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McMaster University, Hamilton, Canada
Köln, 28. November 2008

Integrative Beurteilung der Evidenz – Das GRADE System

Übersicht und Ziele

- Warum „integrativ“
- Hintergrund und Prinzip „GRADE“
  - Information über GRADE
- Beispiele
  - Übertragbarkeit von Studienergebnissen „Directness“

Beispiel: Design and Ausführung von RCTs

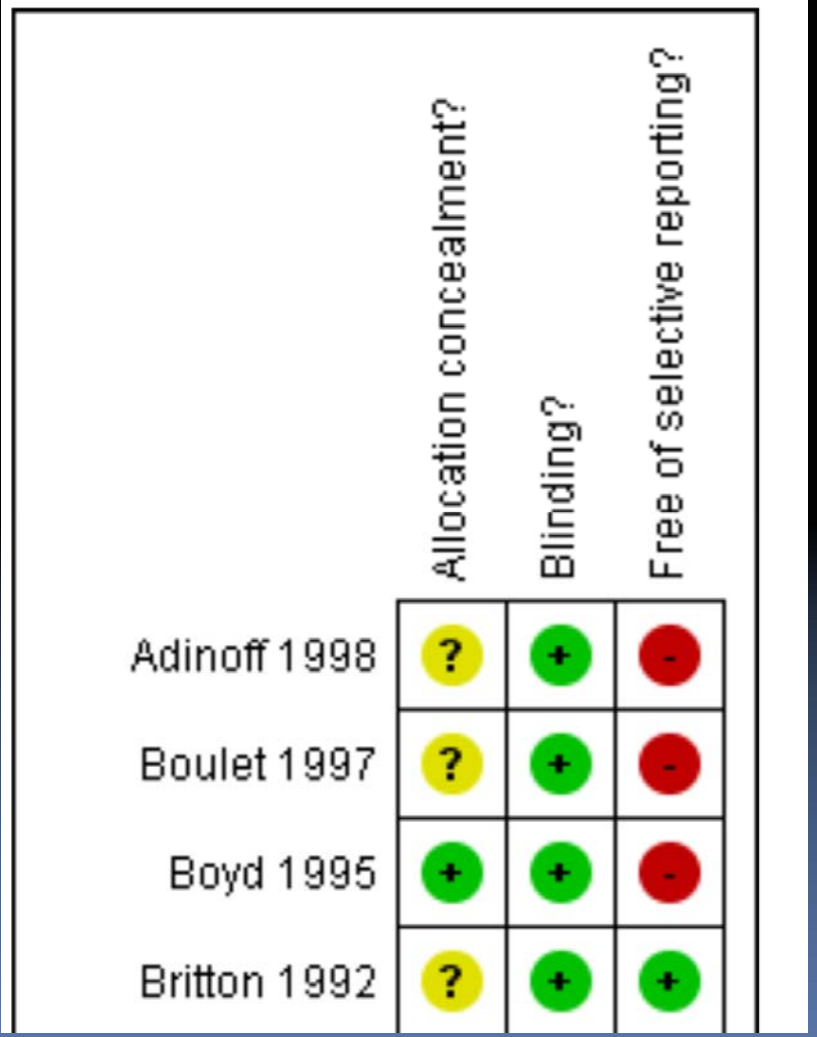
- "Limitations in Design and Execution"
  - Verblindung
  - Randomisierung
  - Verdeckte Behandlungsfolge "Concealment"
  - lack of concealment
  - "intention to treat"
  - Follow-up
  - Studienunterbrechung wegen positiver Effekte
  - "selective outcome reporting"

Design and Ausführung

Regular treatment with salmeterol for chronic asthma: serious adverse events (Review)

Cates CJ, Cates MJ

Figure 4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



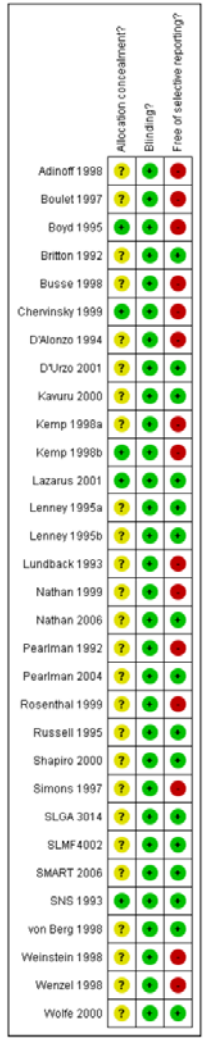
CDSR 2008

Design and Ausführung

Regular treatment with salmeterol for chronic asthma: serious adverse events (Review)

