EFSPI 2014
Berlin, 25.09.2014

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Biometrical Issues in the Framework of Benefit Assessment

Ralf Bender

Institute for Quality and Efficiency in Health Care (IQWiG)
Cologne, Germany

Outline

- IQWiG and the German system
- Benefit assessment and requirements of IQWiG
- Biometrical issues
  - Assessment of added benefit
  - Proof of benefit from 1 study
  - Benefit assessment in case of heterogeneity
  - Extent of added benefit
  - Indirect comparisons
- Example
- Outlook
- Summary

IQWiG and the German system

IQWiG and G-BA were founded during the 2004 health care reform.

The legal foundation of IQWiG and G-BA is Social Code Book V (SGB V).

IQWiG is solely commissioned by the Federal Joint Committee (G-BA) and the Federal Ministry of Health (BMG), but can also cover topics on its own initiative under a general commission.

Legal supervision

Commissions

IQWiG ← G-BA

Assessment of benefits and harms of medical interventions and production of independent, evidence-based reports.

Decision-making body of the self-governing health care system in Germany.

Requirements of IQWiG

- Proof (“Beleg”):
  - Meta-analysis of studies with high certainty of results
  - At least 2 significant studies with high certainty of results
- Indication (“Hinweis”):
  - Meta-analysis of studies with moderate certainty of results
  - One significant study with high certainty of results
- Hint (“Anhaltspunkt”):
  - Meta-analysis of studies with low certainty of results
  - One significant study with moderate certainty of results

Certainty of results:

- High: **RCT with low risk of bias**
- Moderate: **RCT with high of bias**
- Low: **Non-randomized controlled trial**

Risk of bias (key aspects):

- Adequate concealment
- Blinding
- Appropriate application of ITT
- In general: Good clinical practice (GCP) …

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IQWiG:

Update of General Methods

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More Details →

General Methods[a]

Version 4.1 of 28 November 2013

https://www.iqwig.de/en/methods/methods_papers/general_methods.3020.html

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Table: Certainty of conclusions regularly inferred for different evidence situations if studies with the same qualitative certainty of results are available

		Number of studies				
		1 (with statistically significant effect)	≥ 2			
			Homogeneous	Heterogeneous		
			Meta-analysis statistically significant	Effects in the same direction[a]		
				Clear	Moderate	No
Qualitative certainty of results	High	Indication	Proof	Proof	Indication	–
	Moderate	Hint	Indication	Indication	Hint	–
	Low	–	Hint	Hint	–	–

Criteria for 1 study:

- All usual criteria for a proof of benefit are fulfilled
- Clinical study report according to the International Conference on Harmonization (ICH) guidelines is available
- The study is a multi-centre study with at least 10 centres
- The effect estimate observed has a very small corresponding *p*-value ($p < 0.001$)
- The result is consistent within the study
- The analyses are available for all relevant outcomes, i.e. these analyses are not restricted to individual selected outcomes

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Prediction intervals

Guddat *et al. Systematic Reviews* 2012, **1**:34
http://www.systematicreviewsjournal.com/content/1/1/34

