



Comparing Multiple Interventions Workshop 1

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**21st Cochrane Colloquium
Quebec City, Canada
September, 2013**

Disclosures

- ▶ Some of the work presented is funded by the Cochrane Collaboration Innovation Funds
- ▶ None of the presenters have any other conflicts of interest to disclose

Learning Objectives

- ▶ Describe what is an indirect comparison and a network meta-analysis
- ▶ Describe utilities of network meta-analysis for comparing multiple interventions
- ▶ Gain awareness about current methodologic challenges, statistical complexities, and common errors in the literature when multiple interventions are compared
- ▶ Understand the choice of appropriate review type (e.g., intervention review or overview) for the right question

Key Messages

- ▶ Network meta-analysis is an extension of standard, pair-wise meta-analysis.
- ▶ Use of network meta-analysis is often necessary for drawing inference about multiple competing interventions and a formal approach is preferable.
- ▶ The evolution of these methods has led us to re-evaluate the role of Overviews when comparing multiple interventions.

Section 1

Why use network meta-analysis?

Which Treatment Should be Recommended?



A 67-year-old woman was referred by her primary care physician for treatment of osteoporosis and progressive bone loss. One year before the visit, the patient had discontinued hormone-replacement therapy. She had subsequently begun to experience midback pain and lost 1.5 inch in height. A x-ray scan has confirmed a diagnosis of osteoporosis. One year later, a second scan showed a further decrease of bone mineral density at the lumbar spine, as well as a compression fracture of the 11th thoracic vertebra.

Which treatment should be recommended?

Paraphrased from
Favus NEJM 2010

Treatment of Osteoporosis and Risk of Hip Fracture

■ **Medical treatment:**

Over 10 drugs/combination of drugs

- ✓ Estrogen
- ✓ Selective estrogen receptor modulators (SERMs)- Raloxifene
- ✓ Calcium and/or vitamin D
- ✓ Bisphosphonates, e.g., alendronate (Fosamax), risedronate (Actonel)
- ✓ Other hormones, e.g., Teriparatide (Forteo)

■ **Cost: ranges from \$4 to \$130 per month**

Where is the evidence?

14 Cochrane systematic reviews

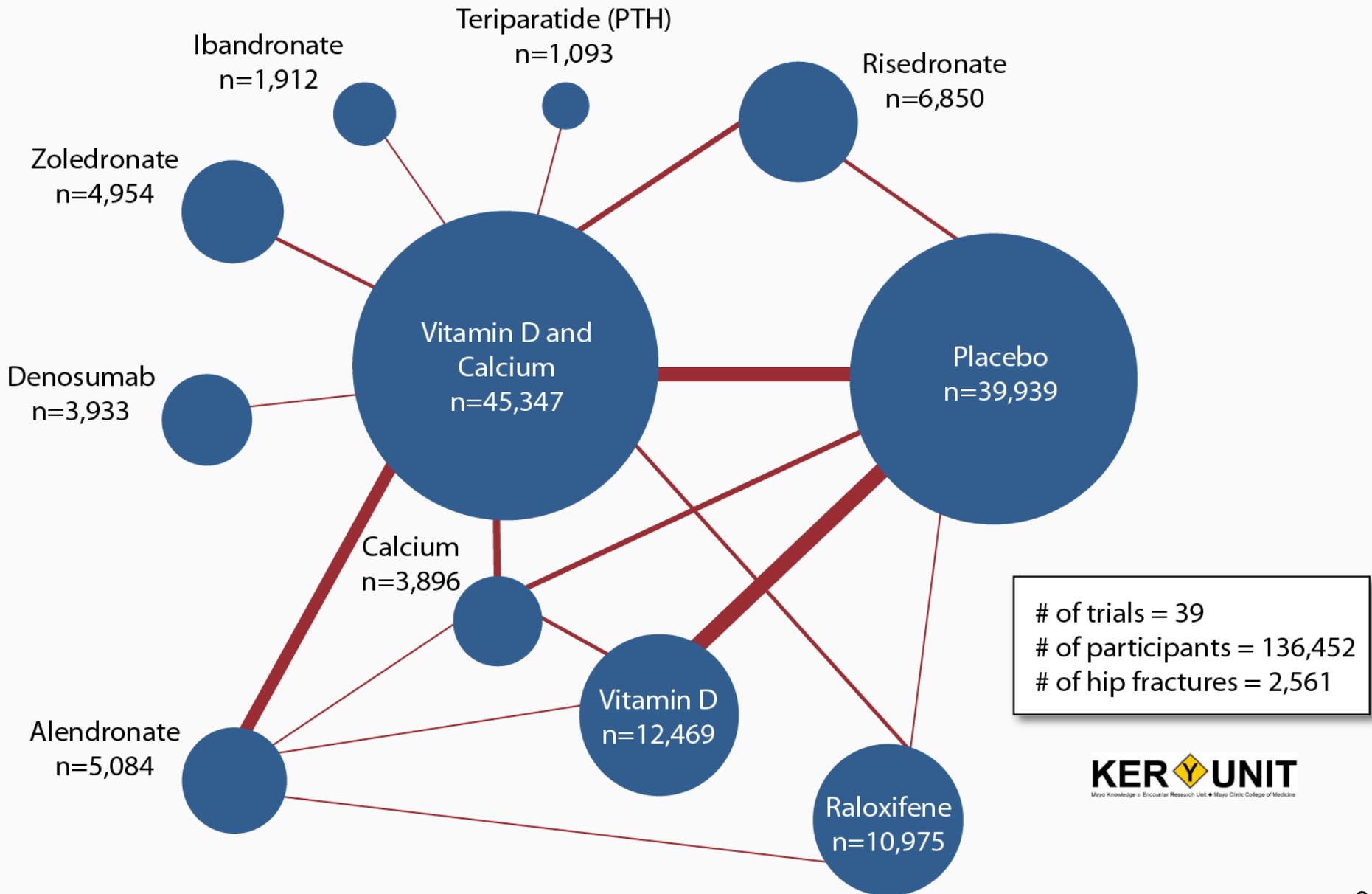
Which interventions work? In Whom?

*“At a dose of 10 mg per day, **alendronate** results in a statistically significant and clinically important reduction in vertebral, non-vertebral, hip and wrist fractures (Wells 2010).”*

*“No statistically significant reductions in non-vertebral, hip, or wrist fractures were found, regardless of whether **etidronate** was used for primary or secondary prevention (Wells 2010).”*

*“**Vitamin D alone** appears unlikely to be effective in preventing hip fracture... **Vitamin D with calcium** reduces hip fractures (Avenell 2009).”*

Osteoporosis and Hip Fracture: Evidence Network



Section 2

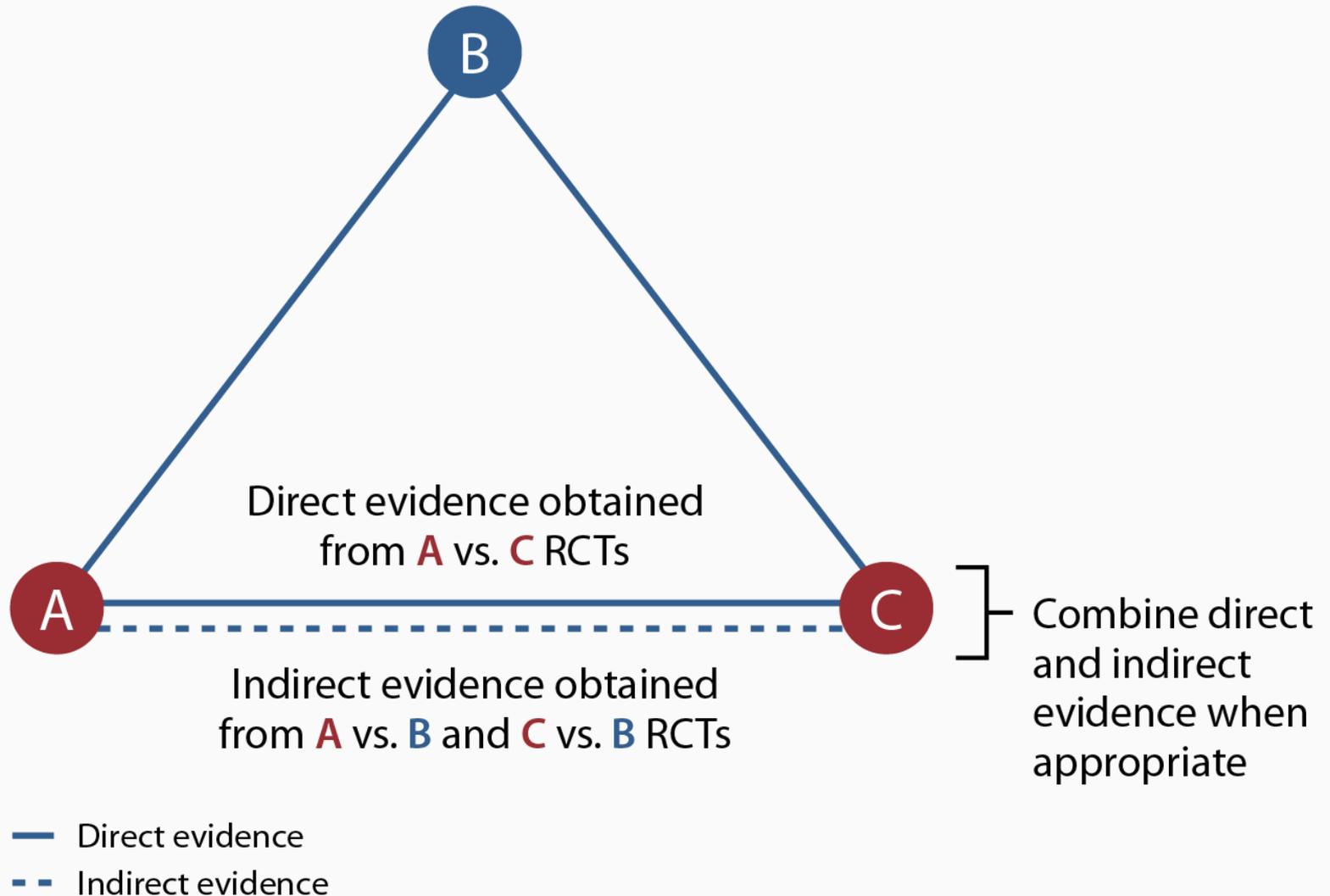
Introduction to network meta-analysis

What is a Network Meta-analysis?

