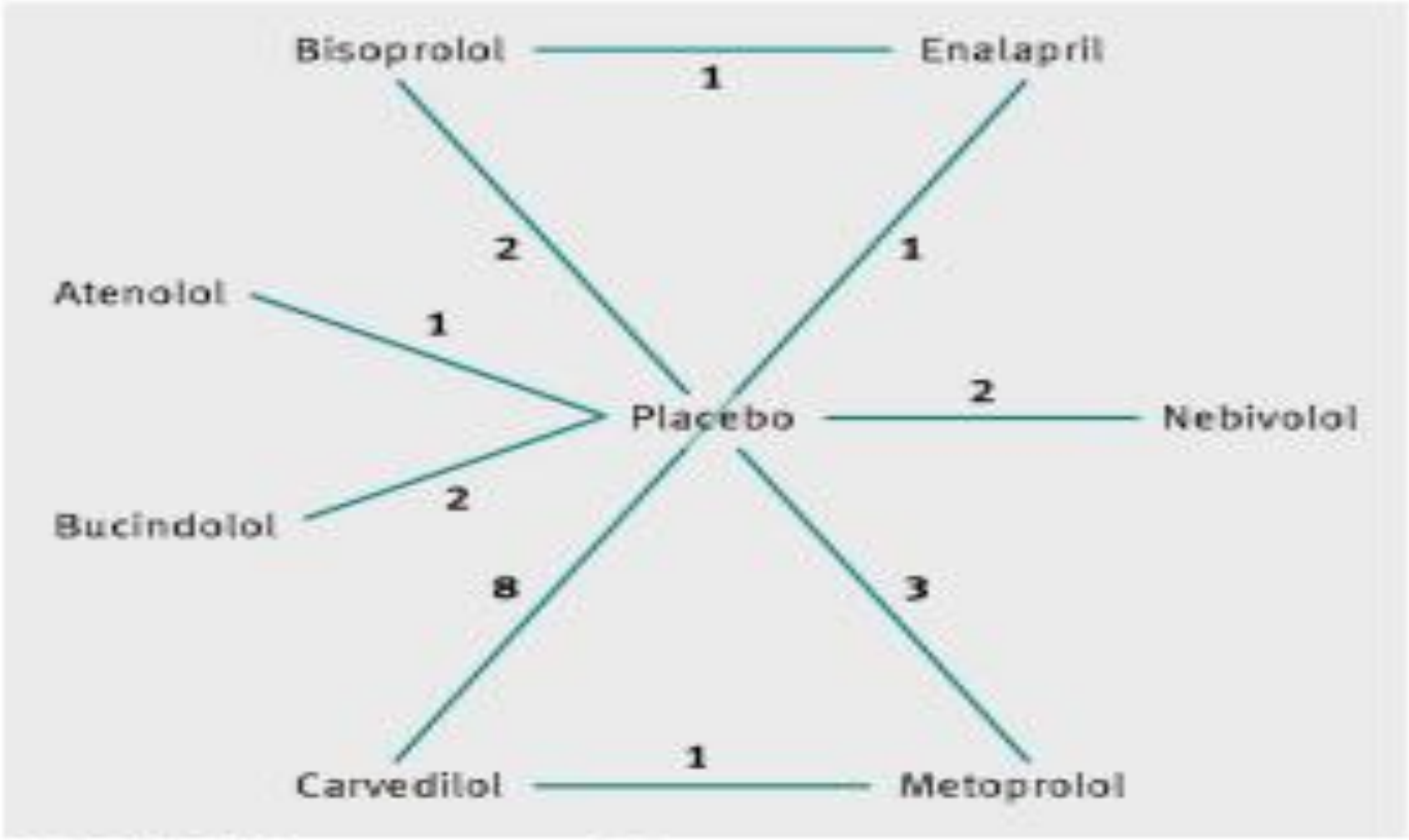


Fig 2 Evidence network

Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis

OPEN ACCESS

Saurav Chatterjee *resident*[1], Giuseppe Biondi-Zoccai *assistant professor of cardiology*[2], Antonio Abbate *assistant professor of cardiology*[3], Fabrizio D'Ascenzo *fellow, interventional cardiology*[4], Davide Castagno *staff*[4], Benjamin Van Tassell *assistant professor*[3], Debabrata Mukherjee *chief of cardiology, and acting chairman of medicine*[5], Edgar Lichstein *chairman of medicine*[1]