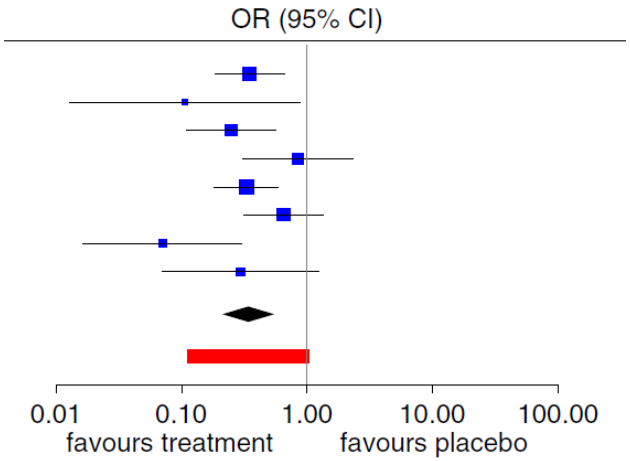
SYSTEMATIC REVIEWS

METHODOLOGY Open Access

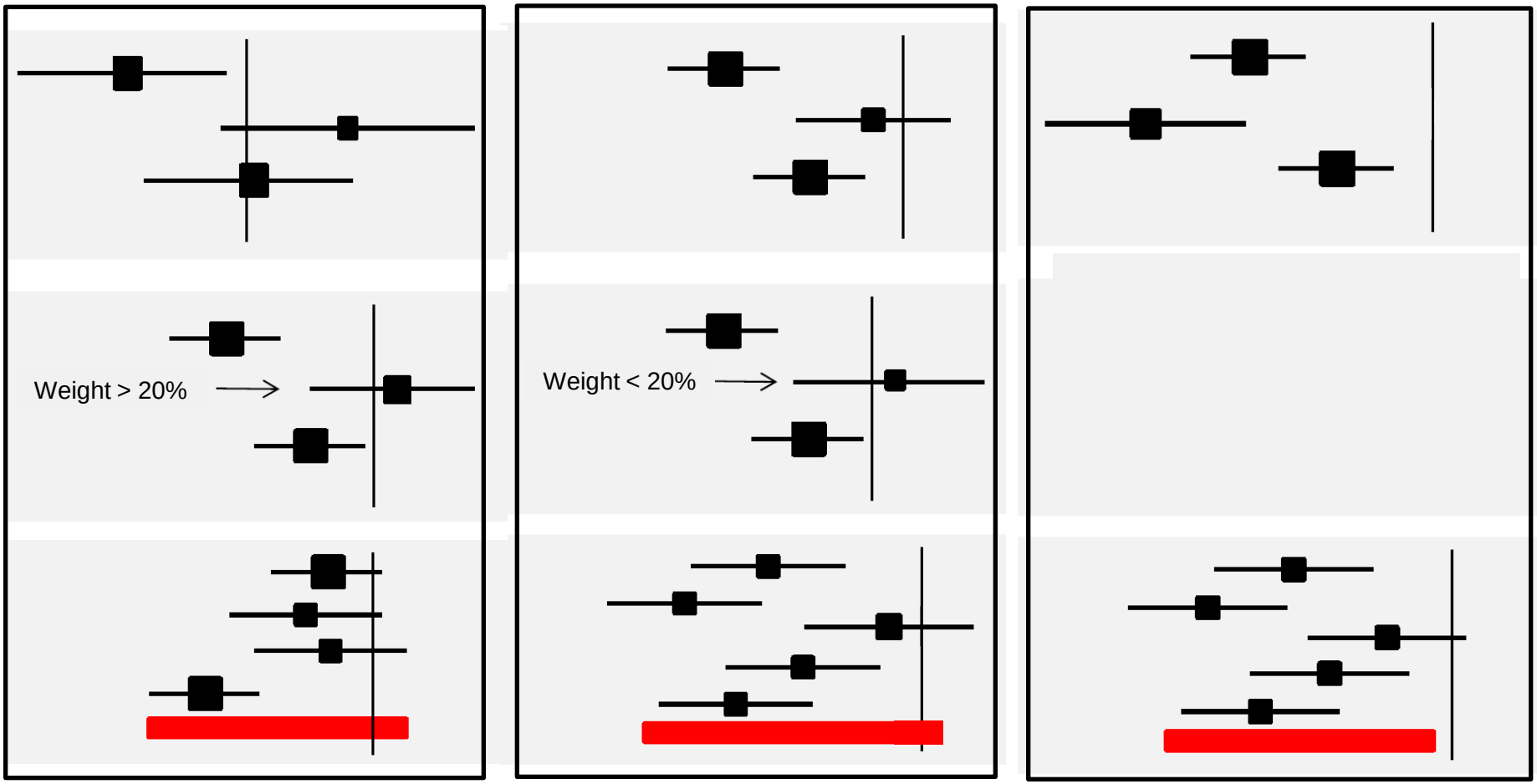
A note on the graphical presentation of prediction intervals in random-effects meta-analyses

Charlotte Guddat[1*], Ulrich Grouven[1,2], Ralf Bender[1,3] and Guido Skipka[1]

- Predicted range for the true treatment effect in an individual study
- Illustration of the degree of heterogeneity in forests plots of RE meta-analyses



Examples for different "i.s.d." situations



Not i.s.d. **Moderately i.s.d** **Clearly i.s.d.**

Prediction intervals

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IBS

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gmds Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V.

