

**ISPOR 14<sup>th</sup> Annual European Congress**

**W22: Meta-Analyses and Indirect Comparisons from RCTs with Small Patient Numbers**

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**Excellent prior presentations!**


**What to add?**

**Probably more questions than answers!?**

**Obligation**

**§ 139a SGB V (IQWiG)**

(4) 'The Institute must ensure that the assessment of medical benefit is carried out according to the **internationally accepted standards of evidence-based medicine**, and the economic assessment according to the relevant internationally accepted standards, in particular of health economics.'



**What to do if no standards exist?**

**Evidence-Based Medicine**

- Precise formulation of questions to be addressed (**P**atient **I**ntervention **C**omparator **O**utcome)
- Systematic (i.e. reproducible, transparent) procedure (search and evaluation of **all relevant** clinical trials)
- Reliability assessment of the result as the basis for a recommendation ('**How credible** are the results?')

Reliability of results

**Evidence synthesis (meta-analysis) necessary**


- Qualitative component (risk of bias)
- Quantitative component (precision, significance level)
- Magnitude (and nature) of the (observed) effect

↳ e.g. Glasziou P, Chalmers I, Rawlins M, McCulloch P. BMJ 2007; 334: 349-52.

**Obligation**

**Regulation on the Benefit Assessment of Drugs\*, §2 (3)**

'If head to head trials are not available for the comparison of the new drug and the appropriate comparator, or if they do not allow any sufficient conclusions regarding additional benefit, available clinical trials of the appropriate comparator can be used which are suitable for an indirect comparison with the new drug.'



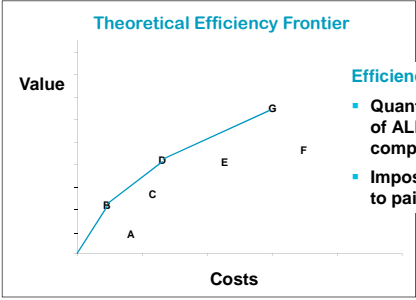
\*According to § 35a (1), S. 6+7, SGB V  
AMNOG (Law on the Reorganization of the Pharmaceutical Market in Statutory Health Insurance)

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**Necessity**

**Cost-benefit assessment**

**Theoretical Efficiency Frontier**



**Efficiency Frontier:**

- Quantitative comparison of ALL (relevant) comparators
- Impossible if restricted to pairwise comparisons

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**Direct vs. indirect comparisons**

'Direct randomized comparisons of treatments are usually more trustworthy than indirect comparisons ...'

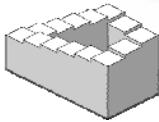
Ioannidis. CMAJ 2009; DOI:10.1503/cmaj.081086

**However ...?**

**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**

Heres et al. Am J Psychiatry 2006; 163: 185-94



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**(In)direct comparisons**

Levels of assumptions	Two sets of trials used in adjusted indirect comparison	Head to head comparison trials
No relevant heterogeneity	Which method: Cochrane's Q, I <sup>2</sup> ? Shifted hypothesis?	Pooling of trials comparing intervention A with B
No relevant dissimilarity	Subjective judgement? Meta regression sufficient/adequate?	Intervention A with B
No relevant inconsistency	Which model? Which limits?	Head to head and indirect comparison of A with B

**Fig 1 | Assumptions underlying adjusted indirect and mixed treatment comparison**

In principle Irrelevance questions ('non-inferiority' questions) → in fact no practical methods exist

Song et al. BMJ 2009; 338: b1147

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**IQWiG methods**

IQWiG Institute for Quality and Efficiency in Health Care

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IQWiG is an independent scientific institute that investigates the benefits and harms of medical interventions for patients. We regularly provide information about the potential advantages and disadvantages of different diagnostic and therapeutic interventions.

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**IQWiG publishes new version of its General Methods**

IQWiG has revised its methods paper and has now published the version "General Methods 4.0". With immediate effect, the new document is the basis for the scientific work of the Institute and its external experts, as well as for cooperation with the contracting agencies (Federal Joint Committee and Federal Ministry of Health). Version 4.0 implements, among other things, the requirements of the German Act on the Reform of the Market for Medicinal Products (AMNOG) with regard to the early benefit assessment of drugs. AMNOG came into effect in January 2011.

> Full text

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**Random or fixed effects model?**

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General Methods<sup>4</sup>

'The question as to which model should be applied in which situation has long been a matter of controversy [...].