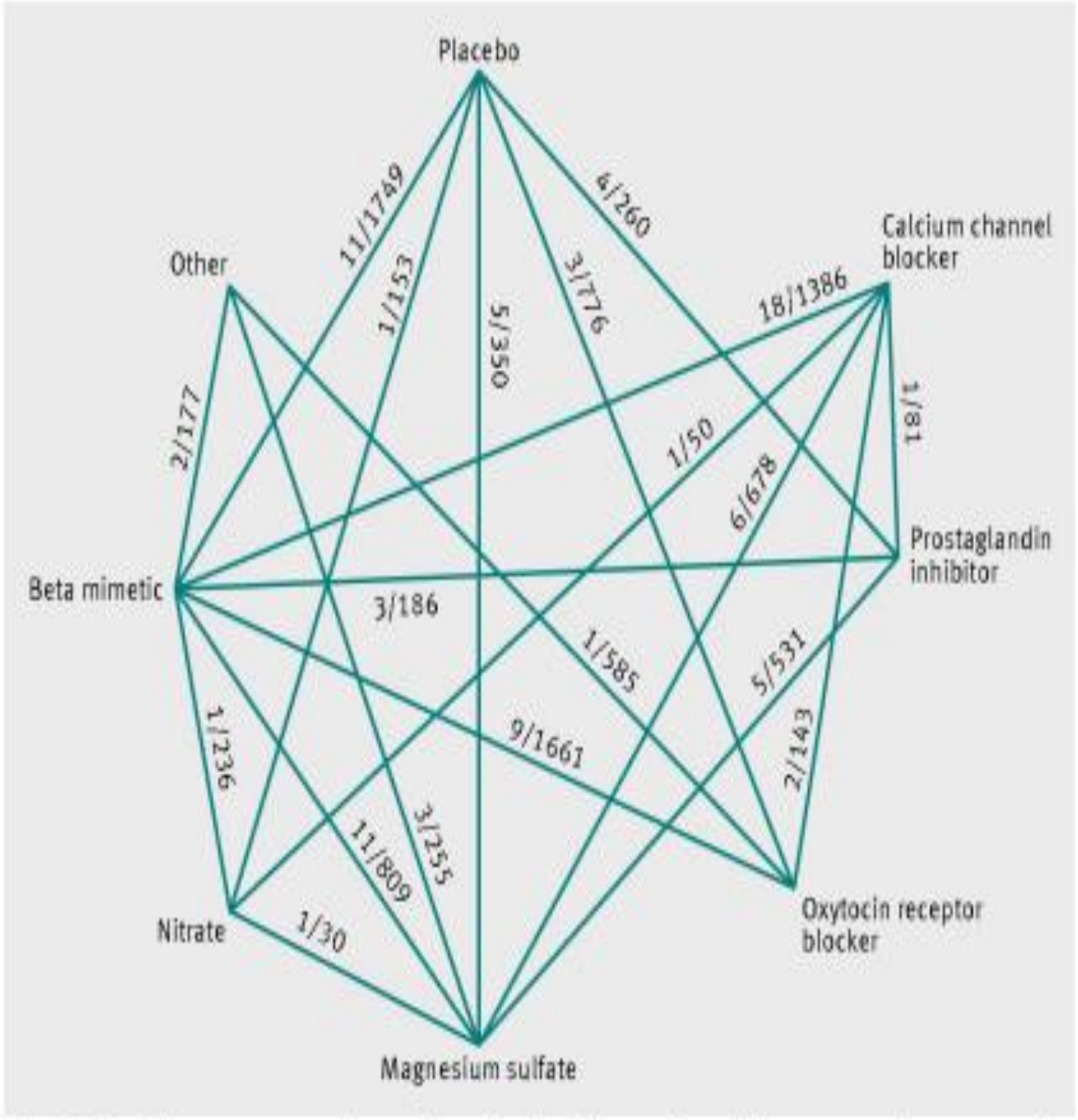


Fig 2 Graphic representation of tocolytic trials retrieved for network meta-analysis. Lines represent trials comparing two classes of drug for treatment of preterm delivery. Numbers on lines represent number of trials and total number of participants in those trials

Tocolytic therapy for preterm delivery: systematic review and network meta-analysis

David M Haas *associate professor of obstetrics and gynecology*[1], Deborah M Caldwell *MRC fellow population health science*[2], Page Kirkpatrick *research associate*[1], Jennifer J McIntosh *medical resident*[1], Nicky J Welton *MRC research fellow*[2]