Application of Prediction Intervals in Meta-Analyses with Random Effects

Joint Statement from IQWiG, GMDS and IBS-DR

Authors: Ralf Bender, Oliver Kuß, Armin Koch, Carsten Schwenke & Dieter Hauschke

Joint statement of IQWiG, GMDS and IBS-DR (07.03.2014):

Application of prediction intervals is a valuable supplement to the present methods for meta-analyses with random effects, especially in the case of marked heterogeneity

http://www.gmds.de/pdf/publikationen/stellungnahmen/140307_Prediction_Intervals.pdf

Issues regarding assessment of added benefit:

- Certainty of results (high, moderate, low)
- RCTs: Risk of bias
- Homogeneity: Significant meta-analysis
- Heterogeneity: Effects clearly, moderately or not i.s.d.
- Prediction intervals
- Derivation of proof, indication or hint of added benefit

AMNOG – new legislation, new HTA products

- New law to reorganize pharmaceutical market for the statutory health insurance
- Came into force on 01/01/2011
- § 35a SGB V directly concerns early benefit assessment of drugs:
  - For new chemical entities / new indications
  - Requirement linked to market entry
  - Now onus of proof on manufacturer to demonstrate added benefit (vs. an appropriate comparator) – submission of a dossier
  - Results used for price negotiations
    (Not for the decision: reimbursement yes/no)

AMNOG – Extent of 'added benefit'

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Criteria in accordance with AM-NutzenV*

Major added benefit → sustained and great improvement[#] (cure, major increase in survival time, long-term freedom from serious symptoms, extensive avoidance of serious side effects)

Considerable added benefit

Minor added benefit

No added benefit has been proven

Less benefit

*Regulation for Early Benefit Assessment of New Pharmaceuticals

[#]in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

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Considerable added benefit

Minor added benefit

No added benefit has been proven

Less benefit

sustained and great improvement[#] (cure, major increase in survival

marked improvement[#] (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant avoidance of serious adverse effects, important avoidance of other adverse effects)

*Regulation for Early Benefit Assessment of New Pharmaceuticals

[#]in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

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Criteria in accordance with AM-NutzenV*

Major added benefit

sustained and great improvement# (cure, major increase in survival

Considerable added benefit

marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant

Minor added benefit →

moderate and not only marginal improvement# (reduction in non-serious symptoms, relevant avoidance of side effects)

No added benefit has been proven

Less benefit

*Regulation for Early Benefit Assessment of New Pharmaceuticals

#in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

AMNOG – Extent of 'added benefit'

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Criteria in accordance with AM-NutzenV*

Major added benefit

Considerable added benefit

Minor added benefit

No added benefit has been proven

Less benefit

Added benefit not quantifiable

sustained and great improvement# (cure, major increase in survival

marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant

moderate and not only marginal improvement# (reduction in non-serious symptoms, relevant avoidance of side effects)

*Regulation for Early Benefit Assessment of New Pharmaceuticals

#in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

AMNOG – Extent of ‘added benefit’