Network (multiple treatments comparison) meta-analysis:

Meta-analysis, in the context of a systematic review, in which three or more treatments have been compared using both direct and indirect evidence from several studies.

Network Meta-Analysis Framework



Network Meta-Analysis Formulation: A Simple Example



$$OR_{Bup\ vs.\ Pla}^{Direct} = 0.51 \text{ (0.36 to 0.73); } I^2 = 54\%$$

$$OR_{NRT\ vs.\ Pla}^{Direct} = 0.57 \text{ (0.48 to 0.67); } I^2 = 12\%$$



$$OR_{Bup\ vs.\ NRT}^{Indirect} = \frac{OR_{Bup\ vs.\ Pla}^{Direct}}{OR_{NRT\ vs.\ Pla}^{Direct}} = \frac{0.51}{0.57} = 0.90 \text{ (0.61 to 1.34)}$$

On the log scale:

$$\log (OR_{Bup\ vs.\ NRT}^{Indirect}) = \log (OR_{Bup\ vs.\ Pla}^{Direct}) - \log (OR_{NRT\ vs.\ Pla}^{Direct})$$

$$Var [\log (OR_{Bup\ vs.\ NRT}^{Indirect})] = Var [\log (OR_{Bup\ vs.\ Pla}^{Direct})] + Var [\log (OR_{NRT\ vs.\ Pla}^{Direct})]$$

*NRT: Nicotine Replacement Therapy

Adapted by CTL from Bucher 1997; Caldwell 2005; Glenny 2005; Song 2003; Song 2009.

Network Meta-Analysis Formulation: A Simple Example



↑ Indirect evidence (28 RCTs) ↑

$$OR_{Bup\ vs.\ NRT}^{Indirect} = \frac{OR_{Bup\ vs.\ Pla}^{Direct}}{OR_{NRT\ vs.\ Pla}^{Direct}} = \frac{0.51}{0.57} = 0.90 (0.61\ to\ 1.34)$$

↑ Direct evidence (1 RCT) ↑

$$OR_{Bup\ vs.\ NRT}^{Direct} = 0.48 (0.28\ to\ 0.82)$$

- Ignore indirect evidence and rely on direct evidence only?
- Refer to indirect evidence and keep direct and indirect evidence separate?
- Cautiously combine the indirect and direct evidence when appropriate?

Inconsistency: discrepancies between the direct and indirect estimates

*NRT: Nicotine Replacement Therapy

Adapted by CTL from Bucher 1997; Caldwell 2005; Glenny 2005; Higgins 1996; Lu 2004, Lumley 2002; Salanti 2008; Song 2003; Song 2009.

Network Meta-Analysis Formulation: A Simple Example



↑ Indirect evidence (28 RCTs) ↑

$$OR_{Bup\ vs.\ NRT}^{Indirect} = 0.90 (0.61\ to\ 1.34)$$

↑ Direct evidence (1 RCT) ↑

$$OR_{Bup\ vs.\ NRT}^{Direct} = 0.48 (0.28\ to\ 0.82)$$

➔ Combining the direct and indirect evidence, a **simple** approach

$$d_{AC}^{pool} = w^{indirect} \times d_{AC}^{indirect} + w^{direct} \times d_{AC}^{direct}$$

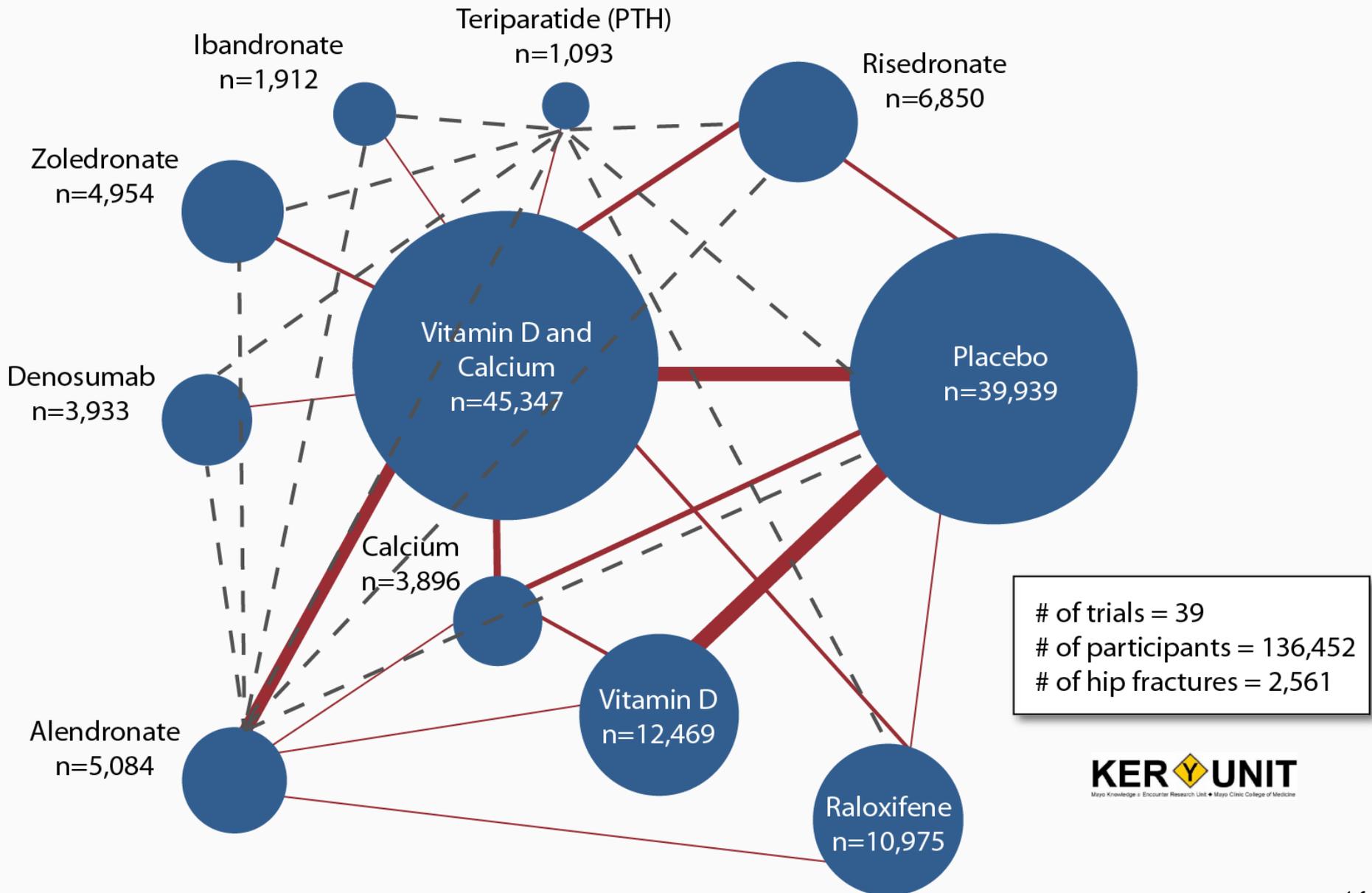
$$\text{Where } w_i = 1/\text{var}(d_{AC_i})$$

$$OR_{Bup\ vs.\ NRT}^{Combined} = \mathbf{0.68 (0.37\ to\ 1.25)}$$

*NRT: Nicotine Replacement Therapy

Adapted by CTL from Bucher 1997; Caldwell 2005; Glenny 2005; Higgins 1996; Lu 2004, Lumley 2002; Salanti 2008; Song 2003; Song 2009.

Osteoporosis and Hip Fracture: Evidence Network



Treatment of Osteoporosis and the Risk of Hip Fracture

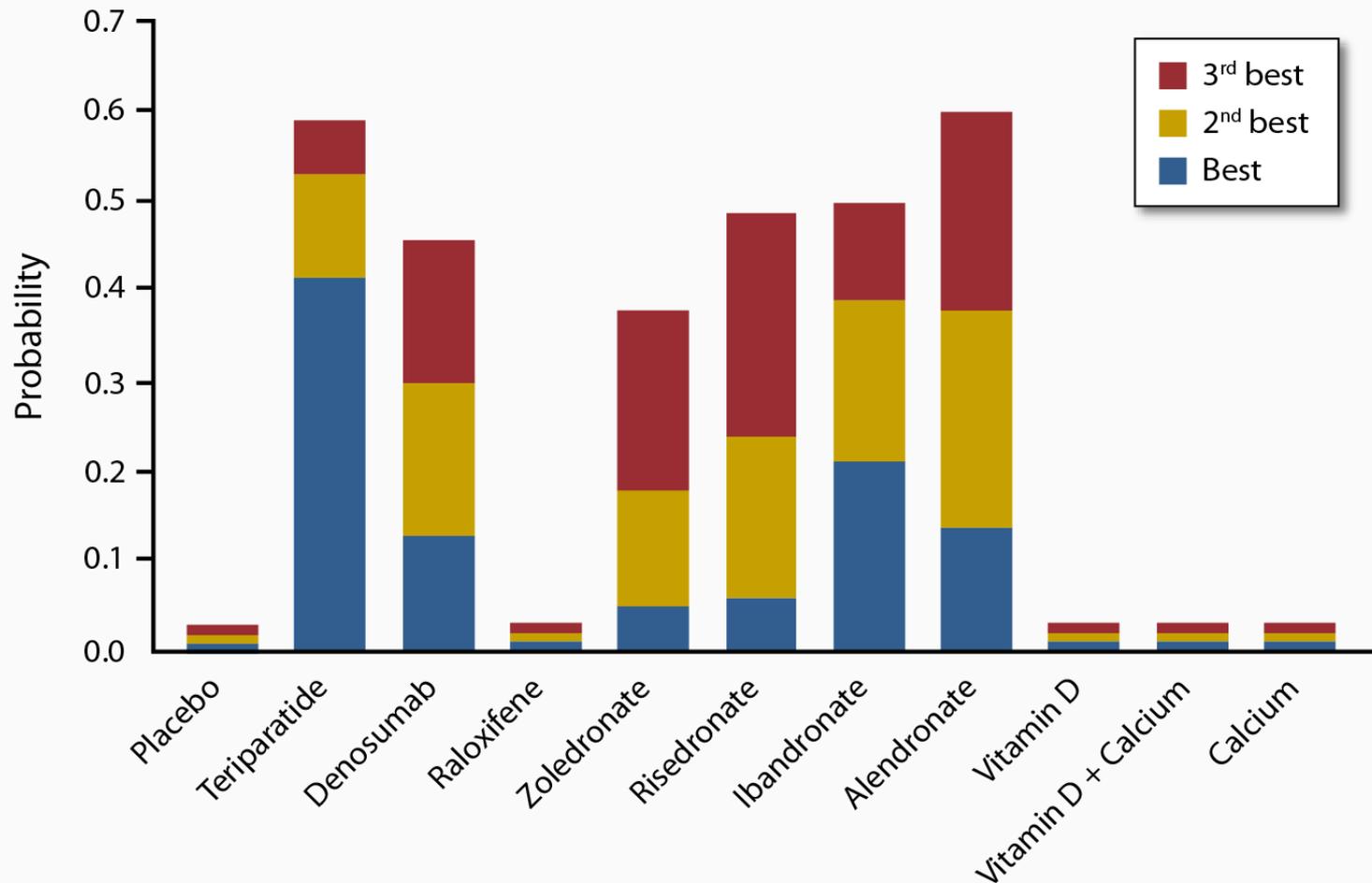
- Pairwise odds ratio and 95% credible interval

