

"You can run, but you cannot hide: decision-making and indirect comparisons in a resource limited healthcare system"

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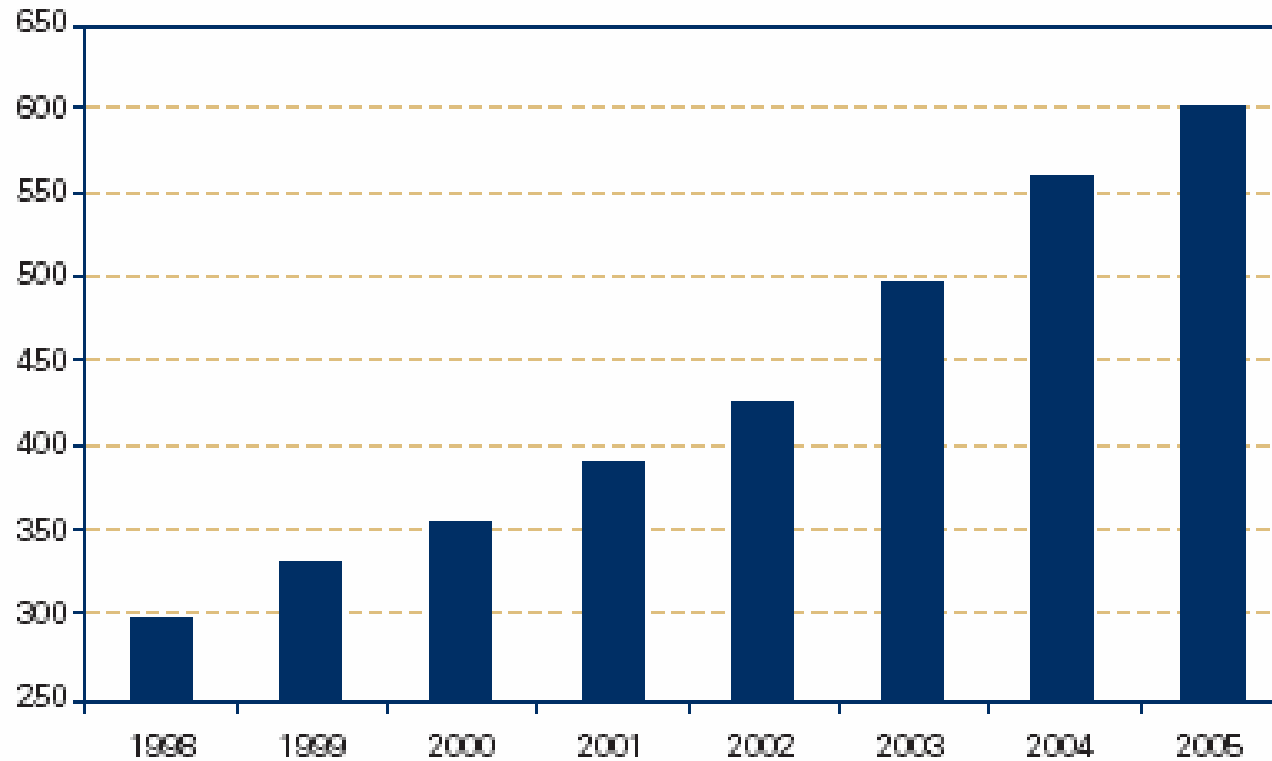
ISCB 2009

Outline

- What makes a useful cost-effectiveness analyses
- Analysis of networks of trial evidence
- Conclusions

The challenge: growth of healthcare costs

Figure 3.1: Global pharmaceutical sales (US \$billion)



Source: IMS, 'Global Pharmaceutical Perspectives 2005', IMS Health Total Market Estimates and Global Pharma Forecasts (total sales include IMS audited figures and IMS estimates for unaudited markets);

One response: growth of Health Technology Assessment

- **Australia: Pharmaceutical Benefits Advisory Committee (PBAC)**
- **Canadian Agency for Drugs and Technologies in Health (CADTH)**
- **Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)**
- **Germany: Institute for quality and efficiency in health care (IQWiG)**
- **Netherlands: College voor Zorgverzekeringen (CVZ)**
- **Poland: Agency for Health Technology Assessment in Poland (AHTAPol)**
- **Spain: Agencia de Evaluación de Tecnologías Sanitarias (AETS)**
- **Taiwan: Center for Drug Evaluation (CDE)**

Cost-effectiveness Analysis

Aim: To provide information to enable decision-makers to maximise health benefit given a restricted budget and equity constraints

By: Identifying treatments with lowest opportunity cost.