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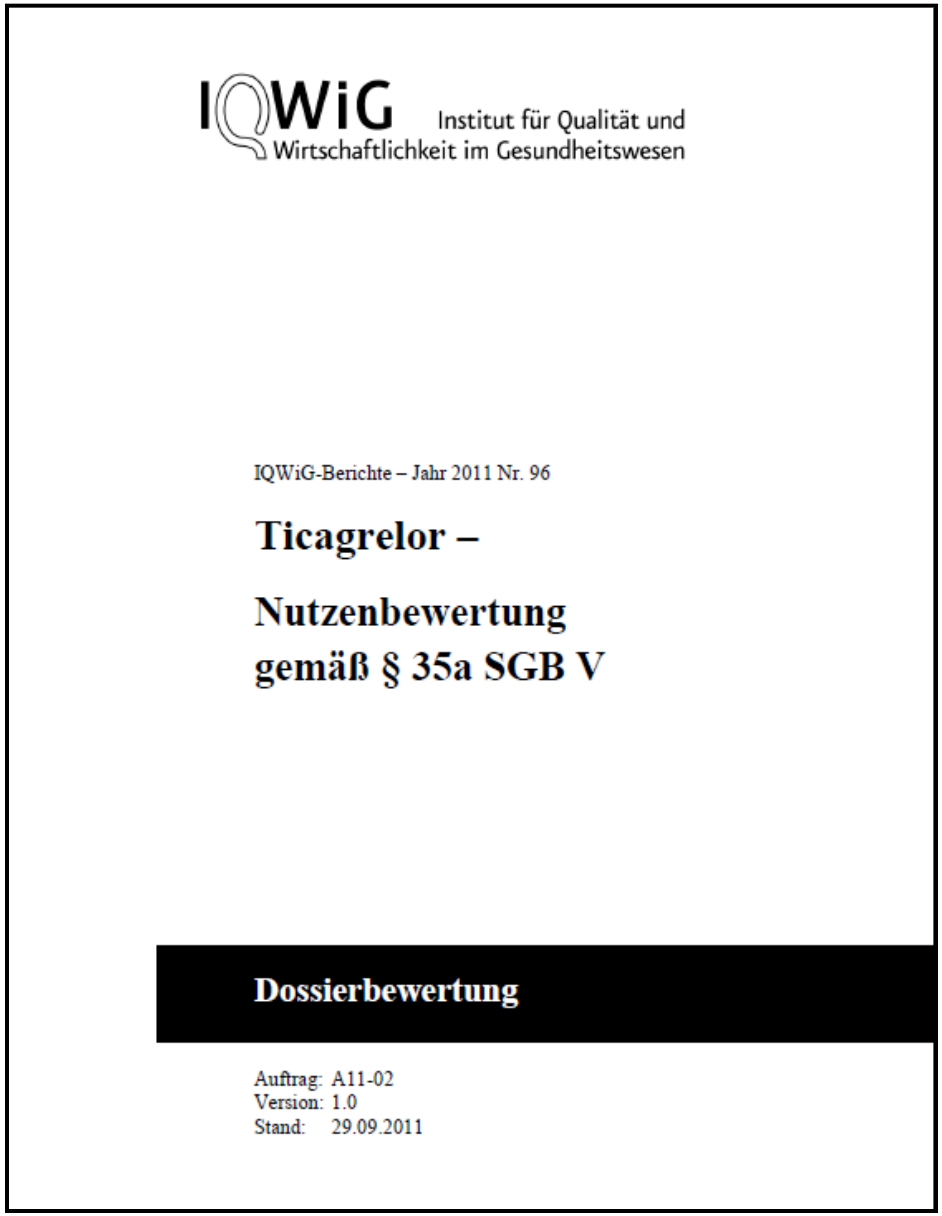
IQWiG:

First proposal to operationalize extent of added benefit based upon shifted null hypotheses

Details →


IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG-Berichte – Jahr 2011 Nr. 96

Ticagrelor –

Nutzenbewertung gemäß § 35a SGB V

Dossierbewertung

Auftrag: A11-02
Version: 1.0
Stand: 29.09.2011

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Update of General Methods

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General Methods[a]