- Odds ratio <1 favors the treatment in the row
- Odds ratio >1 favors the treatment in the column
- # of trials =39
- # of participants =136,452
- # of hip fracture =3,850

Zoledronate		
0.97 (0.55; 1.51)	Risedronate	
0.94 (0.38; 2.44)	0.97 (0.41; 2.55)	Ibandronate
0.90 (0.52; 1.52)	0.93 (0.54; 1.60)	0.94 (0.36; 2.41)

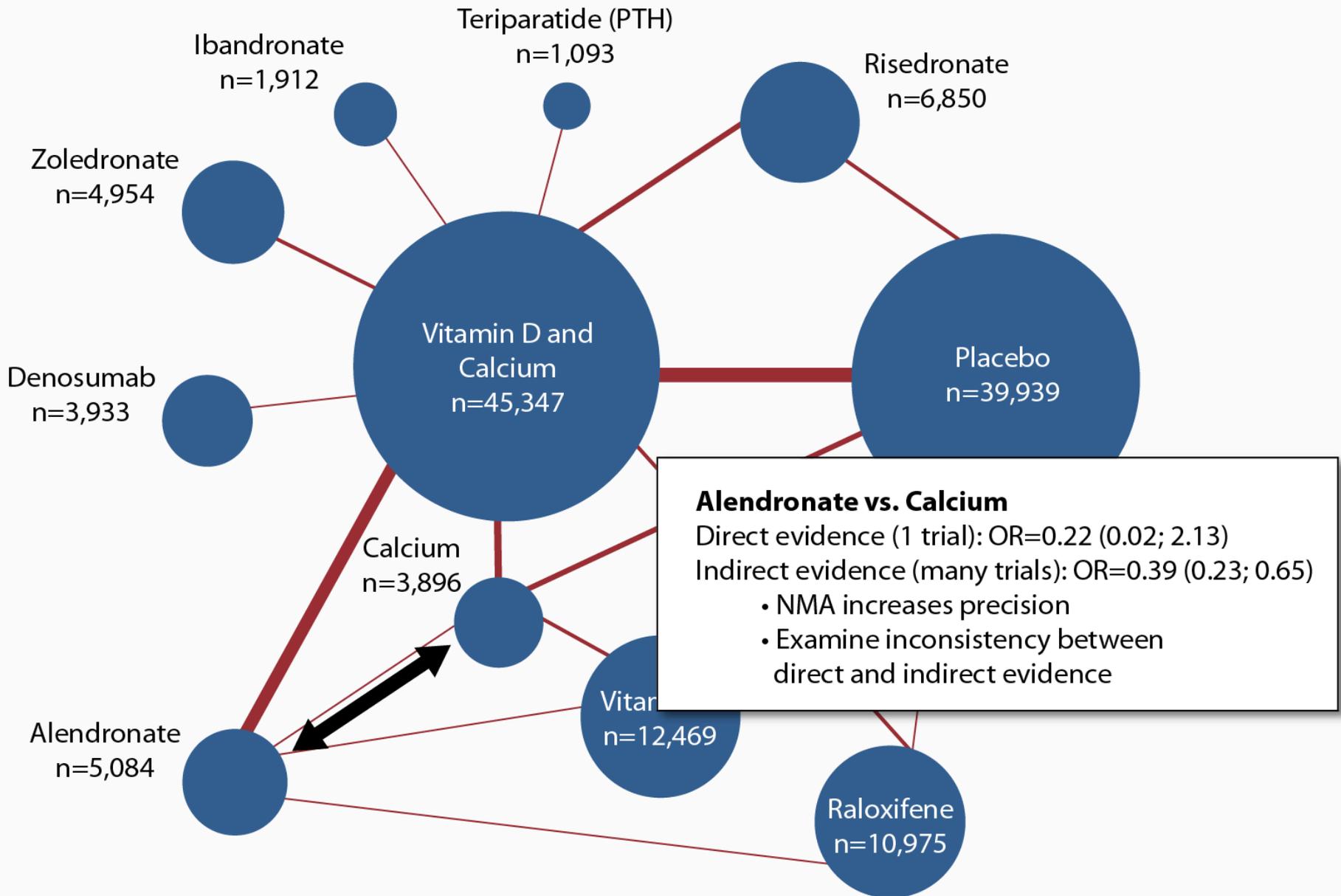
Drugs for Reducing Risk of Hip Fracture: Probability

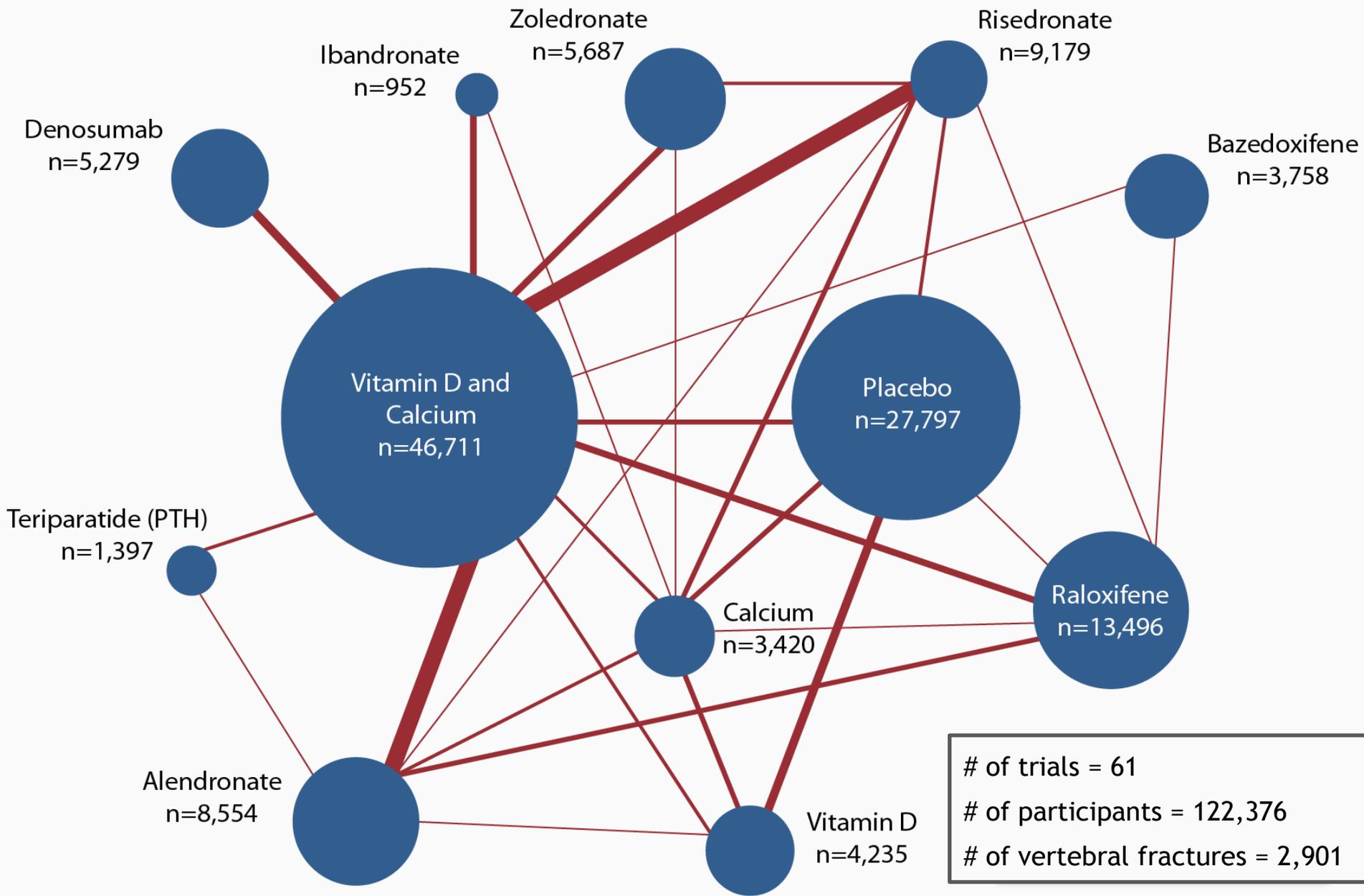
- Probability ranking of drugs in reducing the risk of hip fracture