Eg. 10,000 Euro spent on a new treatment should provide more health benefit than the treatments that could have been funded, or will no longer be funded, with that money.

Or rather more simply

"If there's a blue pill and a red pill, and the blue pill is half the price of the red pill and works just as well, why not pay half price for the thing that's going to make you well?"

Obama 22/7/2009

A useful cost-effectiveness analysis

Sculpher (2000)

- Predicts costs and effects for each treatment option
- An analysis is useful if a better decision will be made at a given time by using an analysis than by not using it
- The purpose of an analysis is not to predict the results of an ideal pragmatic trial:
 - a CE analysis combines information already available
 - a clinical trial generates new information
- A universal guideline of what constitutes good method may not be possible or desirable

However

Two general aims for clinical trials

- Assess the effects of treatments on the patients actually studied – “very difficult”
- Predict future effects of treatments on patients not studied - “extremely difficult if not downright impossible”

‘Statistical Issues in Drug Development’ Senn (1997)

Some statistical challenges

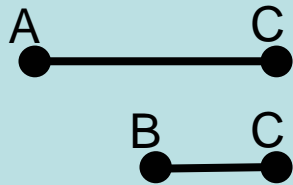
To predict costs and effects:

- On scale(s) that are meaningful to decision makers
- Over an appropriate time horizon
- For relevant patient groups
- **Comparing all relevant interventions**

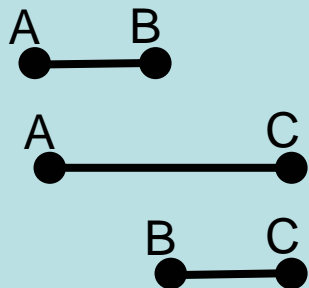
A taxonomy of Comparisons based on trial data



Direct Comparison



'Adjusted' indirect comparison:
Difference between relative treatment



Mixed treatment comparisons or Network
Meta-Analysis:

Adjusted Indirect comparisons extended to
more complex networks of trial evidence

Adjusted Indirect Comparisons

Based on an assumption of transitivity:

$$HR_{AB} = HR_{AC}/HR_{BC}$$

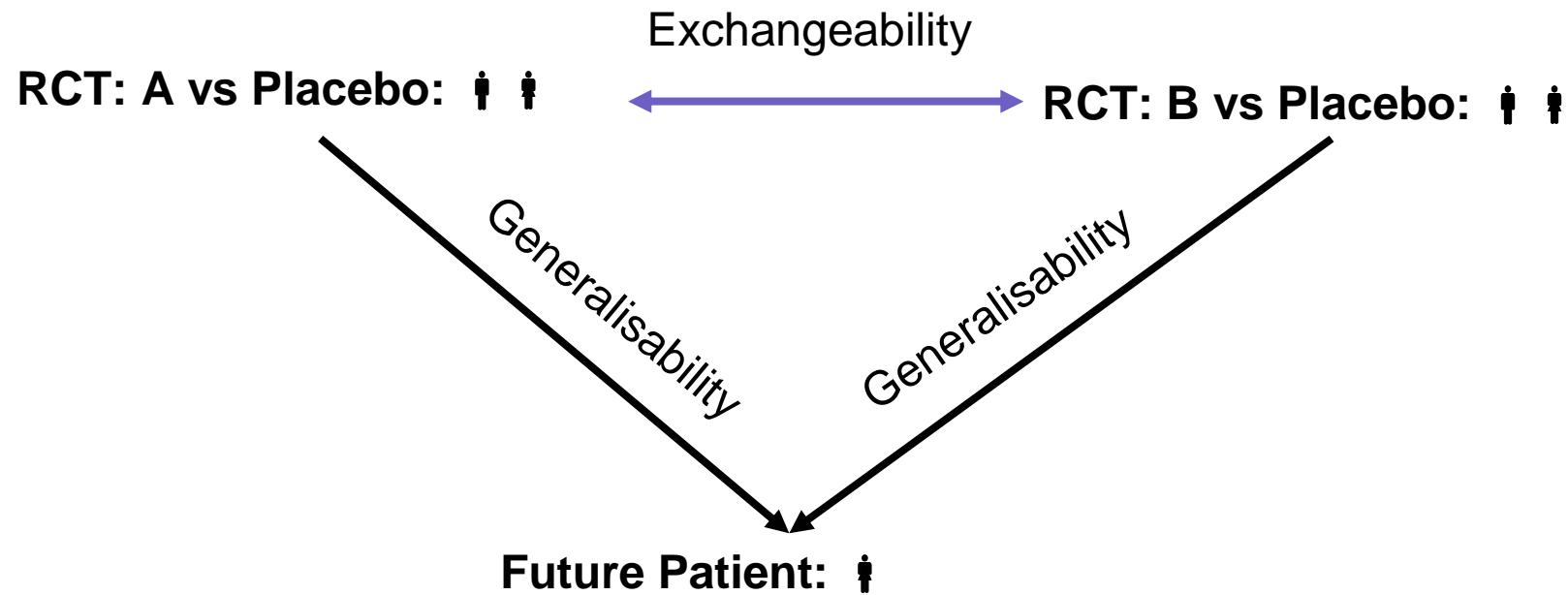
Log transformation:

$$\text{LN } HR_{AB} = \text{LN } HR_{AC} - \text{LN } HR_{BC}$$

Underlying Assumption

- $\delta_{AB} = \delta_{AC} - \delta_{BC}$
- Requires exchangeability of relative treatment effects:
 - Between subjects within trials (randomisation)
 - Between trials including the same comparators (pairwise meta-analysis)
 - Between trials comparing different sets of treatments

Exchangeability is implicit in clinical decision-making



Validity of indirect comparisons

Song et al. (2000)

- Comparison of direct and indirect methods
- Statistically significant discrepancy in 3 out of 44 comparisons
- Equally likely to over- or underestimate difference

Validity of indirect comparisons

Chou et al. (2006)

- Compared indirect and direct analysis of HAART vs. RTI in HIV Patients
 - Direct analysis found RTI more effective
 - indirect analysis found HAART more effective
- Authors Conclusion: Indirect comparisons could be unreliable for complex and rapidly evolving interventions such as HAART.
- Alternative Conclusion: Older trials may be unreliable predictors of effectiveness for complex and rapidly evolving interventions such as HAART.

Indirect comparisons observational Cochrane (2008)

“Indirect comparisons are not randomized comparisons, and cannot be interpreted as such. They are essentially observational findings across trials, and may suffer the biases of observational studies, for example due to confounding. “

Primacy of direct comparisons Cochrane (2008)

“In situations when both direct and indirect comparisons are available in a review, then unless there are design flaws in the head-to-head trials, the two approaches should always be considered separately and the direct comparisons should take precedence as a basis for forming conclusions.. “

Reference: Cochrane Handbook 2.4.6.