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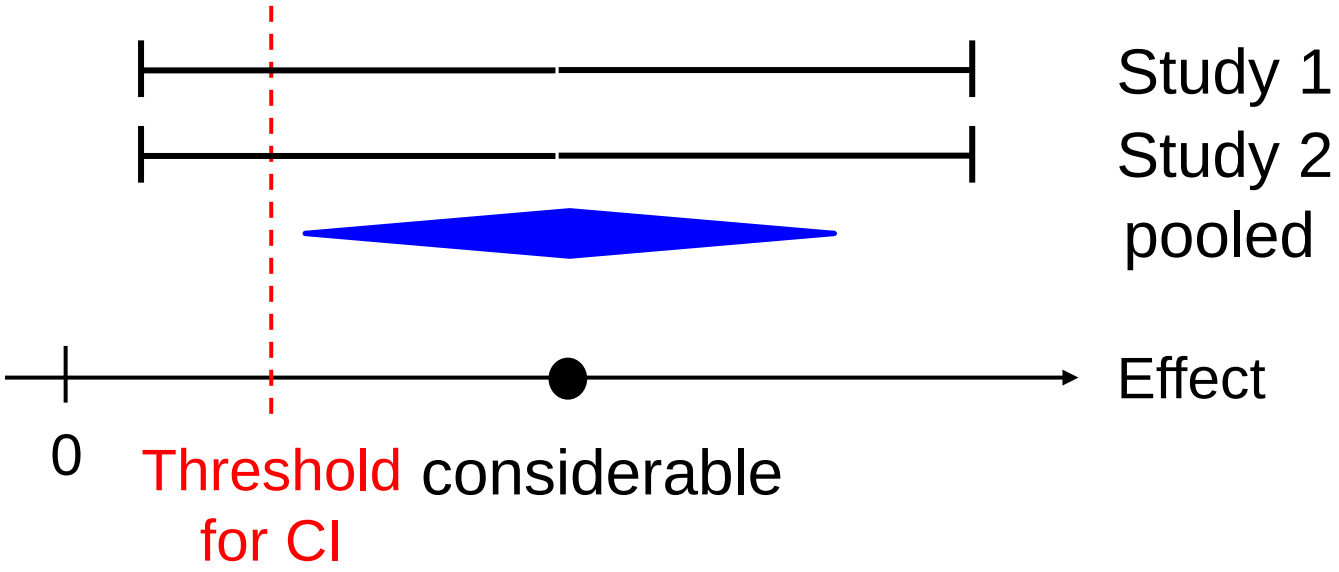
Threshold values for determination of the extent of an effect
Effect measure: RR

Extent category	Outcome category		
	Overall mortality	Serious (or severe) symptoms (or late complications) and adverse events, as well as health-related quality of life[a]	Non-serious (or non-severe) symptoms (or late complications) and adverse events
Major	**0.85**	**0.75** and risk ≥ 5%[b]	n.a.
Considerable	**0.95**	**0.90**	**0.80**
Minor	**1.00**	**1.00**	**0.90**