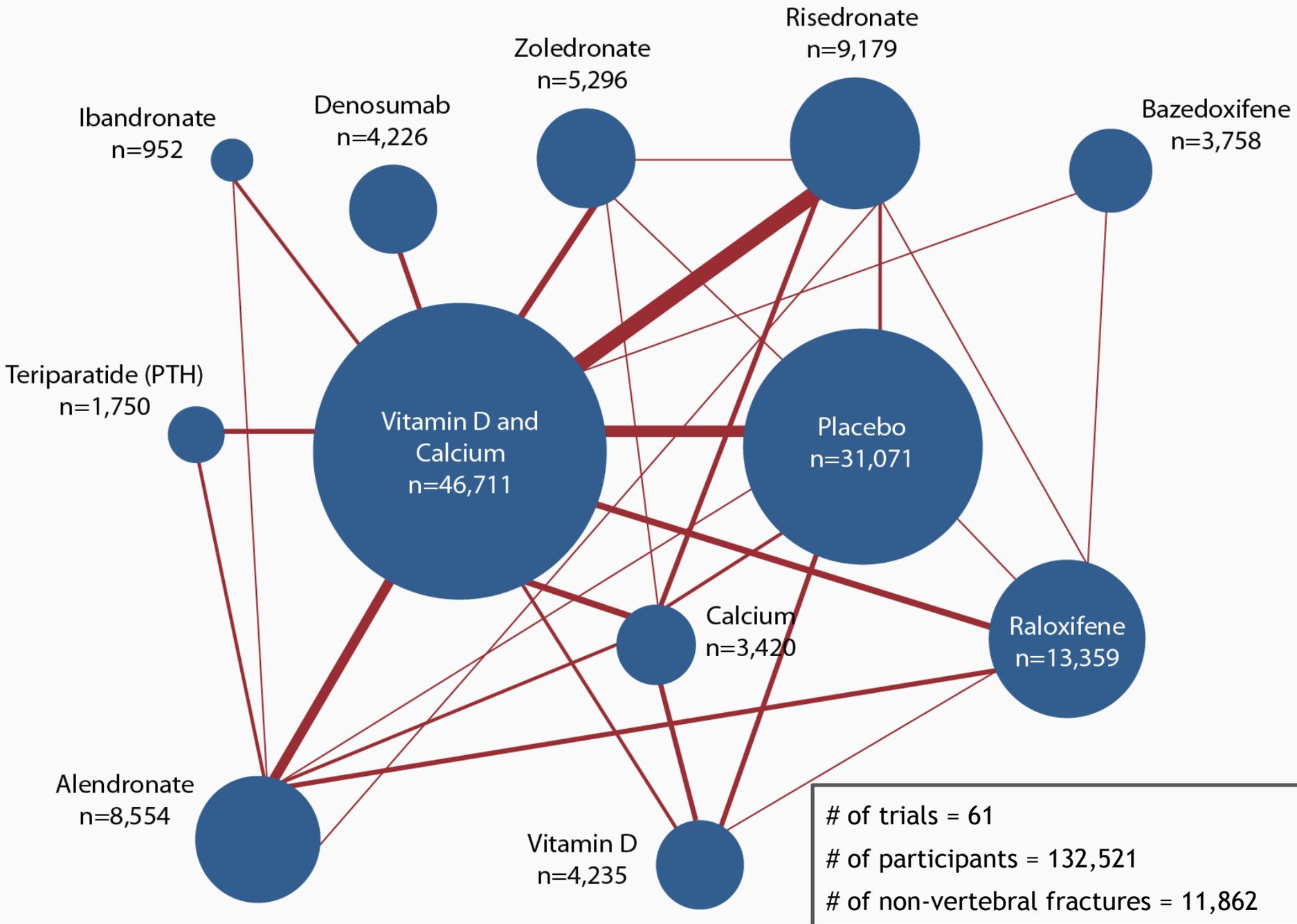
Adapted by CTL from Murad H., Li T., Puhan M., et al. *Journal of Clinical Endocrinology & Metabolism* (in press).

Osteoporosis and Hip Fracture: Evidence Network



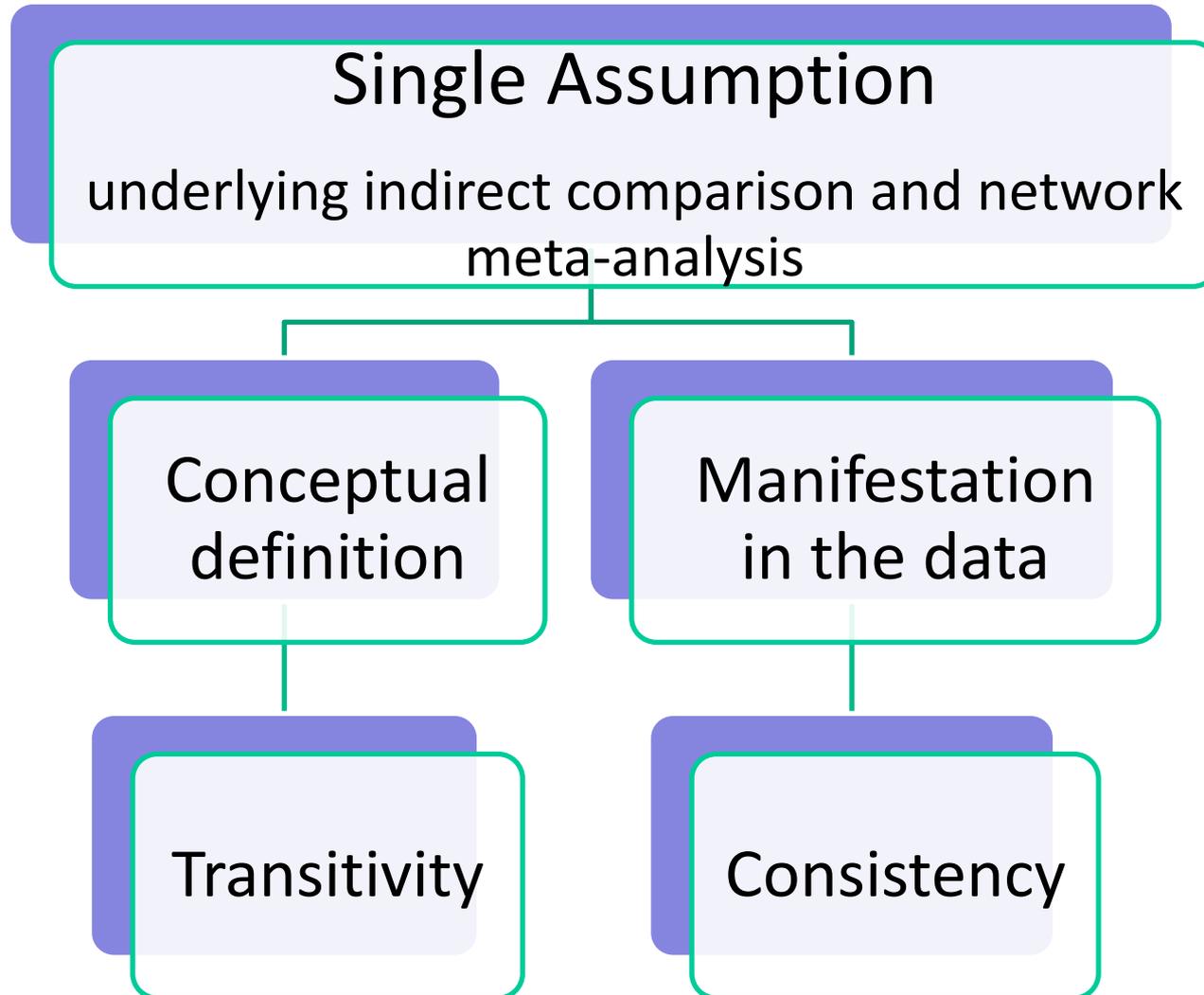


of trials = 61
 # of participants = 122,376
 # of vertebral fractures = 2,901



of trials = 61
 # of participants = 132,521
 # of non-vertebral fractures = 11,862

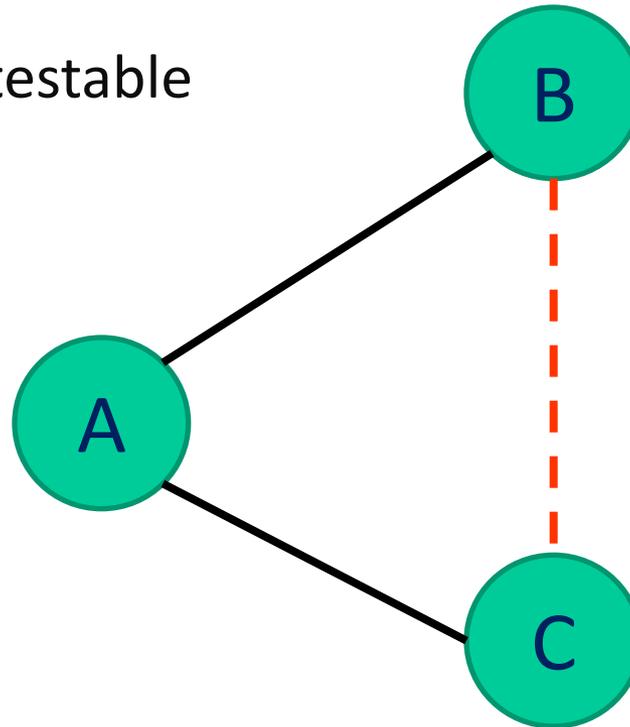
Assumption underlying indirect comparison and network meta-analysis



Transitivity/Consistency

An underlying assumption when μ'_{BC} is calculated is that one can learn about B versus C via A.

Sometime it is an untestable assumption



The anchor treatment A is 'transitive'

....but you can evaluate clinically and epidemiologically its plausibility

Check the Assumptions for Analysis

Example 1: Consider a placebo that may be given in an oral or an intravenous form.

If treatment A is an oral treatment and treatment B is an intravenous one, then it may not be valid to compare A and B indirectly through the placebo C if the different routes of administration produce different effects.

This may violate the transitivity assumption because...

Five Interpretations of Transitivity

1. Participants included in the network could in principle be randomized to any of the three treatments A, B, C.
2. Treatment C is similar when it appears in AC and BC trials
3. 'Missing' treatment in each trial is missing at random
4. There are no differences between observed and unobserved relative effects of AC and BC beyond what can be explained by heterogeneity
5. The two sets of trials AC and BC do not differ with respect to the distribution of effect modifiers

Salanti (2012)

Example 1: Consider a placebo that may be given in an oral or an intravenous form.