ONLY FOR NMA/MTC

Similarity

the effect of the treatment holds true among all included trials irrespective of the various treatments analyzed

NOT YET FORMALIZED

but analyze differences in

- drug dosage

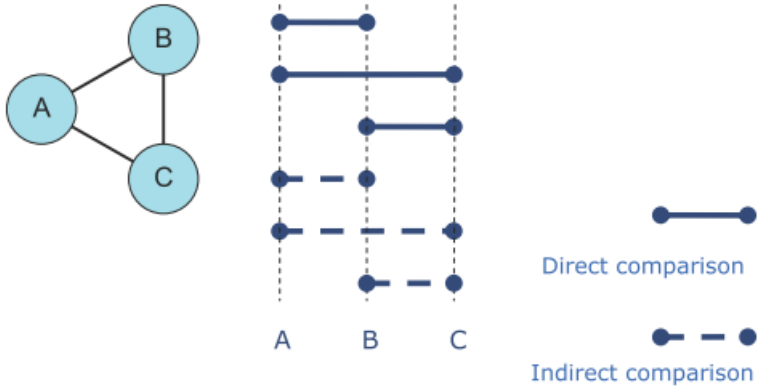
- inclusione/esclusion criteria

ONLY FOR NMA

Consistency

if and how it was appraised

if agreement between direct and indirect of analysis is discussed and explained in the paper



Statistical approaches for conducting network meta-analysis in drug development[†]

Pharmaceut. Statist. **2011,** 10 523–531

Byron Jones,[a*] James Roger,[b] Peter W. Lane,[c] Andy Lawton,[d] Chrissie Fletcher,[e] Joseph C. Cappelleri,[f] Helen Tate,[g] Patrick Moneuse,[h] and on behalf of PSI Health Technology Special Interest Group, Evidence Synthesis sub-team

TABLE 2. Direct and indirect comparison in meta-analysis on the efficacy of two drug regimens compared to standard prophylaxis in randomized controlled trials of primary and secondary prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection

Type of comparison	No. of trials in comparison	Odds ratio (95% CI)	Test for heterogeneity
Indirect comparison			
Trimethoprim-sulfamethoxazole vs. dapsone/pyrimethamine	14	0.37[a] (0.21–0.65)	$p = 0.03$
Direct comparison			
Trimethoprim-sulfamethoxazole vs. dapsone/pyrimethamine	8	0.64[a] (0.45–0.90)	$p = 0.41$
Dapsone/pyrimethamine vs. aerosolized pentamidine	9	0.89 (0.68–1.17)	$p = 0.27$
Trimethoprim-sulfamethoxazole vs. aerosolized pentamidine	13	0.48 (0.36–0.65)	$p = 0.98$