Cates CJ, Cates MJ

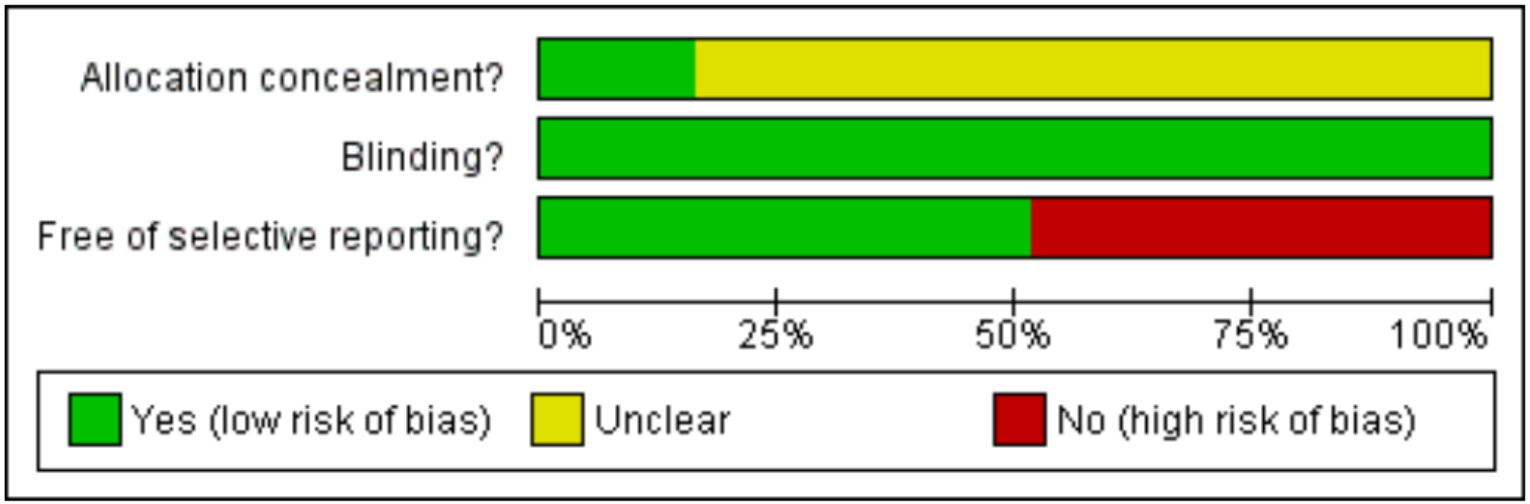
Figure 4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