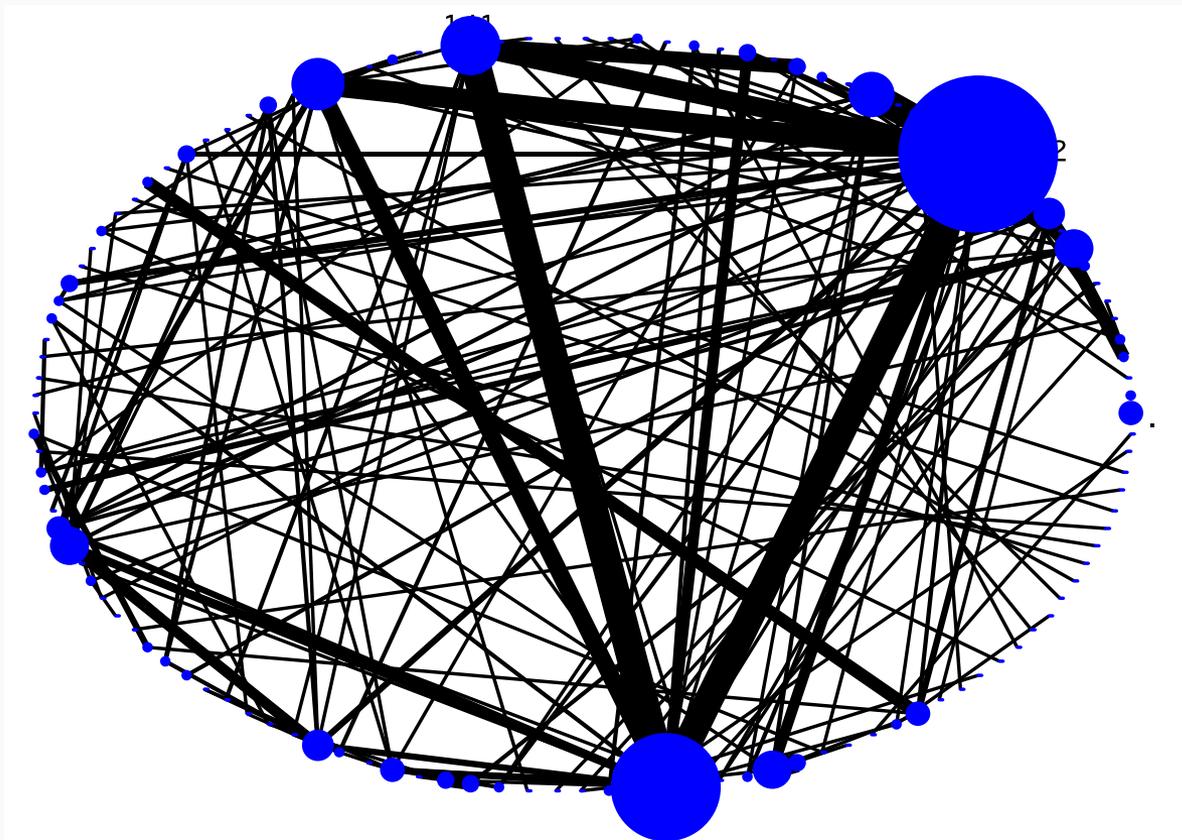
1. The different protocols would preclude examining all treatments together in the same study;
2. The placebo has a different route of administration in the two types of trials;
3. The treatment omitted is not given because it requires a different protocol;
4. The unobserved treatment effect might come from a different distribution than the one observed because it would have a different mode of administration;
5. The route of administration is a potential effect modifier of the treatment effect.

Example 2: Intervention A is clinically indicated only for previously untreated patients and intervention B is clinically indicated only when all other treatments have failed.

- ✓ Initial interventions (for treatment naïve patients) and add-on interventions could be studied in the same review.
- ✓ The key is to analyze incomparable interventions and distinct populations in separate network meta-analyses.

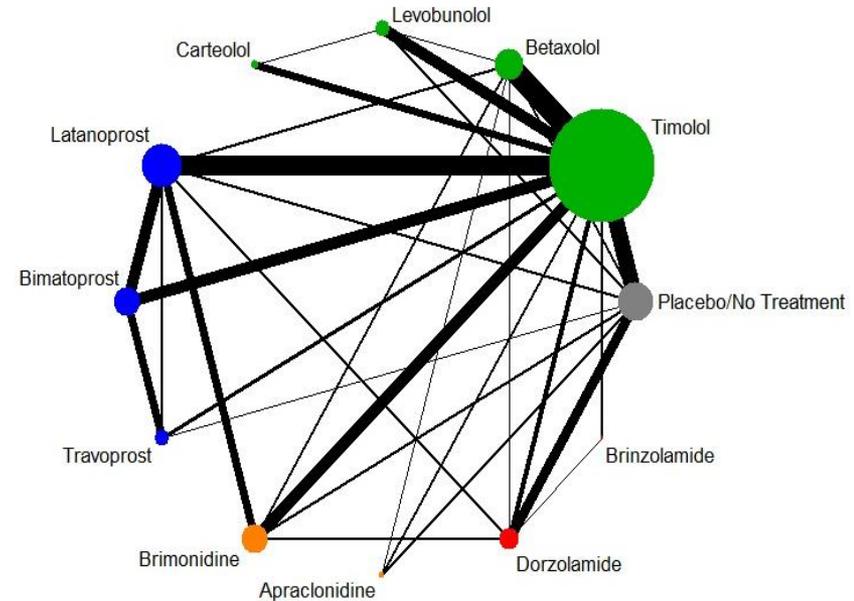
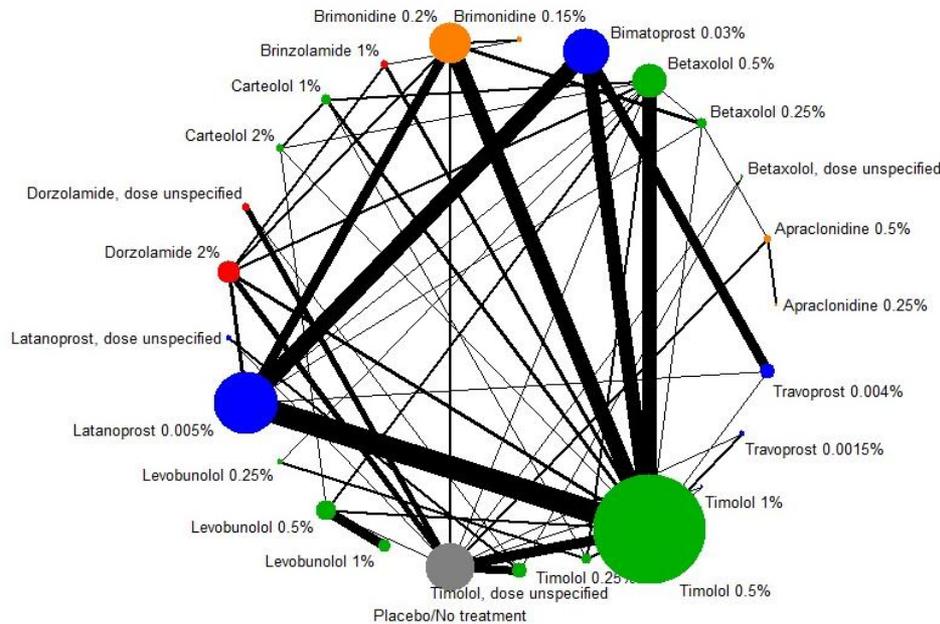
Example 3: Lumping or splitting nodes?

367 RCTs examining 136 unique eye drops for glaucoma



Check the Assumptions for Analysis

Example 3 (cont'd): Lumping or splitting nodes?



O4.02.3 Evaluating the transitivity assumption when constructing network meta-analyses: lumping or splitting? Hamilton (301 B) Monday, Sep 23 from 1:30-3:00

Alpha Agonists
Beta-Blockers
Carbonic Anhydrase Inhibitors
Prostaglandins

Section 3

Methodological challenges and
research opportunities for network
meta-analysis

Wrong Methods for Comparing Multiple Interventions

- In this example, say A vs. B is the comparison of interest

Treatment	A	B	C	D
RCT 1	✓	✓		
RCT 2	✓	✓	✓	
RCT 3	✓		✓	
RCT 4	✓			✓
RCT 5		✓	✓	

- Correct method
- Wrong method

Wrong Methods: Pooling Study Arms Across Trials

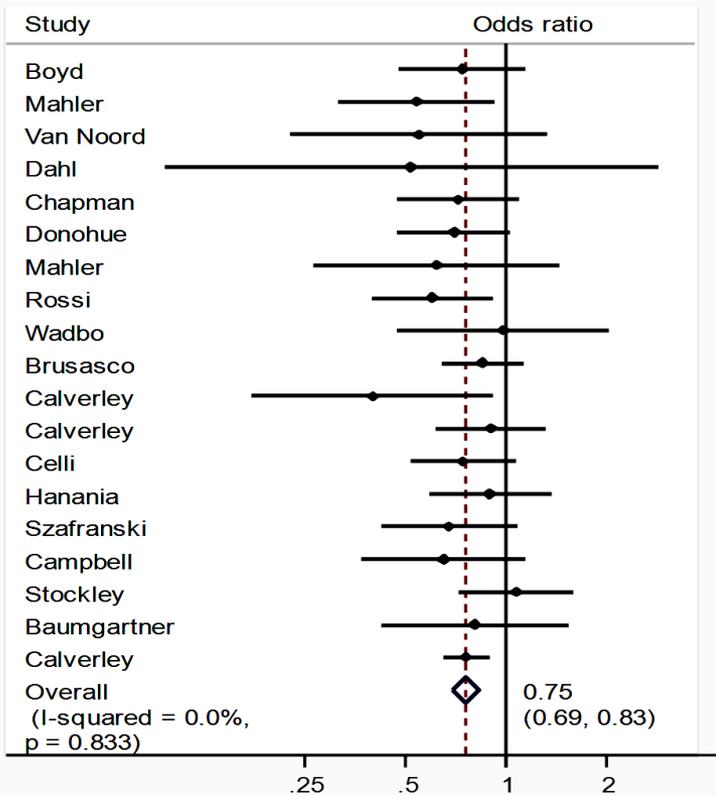
- “When looking at all the study arms of either timolol or the lipid class drugs...”