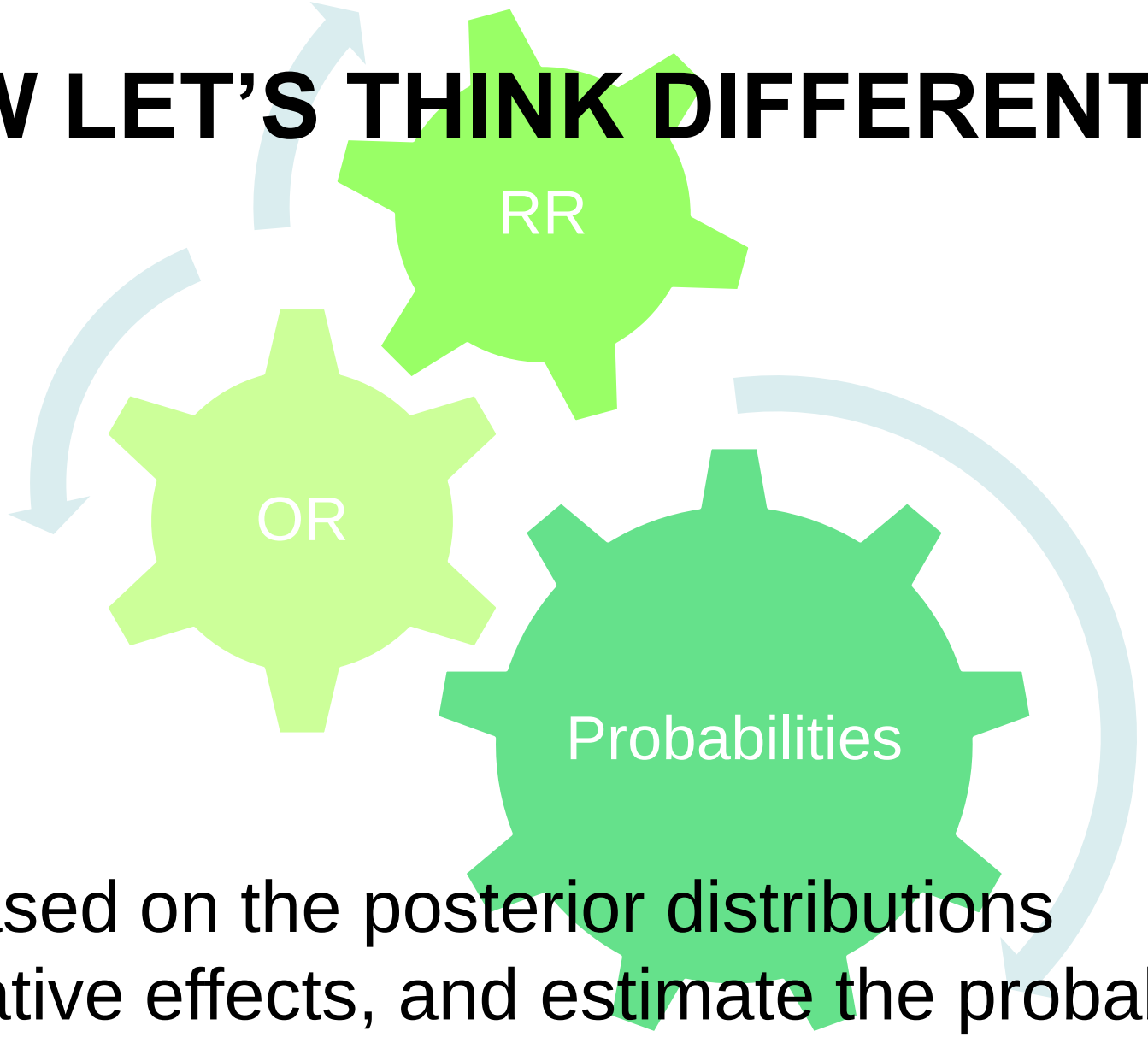
Abbreviations: CI = confidence interval; HIV = human immunodeficiency virus.
[a]p Value for the difference of summary ratio = 0.11.

The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials

Heiner C. Bucher, Gordon H. Guyatt, Lauren E. Griffith, and Stephen D. Walter*

Department of Clinical Epidemiology and Biostatistics,
McMaster University, Hamilton, Ontario,
Canada, L8N 3Z5

NOW LET'S THINK DIFFERENT



based on the posterior distributions
of the relative effects, and estimate the probability
that treatment x has rank I

EACH TREATMENT IS THE MOST EFFECTIVE OUT OF ALL TREATMENTS COMPARED

This is because information of the “spread” of rankings for a treatment is also important. For example, a treatment for which there are few trial data and consequently a wide CI may have a probability approaching 50% of being the best treatment, but may nevertheless have a probability of 50% of being the worst treatment.

Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1

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FROM THIS…

```
⇨# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                                          # *** PROGRAM STARTS
for(i in 1:ns){                                 #   LOOP THROUGH STUDIES
     mu[i] ~ dnorm(0,.0001)                     # vague priors for all trial baselines
     delta[i,1]<-0
     for (k in 1:na[i]) {                       #  LOOP THROUGH ARMS
          se[i,k]<- sd[i,k]/sqrt(n[i,k])
          var[i,k] <- pow(se[i,k],2)            # calculate variances
          prec[i,k] <- 1/var[i,k]               # set precisions
          y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
          theta[i,k] <- mu[i] + delta[i,k]   # model for linear predictor
#Deviance contribution
          dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
        }
#   summed residual deviance contribution for this trial
     resdev[i] <- sum(dev[i,1:na[i]])
     for (k in 2:na[i]) {                       # LOOP THROUGH ARMS
          delta[i,k] <- md[i,k]
          md[i,k] <-  d[t[i,k]] - d[t[i,1]]
        }
   }
totresdev <- sum(resdev[])                      #Total Residual Deviance
d[1]<-0         # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
for (k in 1:nt){
   best[k]<- equals(rank(d[],k),1)
   for (m in 1:nt){
     prob.rank[k,m]<- equals(rank(d[],k),m)
          }
   }
for (k in 1:(nt-1)){
   for (m in (k+1):nt){
     mean.diff[k,m]<- d[m]-d[k]
     }
```