...

Moreover, it should be noted that the confidence intervals calculated from a fixed effects model may show a substantially lower coverage probability with regard to the expected overall effect, even if minor heterogeneity exists when compared with confidence intervals from a random effects model [...]. **The Institute therefore primarily uses random effects models and only applies fixed effects models in well-founded exceptional cases.** In this context, if the data situation is homogeneous, it should be noted that meta-analytical results from models with random and fixed effects at best show marginal differences.'

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**Heterogeneity**

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General Methods<sup>4</sup>

'The existence of heterogeneity can be statistically tested; however, these tests usually show very low power.

...

Besides this, the extent of heterogeneity has to be quantified. For this purpose, specific statistical methods are available, such as the I<sup>2</sup> measure. Studies exist for this measure that allow a rough classification of heterogeneity (for example: probably irrelevant [0-40%], moderate [30-60%], substantial [50-90%], major [75-100%]) [...]. If the heterogeneity of the studies is too great, the statistical pooling of the study results may not prove meaningful [...]. The specification of 'too great' heterogeneity is dependent on the context and will be given in review protocol. **In general, a statistical pooling will not be performed if the test on heterogeneity has a p-value lower than 0,2.'**

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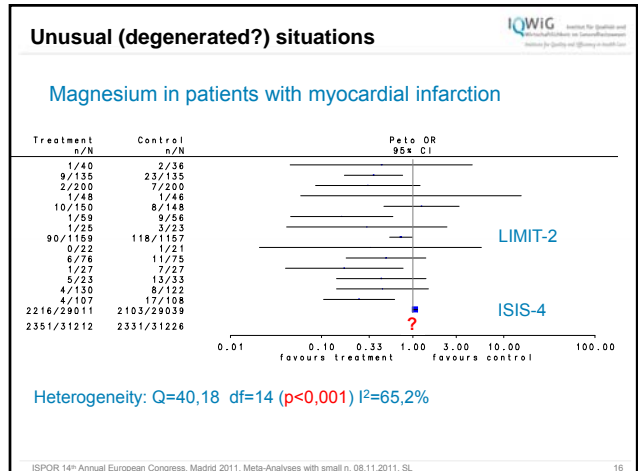
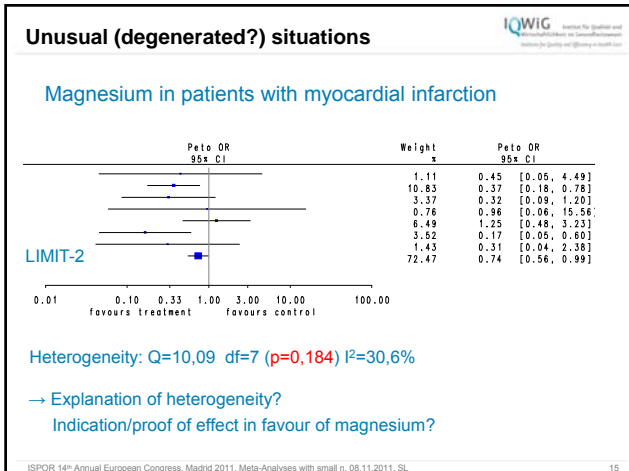
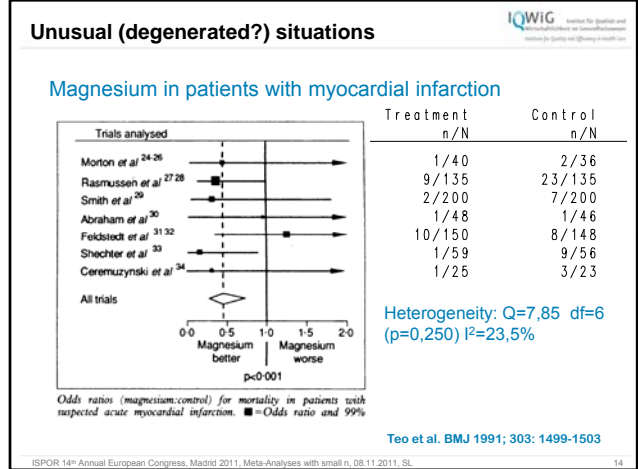
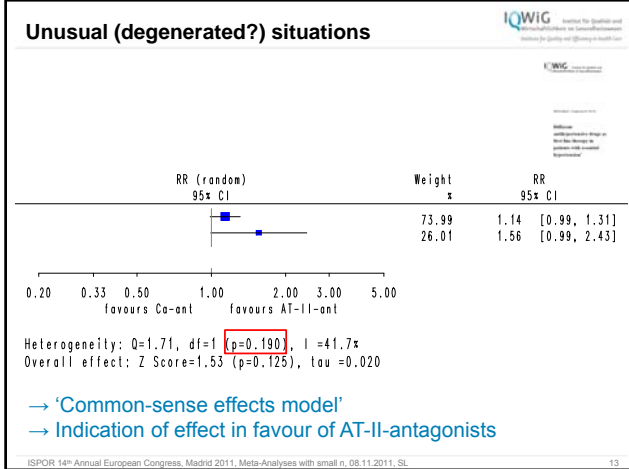
**Unusual (degenerated?) situations**