Table 3. Efficacy of IOP-lowering drugs (all studies)

	Timolol	Latanoprost	Latanoprost + timolol	Bimatoprost	Bimatoprost + brimonidine
0-6 months data					
No. of study arms	21*	33†	11‡	18§	1**
No. of completed patients after 6 months	1946	2135	746	2326	13
Baseline IOP (mmHg), weighted mean	25.62	24.84	24.72	25.74	24.80
IOP reduction (mmHg), mean	5.19	6.44	5.85	7.13	8.50
IOP reduction (mmHg), weighted mean	5.78	6.69	6.18	7.81	8.50
IOP%–reduction, weighted mean	22.2%	26.7%	24.1%	30.3%	34.3%

Conventional Meta-Analysis

- Entire evidence for one estimate



x trials
inform

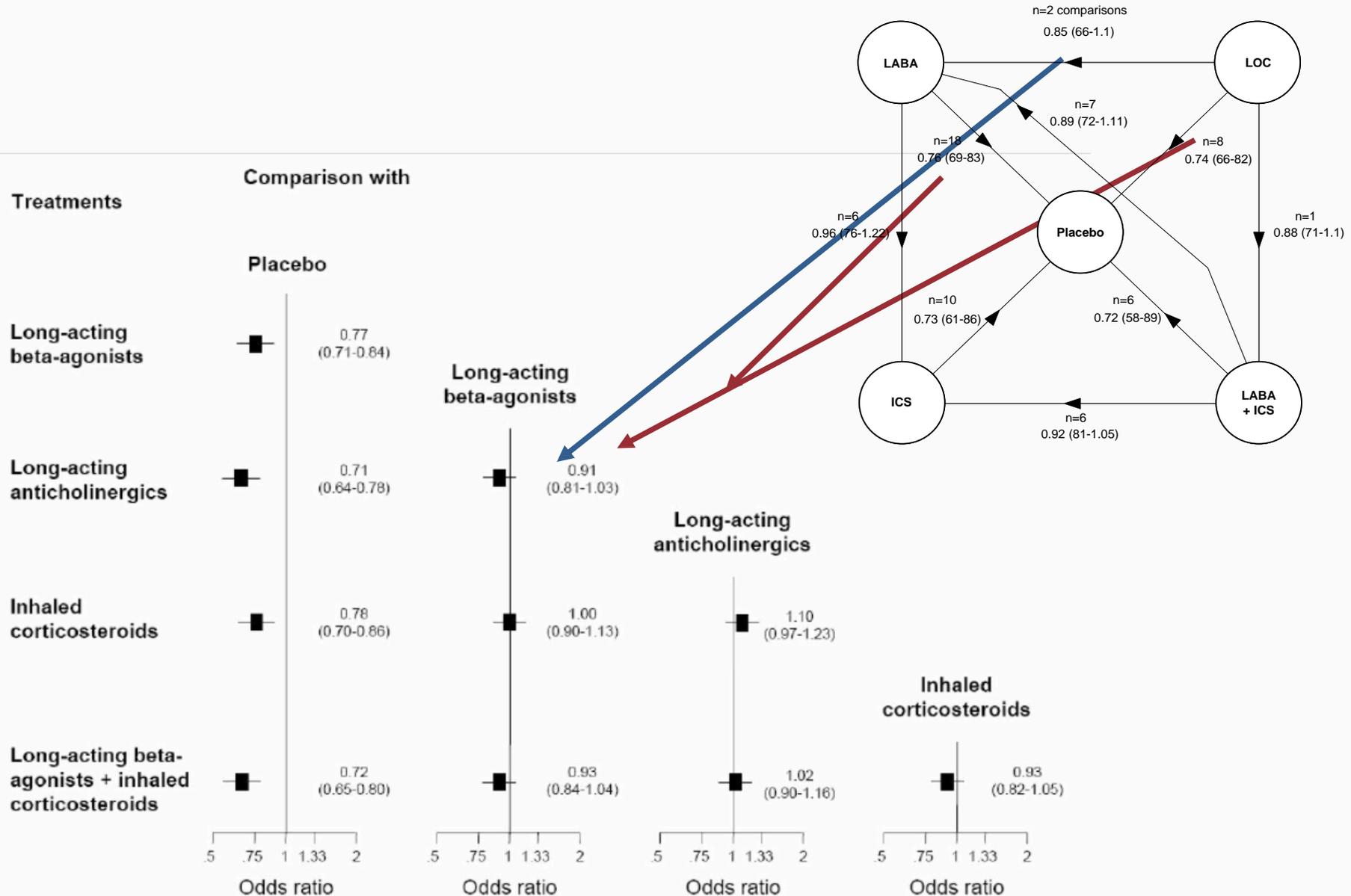


1 point
estimate

Quality of evidence

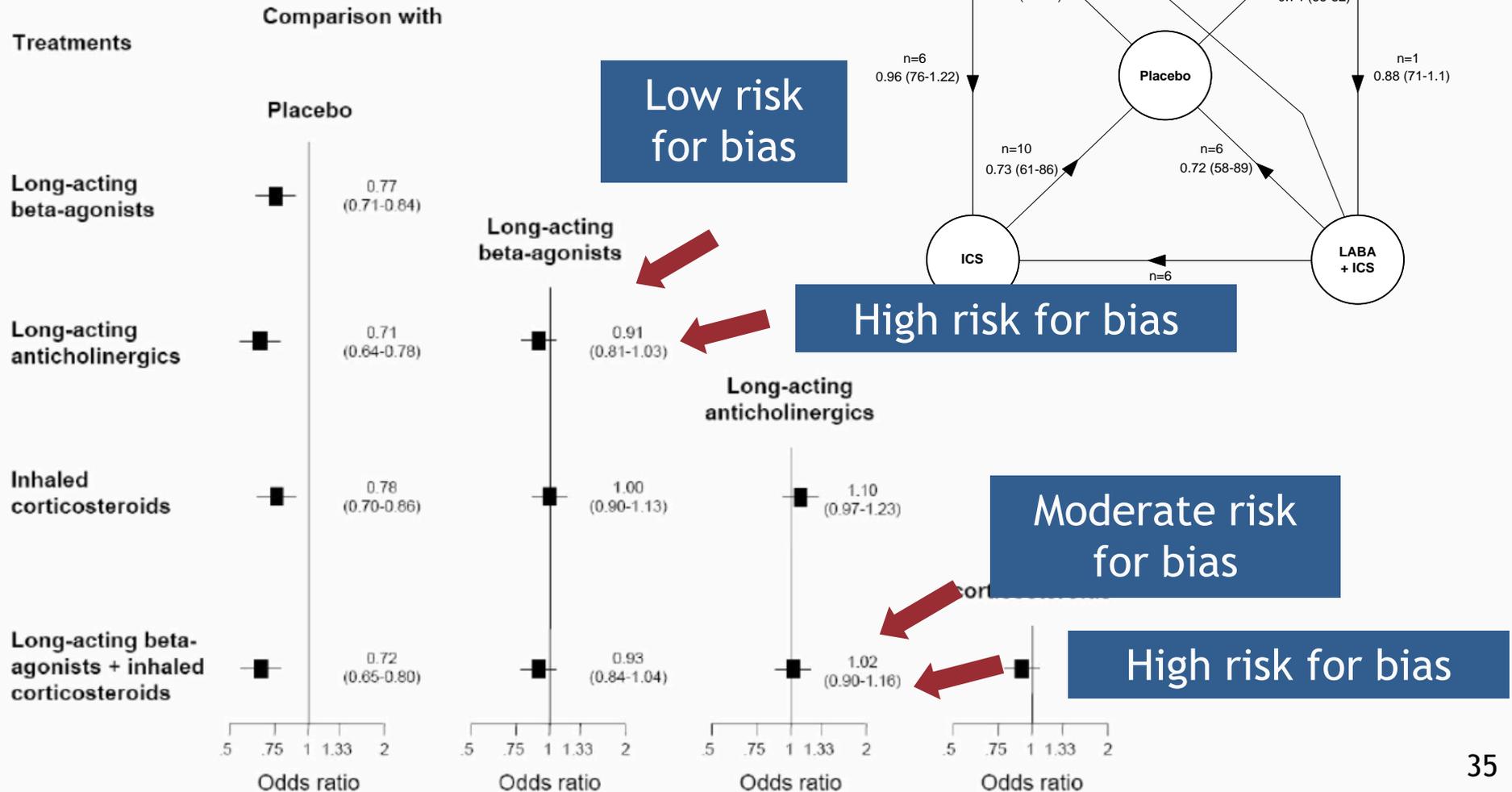
- Risk of bias (Cochrane)
- Summary of quality items
- (GRADE)
- scores (Jadad, etc)

Trials Contribute to Different Estimates



Heterogeneous Quality of Evidence Across Network

Within and across comparisons



Section 4

Should this Review be an Overview
or an Intervention Review?

■ **Misconception**

- ▶ Any review that compares 3 or more interventions must use the Overview format

Why Overviews?

- Summarize a group of related Cochrane Reviews
- “Friendly front end” – What have Cochrane Reviews shown about this question?
- Synthesis of results across Cochrane Reviews