Tocolytic therapy for preterm delivery: systematic review and network meta-analysis

OPEN ACCESS

David M Haas *associate professor of obstetrics and gynecology*[1], Deborah M Caldwell *MRC fellow population health science*[2], Page Kirkpatrick *research associate*[1], Jennifer J McIntosh *medical resident*[1], Nicky J Welton *MRC research fellow*[2]

...TO THIS

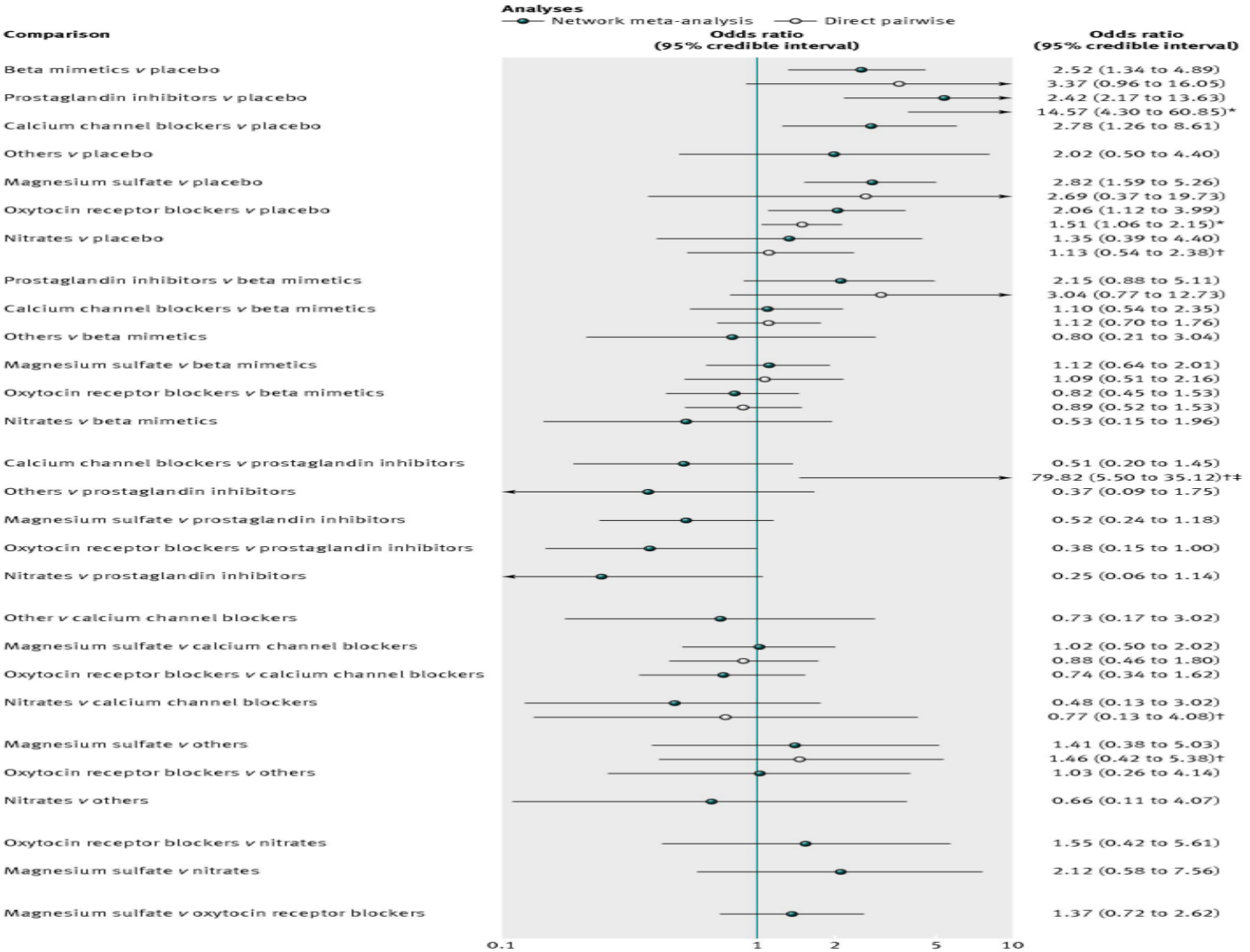