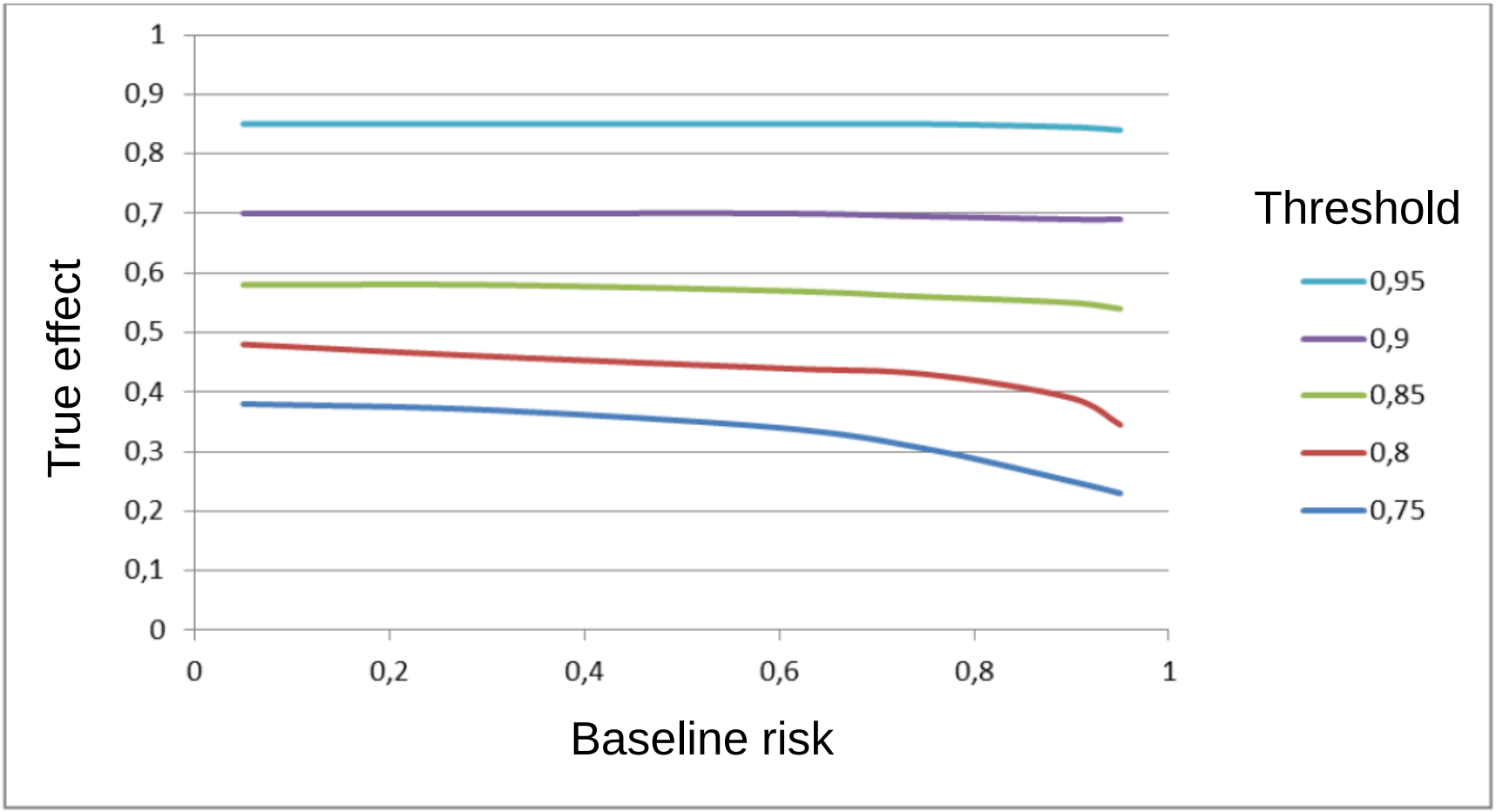
a: Precondition: use of a validated or established instrument and a validated or established response criterion
b: Risk must be at least 5 % for at least one of the two groups being compared

Main idea



If you have 2 studies each with power of 1-β for the usual test of superiority, then the threshold is chosen so that the pooled analysis also has a power of 1-β for the for the shifted hypothesis

True effects (RRs) in dependence on baseline risk



Range of true effects (RRs) for the different extent categories

Extent category	Outcome category		
	Overall mortality	Serious (or severe) symptoms (or late complications) and adverse events, as well as health-related quality of life	Non-serious (or non-severe) symptoms (or late complications) and adverse events
Major	**0.53 – 0.58**	**0.24 – 0.38**	n.a.
Considerable	**0.84 – 0.85**	**0.69 – 0.71**	**0.34 – 0.48**
Minor	n.a.	n.a.	**0.69 – 0.71**

Issues regarding extent of added benefit:

- IQWiG proposal based upon shifted hypothesis
- Pragmatic approach considering power of 2 studies
- Based upon RR (binary data)
- Application also to HR (time-to-event data)
- No standard approach for other scales (continuous, ordinal data)
- Proposal should be extended and refined

Indirect comparisons – requirements

- Adjusted indirect comparisons ONLY
- Description of
  - Method
  - Assumptions
- In case of Bayes methods description of
  - A priori distributions
  - No. of Markov chains
  - Initial values
- Reasons for similarity
- Check of homogeneity