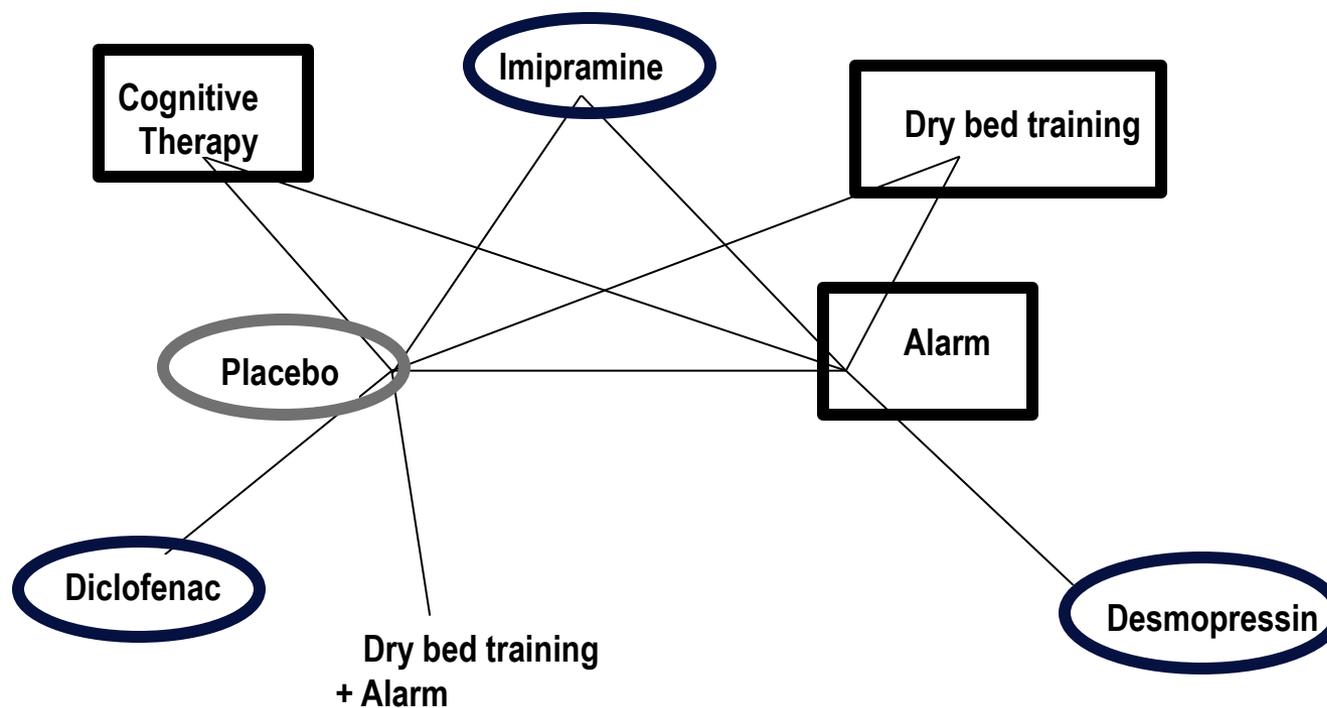
- **The Overview as a “Review of Reviews”**
- **Search Strategy**
 - ▶ Intervention reviews search for trials
 - ▶ Overviews search for reviews
- **Approach to Analysis**
 - ▶ Intervention reviews use a trial level analysis
 - ▶ Overviews may be able to use a review level analysis

Could Overviews use Network Meta-Analysis?

- May be possible sometimes
- But should RARELY be done

- The problem is NOT with the STATISTICS

Interventions for Enuresis



J Clin Epidemiol. 63:875-82 PMID: 20080027

Trial or Review summaries for NMA?

	Review level summaries		Trial level summaries	
Treatment	<i>Prob best</i>	<i>RR (no treatment)</i>	<i>Prob best</i>	<i>RR (no treatment)</i>
No treatment	0	1	0	1
Alarm	0.08	0.40 (0.31, 0.53)	0.03	0.41 (0.30, 0.53)
DBT	0	0.82 (0.66, 1.03)	0.01	0.82 (0.66, 1.02)
Desmopressin	0	0.54 (0.35, 0.84)	0.04	0.58 (0.37, 0.88)
Imipramine	0	0.68 (0.53, 0.89)	0	0.69 (0.52, 0.89)
Psych therapy	0.01	0.65 (0.35, 1.22)	0.02	0.69 (0.35, 1.22)
DBT + alarm	0.78	0.19 (0.05, 0.76)	0.78	0.24 (0.05, 0.73)
Diclofenac	0.13	0.46 (0.16, 1.38)	0.12	0.53 (0.16, 1.35)

Work in progress: do not cite

BUT

- Was the transitivity/consistency assumption satisfied?
 - ▶ Requires detailed knowledge of the trials involved & their methods
- Were all relevant trials included?
 - ▶ Out-of-date Reviews
- Were all relevant interventions included?
- Was outcome selection consistent across Reviews?

Could Overview Methods Be Adapted?

■ **Search Strategy**

- ▶ Start with a search for reviews
- ▶ Extend the search to include additional trials discovered by other means

■ **Approach to Analysis**

- ▶ Abandon the review level analysis
- ▶ Use a trial level analysis instead

■ **Too confusing!**

■ **Inferior method**

Cochrane Methods Innovations Fund Project

- Consultation with Cochrane Collaborators
 - ▶ Paris and Oxford mid-year meetings
- Paper & recommendations available on cmimg.cochrane.org



Comparing Multiple Interventions Methods Group

Welcome

The Cochrane Comparing Multiple Interventions Group

The Comparing Multiple Interventions Group focuses on *methodology for comparing multiple interventions* in Cochrane Intervention Reviews or Overviews. We consider how to best meet the needs of a healthcare decision-maker approaching The Cochrane Library asking "*which intervention should I use for this condition?*"

Cochrane Overviews were developed by the Collaboration's 'Umbrella Reviews Working Group', and aim to summarize the findings of multiple standard Cochrane reviews, for example when different reviews address different interventions for a single clinical condition. A key aim of the Methods Group is to consider how the aims, methods and processes for Overviews might evolve over time.

The Methods Group also brings together expertise in *network meta-analysis* (also known as *multiple treatments meta-analysis* or *mixed treatment comparisons meta-analysis*). We are exploring issues around the validity, breadth, structure and interpretation of these methods in standard intervention reviews as well as their potential role in Overviews.

Overview or Intervention Review?

Guidance for the preparation of Overviews is included in The Cochrane Handbook for Systematic Reviews of Interventions [Chapter 22: Overviews of reviews](#).

The contents of this chapter have been supplemented by [an additional set of recommendations](#) prepared by the CMIMG as part of a [project funded by the Cochrane Methods Innovations Fund](#).

Statistical Issues in Comparing Multiple Interventions

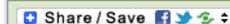
These are addressed in the Cochrane Handbook - [Chapter 16.6: Indirect comparisons and multiple-treatments meta-analysis](#).

Stream 2 of our Cochrane Methods Innovations Fund Project is expanding on this guidance and has produced a number of useful resources which are available on the [Statistical Issues](#) section of our website.

How to interpret and present results

Search

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Our news

[STATA Workshop for Network Meta-analysis in Quebec: 'Graphs to enhance understanding and improve interpretability of the evidence from network meta-analysis: a hands-on tutorial in STATA'](#)

[R package 'netmeta' for network meta-analysis by G. Rücker](#)

[A 3-day course on "Indirect and Mixed Treatment Comparisons" in Leicester, November 11-13, 2013.](#)

[Seven tutorial papers on evidence synthesis for medical decision making](#)

[New Recommendations for comparing multiple interventions in Cochrane Reviews](#)

[New methods article on missing outcome data in network meta-analyses](#)

[Special Issue on Network Meta-analysis published in Research Synthesis Methods](#)

Welcome

About US

[Comparing Multiple Interventions in Cochrane Reviews](#)

[Authoring and Editing](#)

[Statistical Issues](#)

[Glossary](#)

Relevant Publications and Links

[Cochrane Overviews & Protocols](#)

[Publications on Methodological Issues](#)

[Publications That Include a Network Meta-Analysis](#)

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Workshops and Presentations

[2013 Cochrane Methods Training Event](#)

[Statistical considerations in indirect comparisons and network meta-analysis](#)

[Editorial considerations for reviews that compare multiple interventions](#)

[Auckland 2012](#)

[Madrid 2011](#)

[Workshops - 2010 and earlier](#)

Newsletters

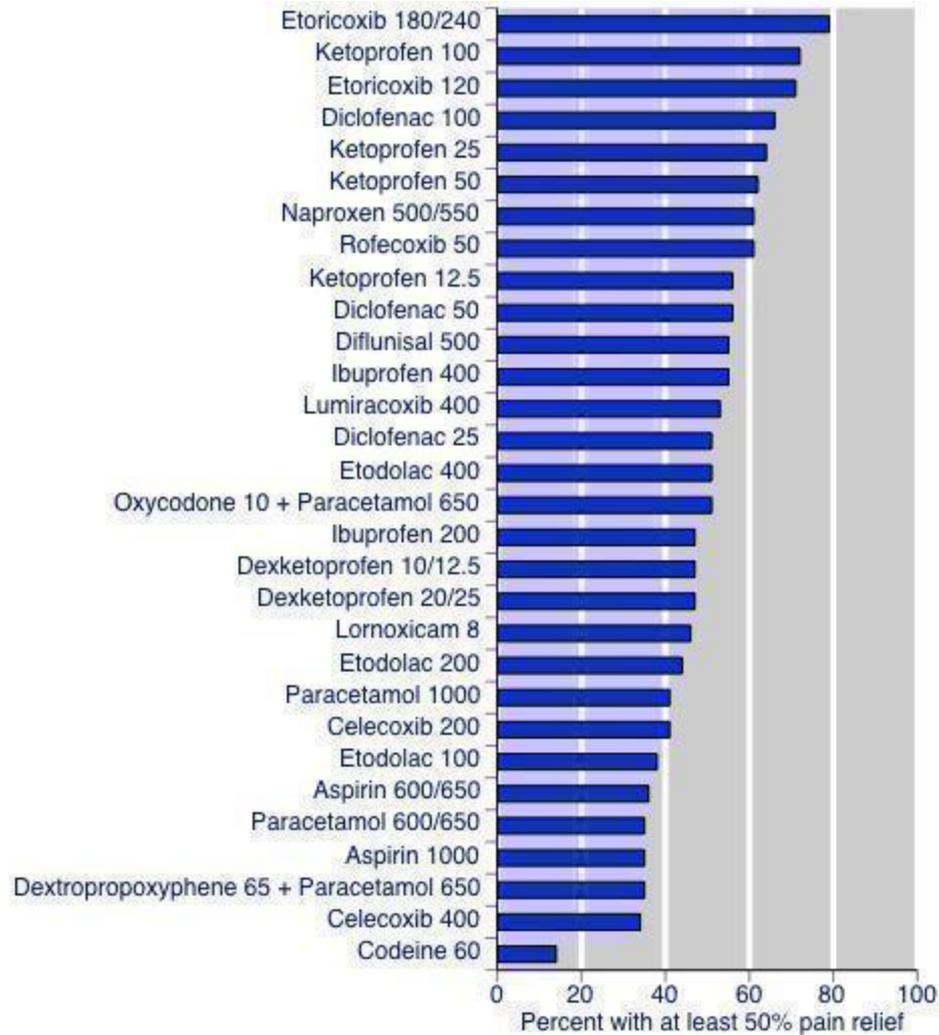
- **The Overview as a “Review of Reviews”**
- **Search Strategy**
 - ▶ Overviews search for Reviews
- **Approach to Analysis/Synthesis**
 - ▶ Overviews should use a Review level synthesis
 - ▶ May be a narrative synthesis or a juxtaposition of Review results
 - ▶ Network meta-analysis may be possible on RARE occasions