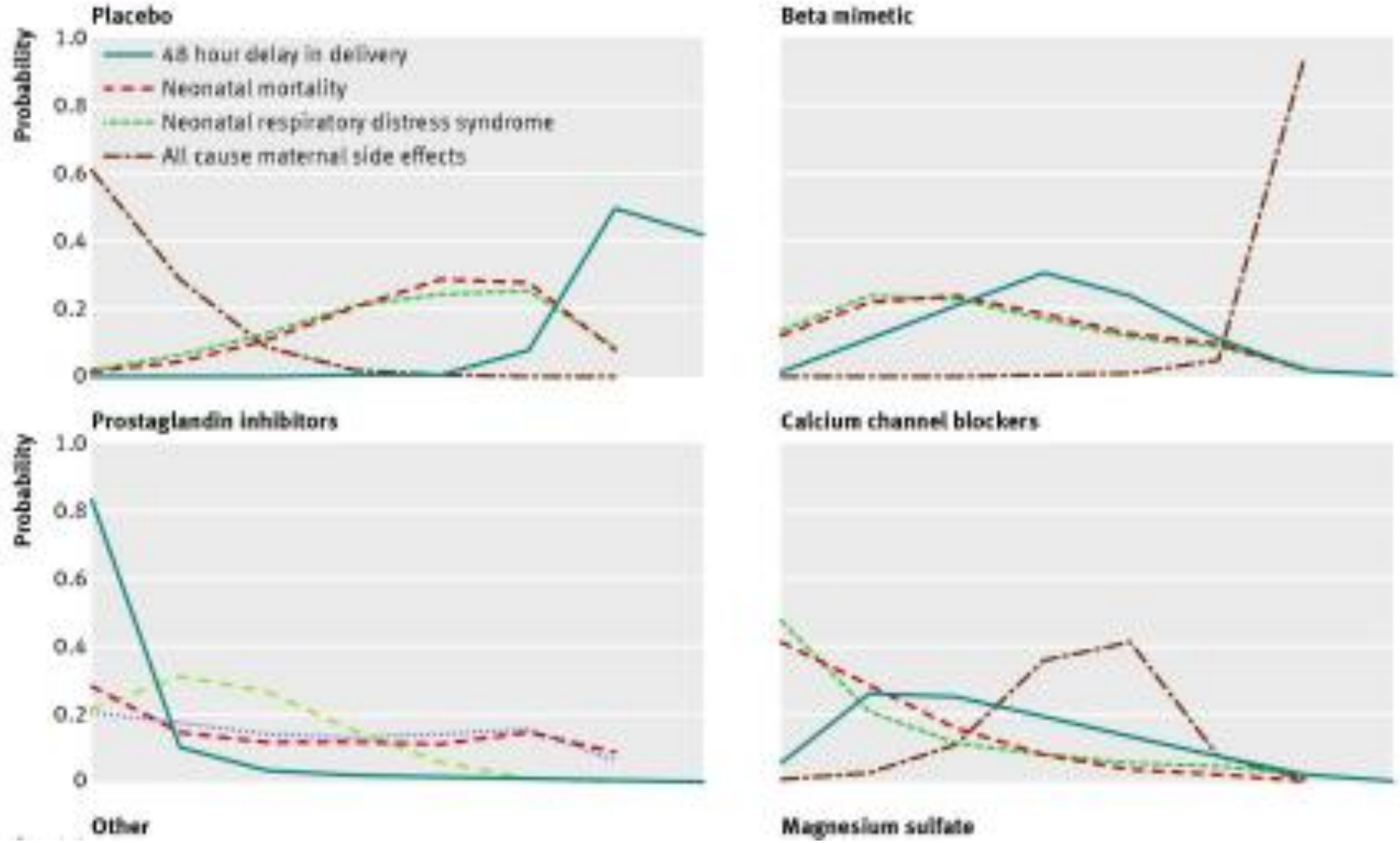


Fig 3 Results from network and pairwise meta-analyses for 48 hour delay in delivery. Direct meta-analysis refers to trials that compared two drug classes directly. In most cases analyses were undertaken using a random effects model. *Fixed effect meta-analyses. †Single trial. ‡Continuity correction used (0.5 added to each cell of 2×2 table)