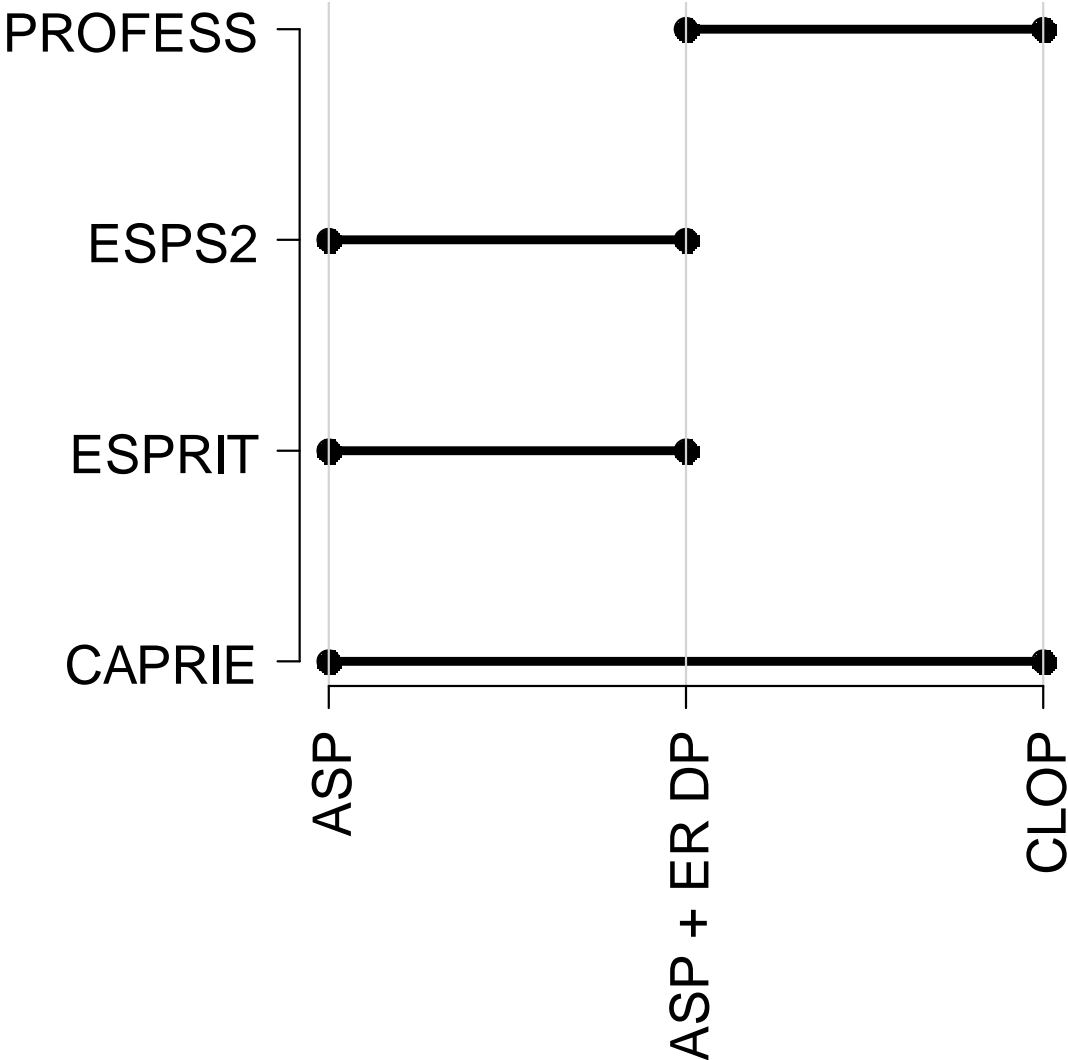
A practical Example

Stroke Prevention — Insights from Incoherence

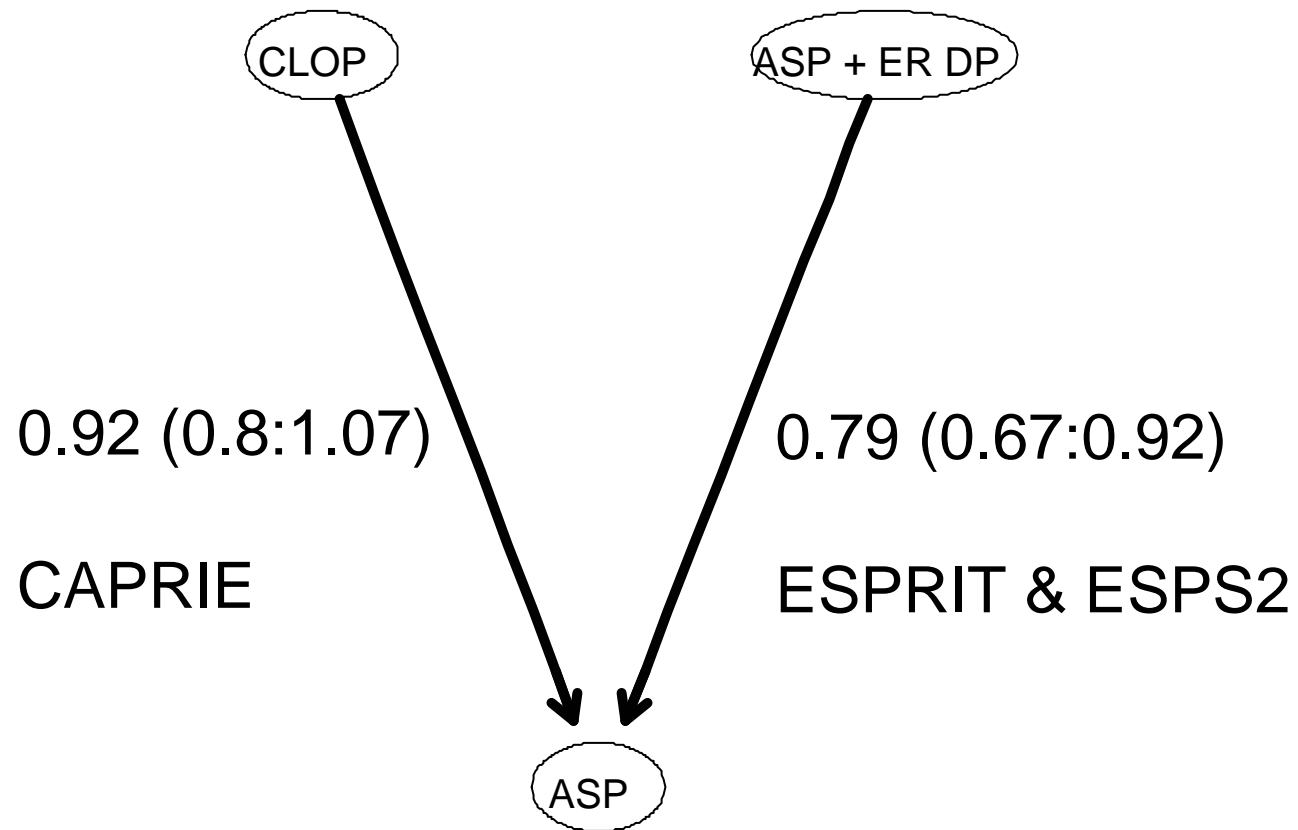
David M. Kent, M.D., and David E. Thaler, M.D., Ph.D.

If clinical trials were sporting contests, then it would be fair to say that low-dose aspirin plus extended-release dipyridamole (Aggrenox) was the clear favorite against clopidogrel going into the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial (ClinicalTrials.gov

Network of trial evidence



Network Graph (Stroke Endpoint)



Network Graph (Stroke Endpoint)

1.02 (0.93 to 1.11)

PROFESS



0.92 (0.8:1.07)

0.79 (0.67:0.92)