- The *Intervention Review* format is ***strongly recommended*** for reviews that include indirect comparisons.
- Because these comparisons require detailed knowledge of the trials.
- There may be exceptions

Possible Exceptions

- The Overview authors know the trials in detail
 - ▶ Because the trialists used a standardized protocol
 - ▶ Because the Overview authors were authors of all of the included Cochrane Reviews

Single Dose Oral Analgesics For Acute Postoperative Pain



Recommendation

Overviews that facilitate “informal” indirect comparison by readers must address transitivity issues

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Treatments versus Placebo			
Alcohol withdrawal seizures - Benzodiazepine objective Follow-up: mean 10 days	Study population		RR 0.16 (0.04 to 0.69)	324 (3 studies)	■■■■ moderate ¹
	80 per 1000	13 per 1000 (3 to 55)			
	Medium risk population				
	69 per 1000	11 per 1000 (3 to 48)			
Alcohol withdrawal seizures - Anticonvulsants objective Follow-up: mean 10 days	Study population		RR 0.52 (0.25 to 1.07)	1108 (10 studies)	■■■■ moderate ²
	101 per 1000	53 per 1000 (25 to 108)			
	Medium risk population				
	150 per 1000	78 per 1000 (38 to 161)			
Alcohol withdrawal seizures - Benzodiazepine	80 per 1000	13 per 1000 (3 to 55)	RR 0.16 (0.04 to 0.69)	324 (3 studies)	■■■■ moderate ¹
Alcohol withdrawal seizures - Anticonvulsants	101 per 1000	53 per 1000 (25 to 108)	RR 0.52 (0.25 to 1.07)	1108 (10 studies)	■■■■ moderate ²

Recommendation

- **The Collaboration should re-examine the issue of “overlapping” Reviews**
- When one of the Reviews is an Intervention Review that:
 - ▶ Compares multiple interventions
 - ▶ Using formal methods (such as network meta-analysis)
 - ▶ With the intent of finding the interventions likely to have the highest efficacy or fewest adverse effects.
- Agreement from the Co-ordinating Editors and the Methods Executive at the 2013 mid-year meeting in Oxford
- Tech team and Wiley working on a flag to clearly indicate these reviews on The Cochrane Library

Can Overviews Sometimes Be Used to Compare Interventions?

- Still under active discussion
- Your input needed
- Some examples from existing overviews
 - ▶ Direct comparisons only
 - ▶ Maps of the available evidence
 - ▶ Analogous comparisons

Surgical Approaches to Cholecystectomy

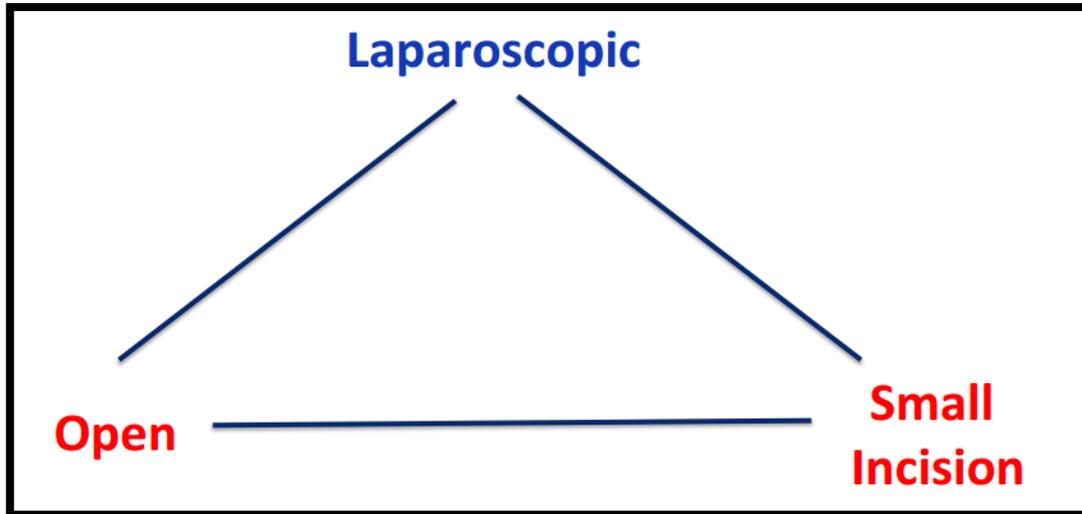


Table 5. Summary of Findings table: OC vs SIC

Table 6. Summary of Findings table: OC vs LC

Table 7. Summary of Findings table: LC vs SIC

Direct Only - Surgical Techniques for Laparoscopy

- Simple network
- All direct comparisons covered by existing Cochrane Intervention Reviews
- All reviews were up to date
- Overview authors were also the authors of all 3 Intervention Reviews

- How often are all of these conditions met?
- When is the direct evidence “good enough” on its own?

Overviews that Map the Evidence

- Consumer-oriented interventions for ***evidence-based prescribing and medicines use***: an overview of systematic reviews
- • ***Pain management for women in labour***: an overview of systematic reviews
- • An overview of reviews evaluating the ***effectiveness of financial incentives*** in changing healthcare professional behaviours and patient outcomes
- • ***Interventions for fatigue and weight loss*** in adults with advanced progressive illness
- ***Assisted reproductive technology***: an overview of Cochrane Reviews.

Overviews that Map the Evidence

- No attempt at a statistical synthesis
- Review-by-review narrative synthesis
- May include a new conceptual framework
 - ▶ Taxonomies of interventions or outcomes
- May include vote counts

Pain management for women in labour

Table 13. (1.) Results by individual review - hypnosis

Table 14. (2.) Results by individual review - biofeedback

Table 15. (3.) Results by individual review - sterile water

Table 16. (4.) Results by individual review - immersion in water

Table 17. (5.) Results by individual review - aromatherapy

Table 18. (6.) Results by individual review - relaxation techniques

Table 19. (7.) Results by individual review - acupuncture

Table 20. (8.) Results by individual review - massage, reflexology and other manual methods

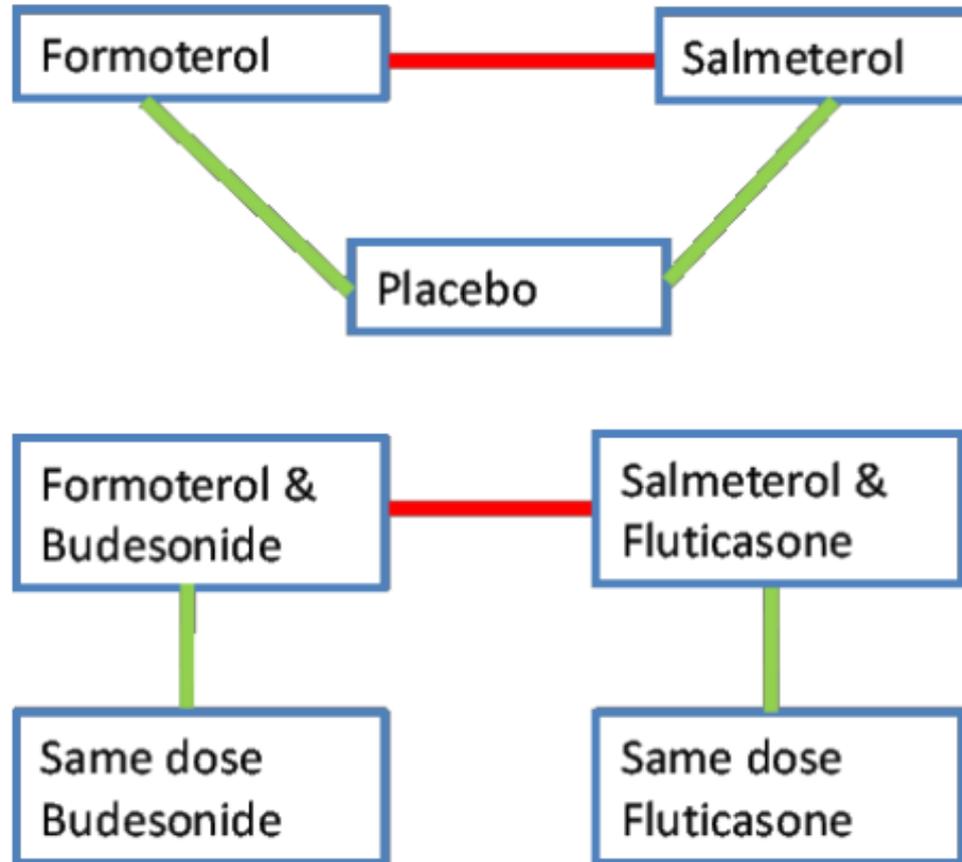
Table 21. (9.) Results by individual review - TENS

Table 22. (1.) Results by individual review - inhaled analgesia

Table 23. (2.) Results by individual review - parenteral opioids versus placebo/IM opioids versus different IM opioids

Table 24. (2.) Results by individual review - parenteral opioids - IV opioids versus different IV opioids/parenteral opioids versus different intervention

Analogous - Adverse effects of LABAs for Asthma



Other Uses for Overviews

- That do not involve comparing multiple interventions

*Some Overviews Do Not **Compare** Interventions*

- Different outcomes of a single intervention
 - ▶ e.g. Hormone Replacement Therapy
- Different conditions, problems, or populations
 - ▶ e.g. Aspirin to prevent stroke
- Related non-competing interventions

Conclusions

- ▶ In many problems, investigators would like to synthesize evidence from multiple interventions tested in multiple trials.
- ▶ When good trial-level data that satisfy assumptions of network meta-analysis are available and goal is to rank interventions, network meta-analysis is preferred.
- ▶ When the objective is not to compare competing interventions, network meta-analysis is not useful.

Key Messages

- ▶ Network meta-analysis is an extension of standard, pair-wise meta-analysis.
- ▶ Use of network meta-analysis is often necessary for drawing inference about multiple competing interventions and a formal approach is preferable.
- ▶ Intervention reviews are encouraged if indirect comparisons are to be performed.
- ▶ The choice between the Intervention Review or Overview format is less clear for reviews where no indirect comparisons are planned.