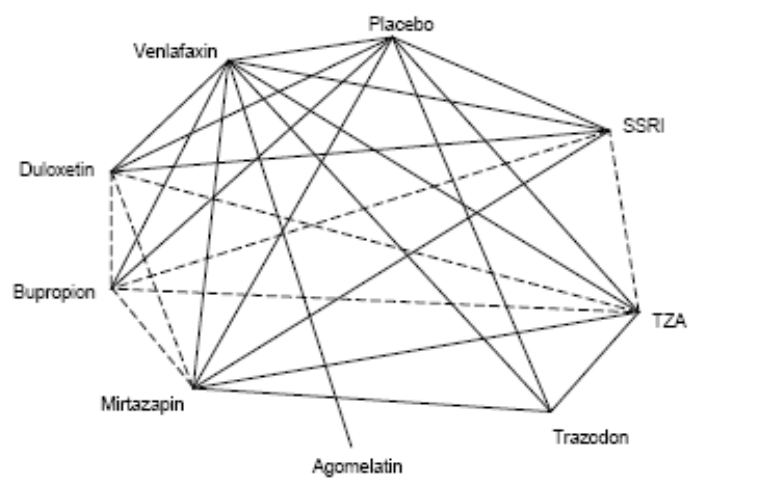


Abbildung 2: Exemplarisches Netzwerk für den Endpunkt Response basierend auf der Studienlage der Nutzenbewertungen A05-20A und A05-20C

- Check of consistency
- Computer code
- Sensitivity analyses

Indirect comparisons: Details

Original Article

Research Synthesis Methods

Received 28 June 2011, Revised 10 July 2012, Accepted 19 July 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1057

Unsolved issues of mixed treatment comparison meta-analysis: network size and inconsistency

Sibylle Sturtz[a*†] and Ralf Bender[a,b]

Impact of network size:

Larger networks are based upon more evidence but have more potential for heterogeneity and inconsistency

Indirect comparisons

INTERNATIONAL BIOMETRIC SOCIETY

German Association for Medical Informatics, Biometry and Epidemiology

Importance of Results from Indirect Comparisons

Joint Statement from IQWiG, GMDS and IBS-DR

Authors: Ralf Bender, Carsten Schwenke, Claudia Schmoor, Dieter Hauschke

<u>Joint statement of IQWiG, GMDS and IBS-DR (07.03.2012):</u>

Network meta-analyses lead to lower certainty of results compared to meta-analyses of direct head-to-head studies

Unadjusted indirect comparisons are not acceptable

http://www.gmds.de/pdf/publikationen/stellungnahmen/120202_IQWIG_GMDS_IBS_DR_engl.pdf