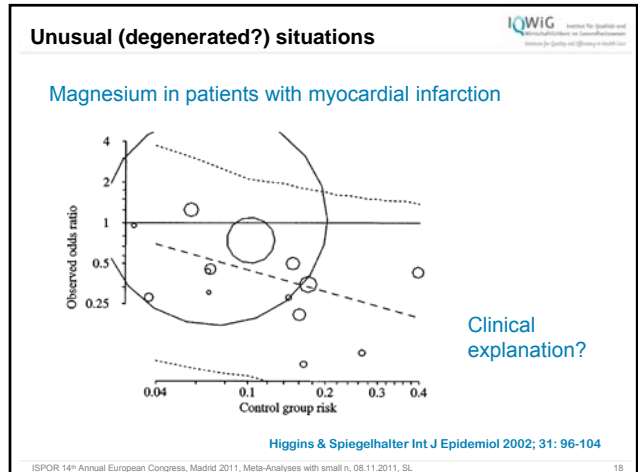
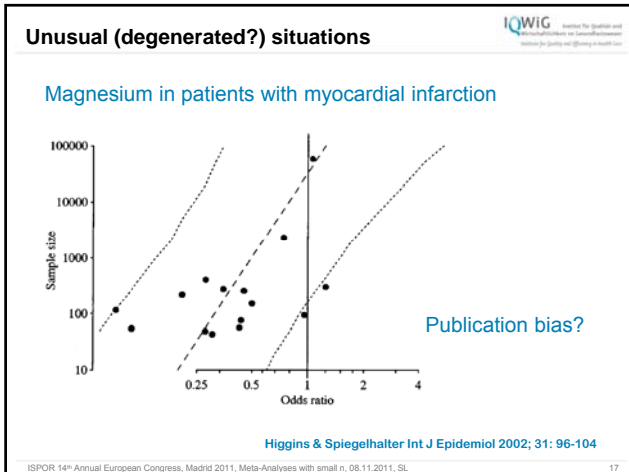
IQWiG Institute für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A05-09

**Different antihypertensive drugs as first line therapy in patients with essential hypertension<sup>1</sup>**

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### (In)direct comparisons

In general, use of only direct (head-to-head) comparisons for benefit assessment

In certain circumstances (i.e. early benefit assessment according to AMNOG\*, cost-benefit-assessment), use of indirect comparisons may be necessary

→ In general, **decreased credibility** of results

General Methods\*

Proof ('Beleg')  
Indication ('Hinweis')  
Hint ('Anhaltspunkt')

\*Law on the Reorganization of the Pharmaceutical Market in Statutory Health Insurance

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→ In general, **decreased credibility** of results

→ **Extent of added benefit (AMNOG\*) will be downgraded due to low(er) precision**

General Methods\*

Extent of added benefit (AMNOG\*):  
Major  
Considerable  
Minor  
Unquantifiable

\*Law on the Reorganization of the Pharmaceutical Market in Statutory Health Insurance

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## Conclusions

More questions than answers!?

No established standards for dealing with heterogeneity, (dis)similarity, and (in)consistency

Problems will be exaggerated by small no. of studies or small no. of patients within studies

Ethical and trial-design-efficiency considerations (e.g. early stopping, ban of replication, adaptive designs), and the use of the traditional 5% (2,5%) level promote studies/meta-analyses with imprecise estimates

What is better: one large trial or many small trials?

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**Thank you very much!**