CAPRIE

ESPRIT & ESPS2



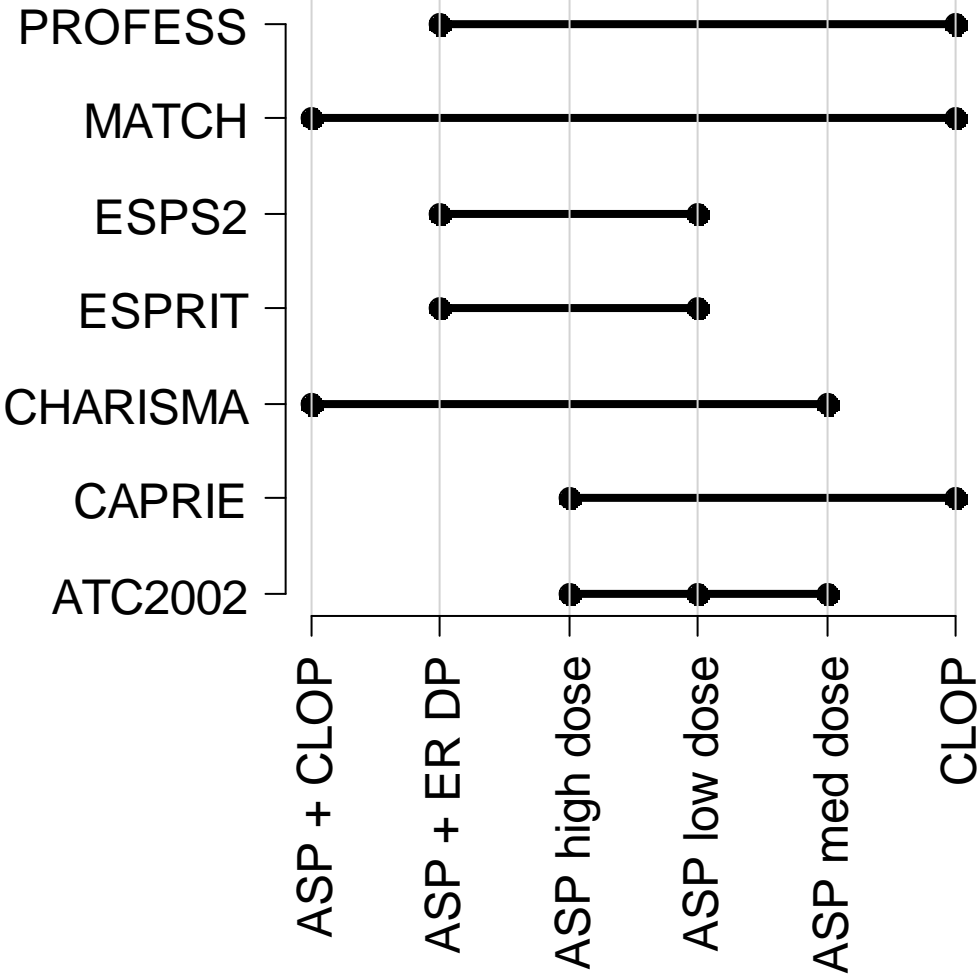
ASP + ERDP vs. CLOP

- Indirect Comparison: ESPS2, ESPRIT & CAPRIE Trials
 - Odds Ratio 0.85 (0.66:1.06)
- Direct Comparison: PRoFESS Trial
 - Odds Ratio 1.02 (0.93 to 1.11)
- Results are incoherent
- What happened?

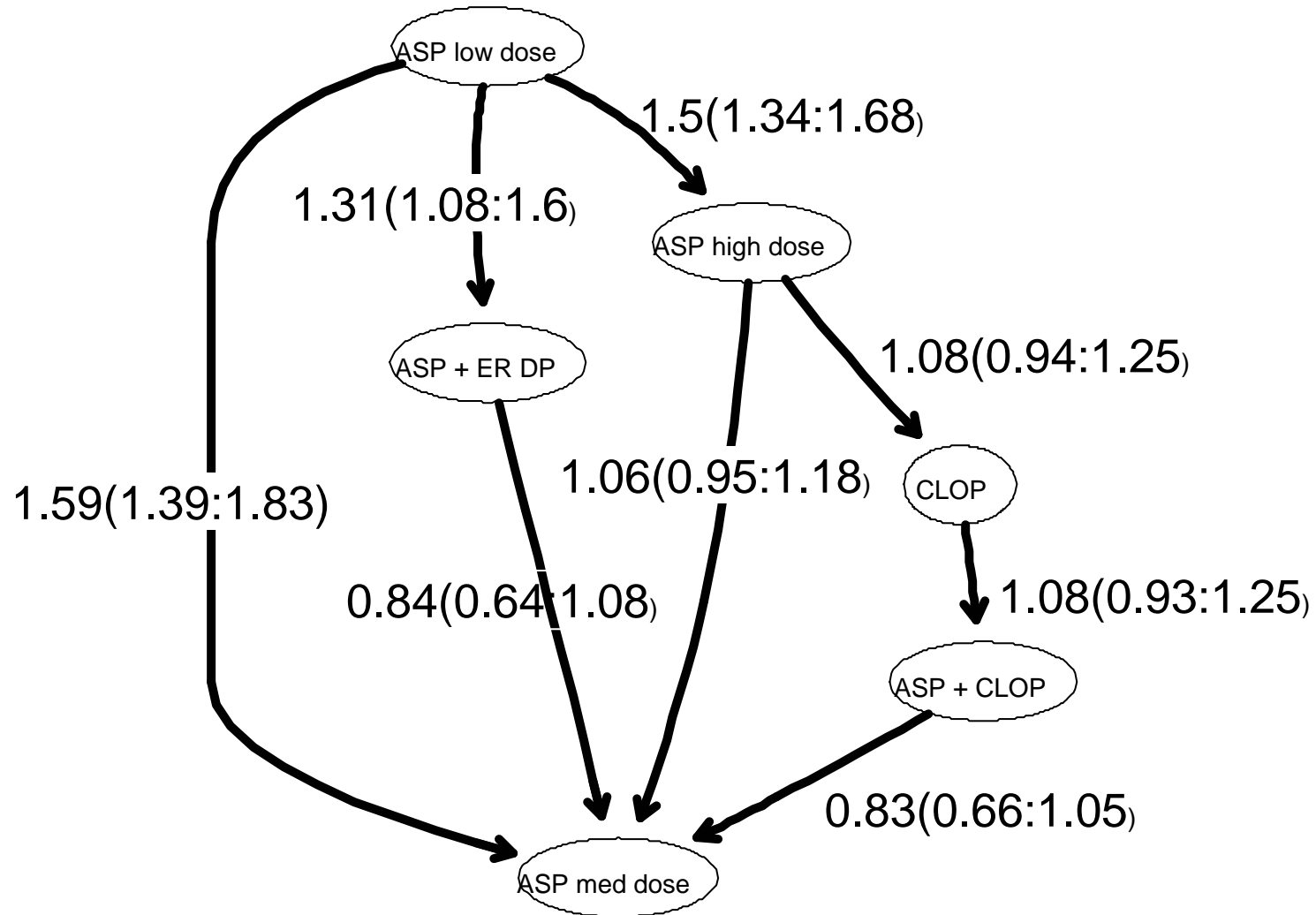
Kent & Thaler (2008)