Tocolytic therapy for preterm delivery: systematic review and network meta-analysis

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kings for efficacy of tocolytics and adverse events. Graph displays distribution of probabilities for each outcome. Ranking indicates probability that drug class is first "best," second "best," etc. Dot-dashed line represents 48 hour delay in delivery. Solid line indicates neonatal mortality. Dashed line indicates respiratory distress syndrome. Dotted line represents all cause maternal side effects

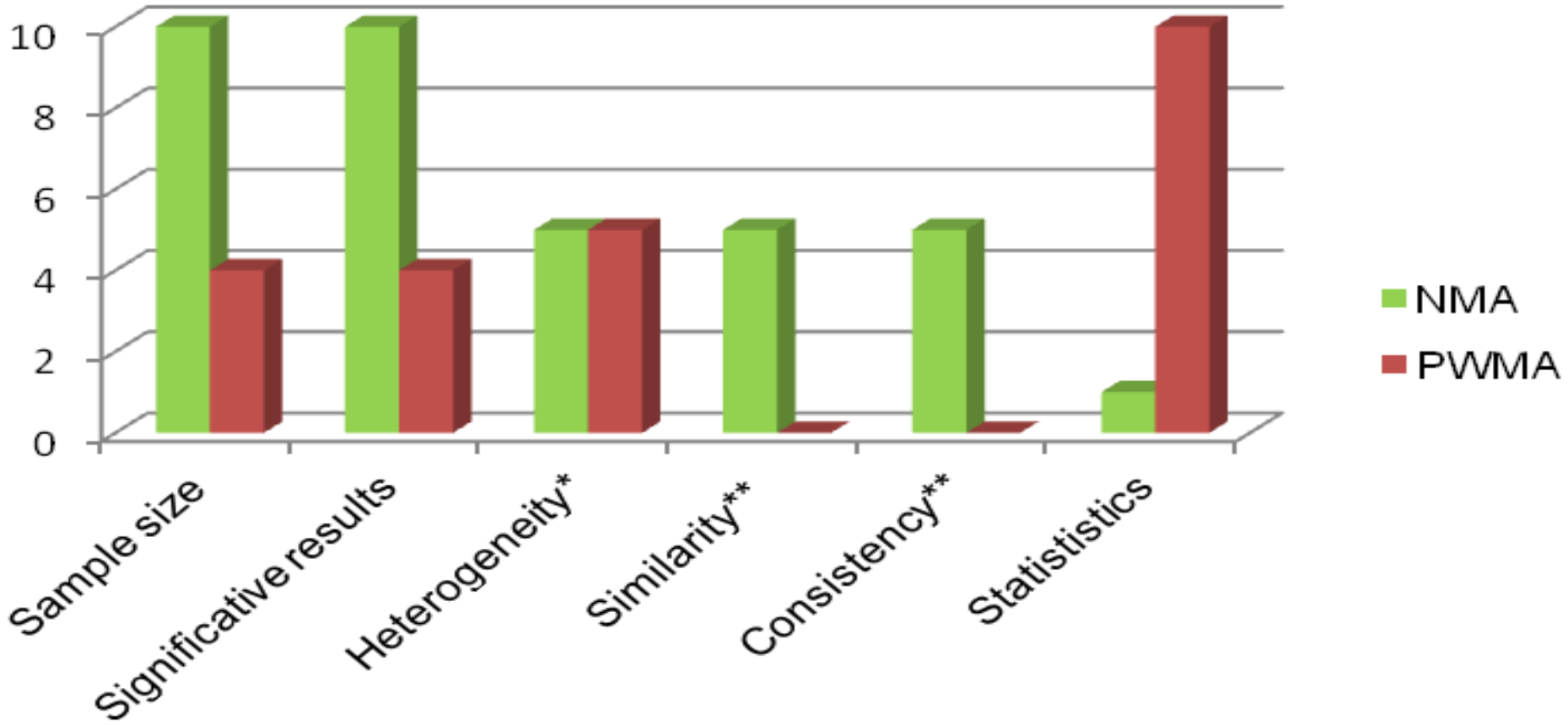
IN THIS PAPER

Each treatment was superior to placebo

No treatment was superior to other

But two strategies had the highest probabilities to perform best

PROS AND CONS OF PWMA AND NMA/MTC



D'Ascenzo et al, 2013 in press


That's all Folks!

FOR FURTHER INFORMATION

Please visit

www.metcardio.org