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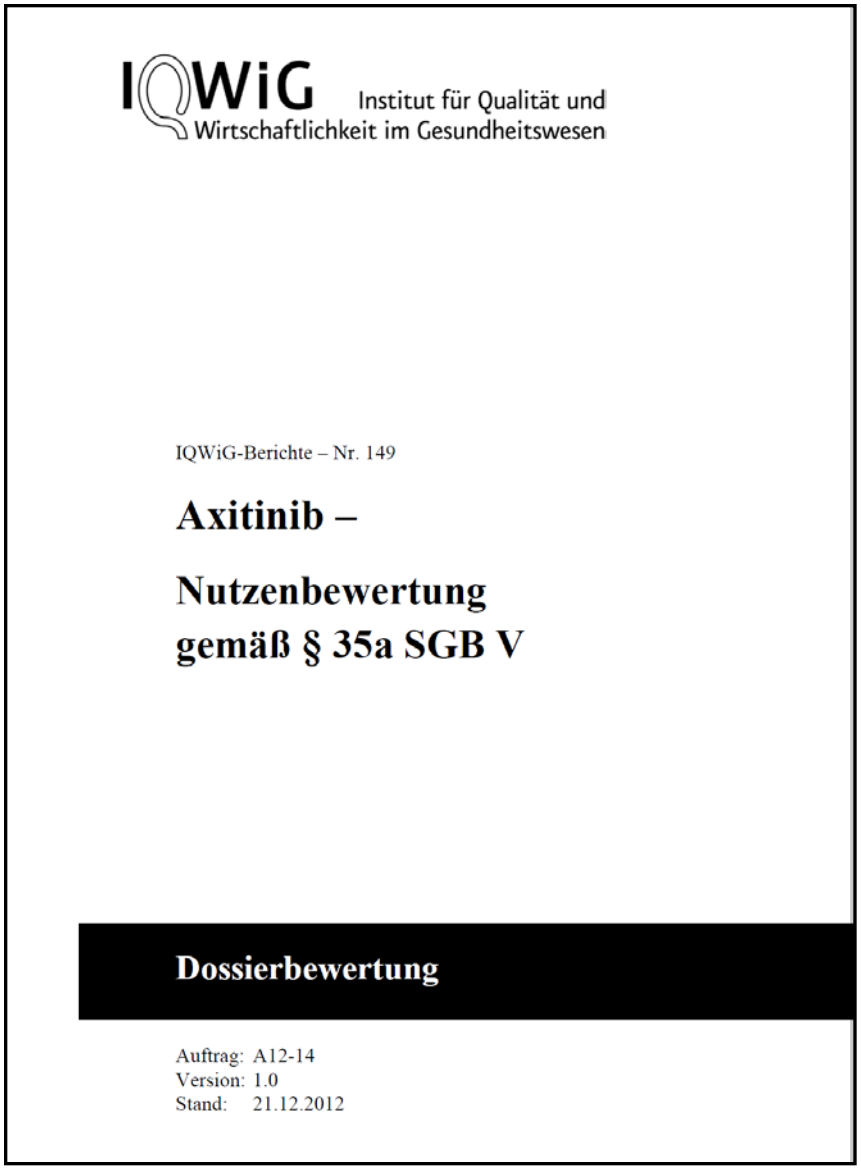
Axitinib for kidney cancer

Example of a dossier, in which an unadjusted indirect comparison was used



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IQWiG-Berichte – Nr. 149

Axitinib –

Nutzenbewertung gemäß § 35a SGB V

Dossierbewertung

Auftrag: A12-14
Version: 1.0
Stand: 21.12.2012

Example: Axitinib for kidney cancer

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- No direct head-to-head trial available
- No bridge comparator available
- No adjusted indirect comparison possible

Company used **STC**, which represents an <u>unadjusted indirect comparison</u>

METHODOLOGICAL CONSIDERATIONS

Pharmacoeconomics 2010; 28 (10): 957-967
1170-7690/10/0010-0957/$49.95/0

No Head-to-Head Trial? Simulate the Missing Arms

J. Jaime Caro[1,2] and *K. Jack Ishak*[3]

1 Division of General Internal Medicine and Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, Quebec, Canada
2 United BioSource Corporation, Lexington, Massachusetts, USA
3 United BioSource Corporation, Dorval, Quebec, Canada

<u>Assessment of IQWiG:</u>

In its dossier, the drug manufacturer did not present any data suitable for the comparison with everolimus … **An added benefit of axitinib for this treatment situation is therefore not proven**.

Outlook

- New Draft of IQWiG General Methods Paper Version 4.2
  - New chapter on cost-benefit assessment
  - New IQWiG product: Assessment of potential of a new examination or treatment method
  - Published 18.06.2914
  - 31 comments until 07.08.2014
  - Hearing on 01.10.2014
- Forthcoming (2015):
  Special Issue on benefit assessment in the *Biometrical Journal* (guest editors: C. Schmoor & D. Hauschke)
- Planned:
  Special article series on analysis of adverse events in *Biopharmaceutical Statistics*

Summary

- Proof of (additional) benefit requires – in general – a meta-analysis of studies with high certainty of results
- Study design and analysis according to GCP
- Criteria for a proof of benefit from 1 study
- Prediction intervals as new tool in the case of heterogeneity
- IQWiG proposal to operationalize the assessment of the extent of added benefit
- In early benefit assessment situations with lower certainty of results are expected
- IQWiG tries to solve problems to deal with situations leading to lower certainty of results