“the results of the PRoFESS trial show us once again that the compelling logic of the transitive property, so reliable in mathematics, has little authority in the often illogical world of clinical trials”

Incorporating different aspirin doses



Allowing for different aspirin doses



ASP + ERDP vs. CLOP

Allowing for differing aspirin doses

- Indirect Comparison
 - Odds Ratio 1.11 (0.87 to 1.4)
- Direct Comparison: PRoFESS Trial
 - Odds Ratio 1.02 (0.93 to 1.11)
- Results are more coherent
- Aspirin dose is important

Is direct evidence always better?

Reviews and Overviews

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Stephan Heres, M.D.

John Davis, M.D.

Katja Maino, M.D.

Elisabeth Jetzinger, M.D.

Werner Kissling, M.D.

Stefan Leucht, M.D.

Objective: In many parts of the world, second-generation antipsychotics have largely replaced typical antipsychotics as the treatment of choice for schizophrenia. Consequently, trials comparing two drugs of this class—so-called head-to-head studies—are gaining in relevance. The authors reviewed results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship existed between the sponsor of the trial and the drug favored in the study's overall outcome.

sources of bias that could have affected the results in favor of the sponsor's drug.

Results: Of the 42 reports identified by the authors, 33 were sponsored by a pharmaceutical company. In 90.0% of the studies, the reported overall outcome was in favor of the sponsor's drug. This pattern resulted in contradictory conclusions across studies when the findings of studies of the same drugs but with different sponsors were compared. Potential sources of bias occurred in the areas of doses and dose escalation, study entry cri-

(Am J Psychiatry 2006; 163:185–194)

TABLE 1. Number of Reports That Favor the Study Sponsor's Drug or the Comparison Drug in Industry-Sponsored Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Second-Generation Antipsychotic Pair and Sponsor of Study	Number of Reports Favoring Sponsor's Drug or Comparison Drug	
	Sponsor's Drug	Comparison Drug
Olanzapine versus risperidone		
Lilly	5	0
Janssen	3	1
Olanzapine versus clozapine		
Lilly	2	1
Novartis	1	0
Clozapine versus risperidone		
Novartis	1	0
Janssen	1	0
Ziprasidone versus olanzapine		
Pfizer	1	1
Lilly	2	0
Amisulpride versus olanzapine		
Lilly	1	0
Sanofi-Synthelabo	1	0

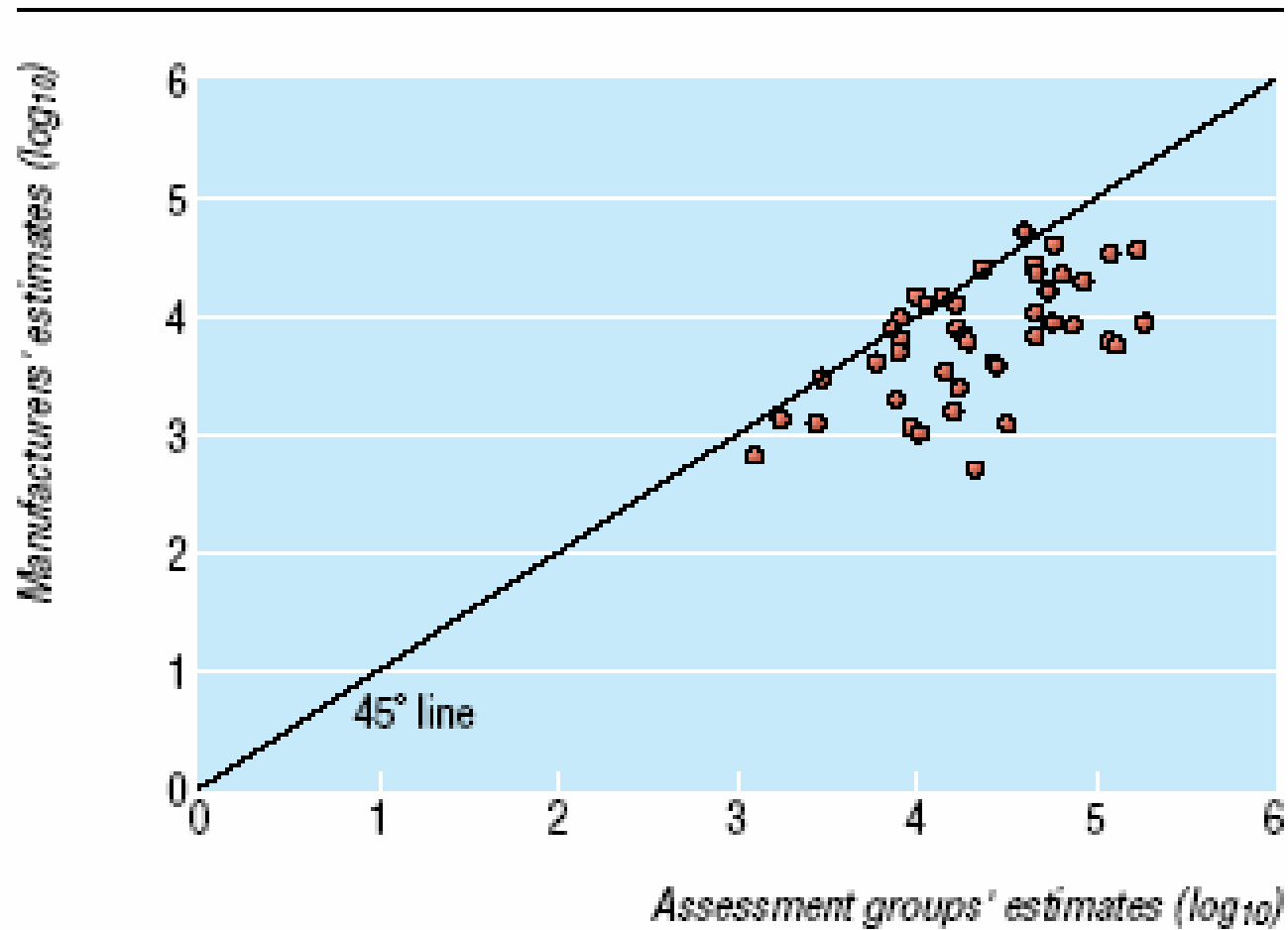
In conclusion

- Predicting future effects is 'extremely difficult'.
- Methods of indirect comparisons are invaluable for analysing networks of trial evidence
- They do not replace or predict direct comparisons
- Incoherence can be our friend
- An inability to observe incoherence is a problem
- Need to be cautious in applying simple rules

Final Word: Kent and Thaler (2008)

“In the era of comparative effectiveness, when multiple agents are pitted against one another, randomized trials often cannot be understood in isolation. Rather, they need to be interpreted in the context of a sometimes complex network of other similar or relevant evidence.

A comparison of manufacturers and assessment group estimates of incremental cost-effectiveness ratios



Miners (2004) BMJ