CDSR 2008

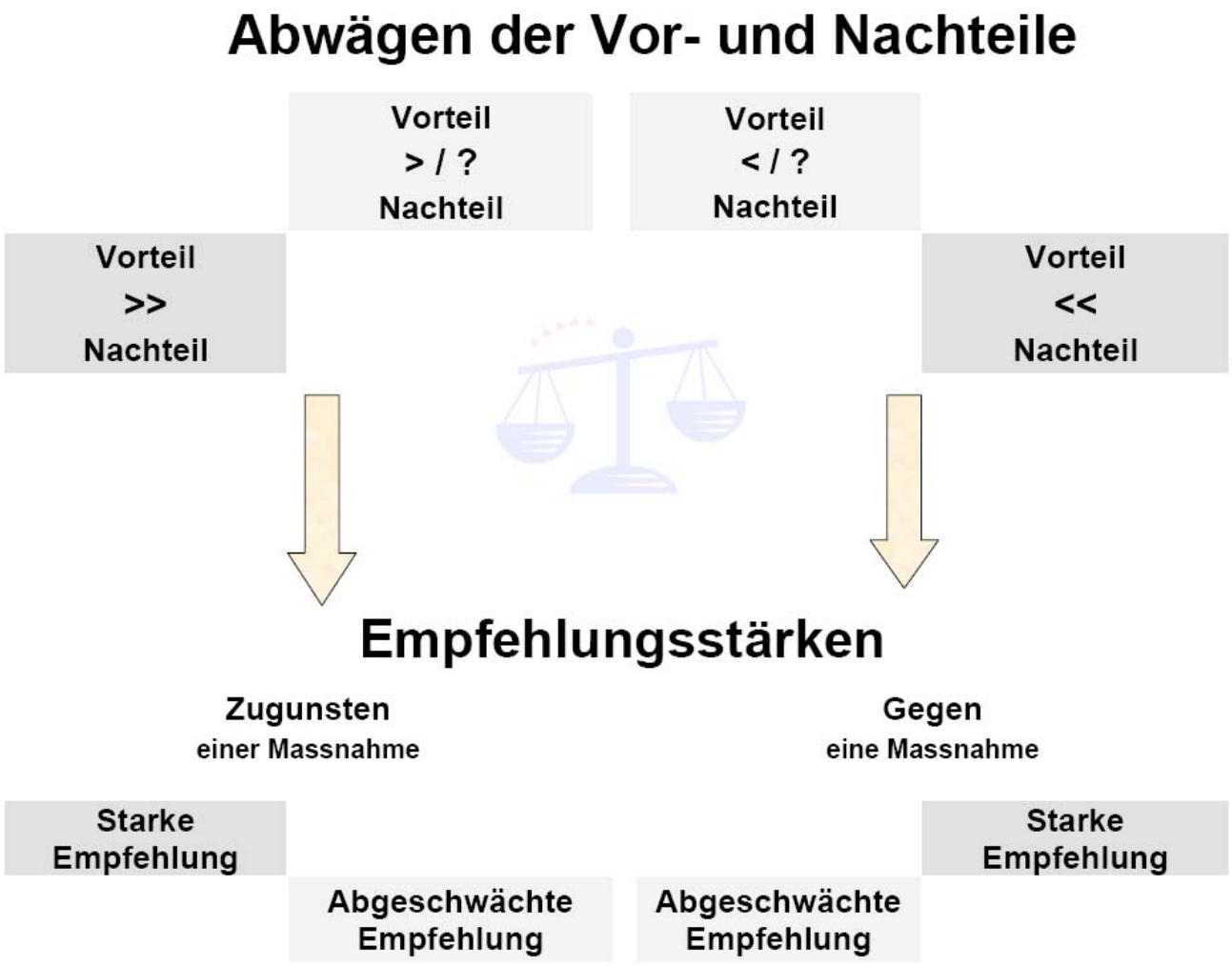
Design and Ausführung

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Overall judgment required

Nutzen und Schaden



5.1 Should H5N1 patients receive treatment with oseltamivir?

Benefits

There are too few events in the reported studies to provide evidence of benefit of oseltamivir on mortality or duration of hospitalization in either seasonal influenza or H5N1 infection. In seasonal influenza lower respiratory tract complications (including pneumonia) were reduced (RR 0.15, 95% CI 0.03 to 0.69) in a series of 5 similarly designed trials (n = 1644) that addressed this outcome in otherwise healthy adults with seasonal influenza (Kaiser et al, 2003), but there were only 11 events. This same analysis also reported a significant reduction (RR 0.40, 95% CI 0.18 to 0.88) in all-cause hospitalizations within 30 days of diagnosis in oseltamivir recipients compared to placebo, but this finding was based on a total of 27 events (18 out of 1063 patients treated with placebo compared with 9 out of 1350 treated with oseltamivir).[2] The most recent case series describes 37 H5N1 patients, of whom 25 were treated with oseltamivir (19 deaths) and 12 described as not being treated with oseltamivir (9 deaths) (Beigel 2005). Treatment regimens differed across these patients beginning between day 4 to 22 of illness.

Harms

Serious adverse events and drug resistance were generally not reported in systematic reviews of oseltamivir use in adults with seasonal influenza. There have been 2 trials in paediatric populations that reported very few adverse events (RR 2.00, 95% CI 0.61 to 6.61). However, reporting of harms is often complicated by withdrawals of patients from trials due to adverse events that are not fully described in published reports. Data from regulatory trials submitted by the manufacturer to the US Food and Drug Administration included nausea and vomiting as the most frequent adverse event in both children and adults (FDA label information, Dutkowski 2003). Rare cases of anaphylaxis and serious skin reactions were also reported during post-marketing experience with oseltamivir. Spontaneous reports to WHO of adverse reactions listed 644 reports of adverse reactions, but there is no assessment of causality or severity of these events in relation to oseltamivir. The most commonly reported adverse event was nausea (n = 110 cases). There were 86 reports of exposure to oseltamivir in pregnancy (maternal exposure) recorded on the Roche Drug Safety database as at 31 March 2005. Twenty-five of these women were either lost to follow up or the outcome of the pregnancy was unknown. For 33 women, the pregnancy was still

Rec 01: In patients with confirmed or strongly suspected H5N1 infection, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation, very low quality evidence).

Einheitliche und integrative Beurteilung der Evidenz?

Empfehlung für Vitamin K Antagonisten in Patienten mit Vorhofflimmern und Mitralklappenstenose

Evidenz	Empfehlung	Organisation
B	Class I	AHA
C+	1	ACCP
IV	C	SIGN

Grades of **R**ecommendation **A**ssessment,
Development and **E**valuation

GRADE
WORKING GROUP


Education and debate

Grading quality of evidence and strength of recommendations

GRADE Working Group

Clinical guidelines are only as good as the evidence and judgments they are based on. The GRADE approach aims to make it easier for users to assess the judgments behind recommendations


RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide

*Grade Working Group. CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, AJRCCM 2006, BMJ 2008

Über GRADE*

- Ziel: ein einheitliches System zur transparenten Beurteilung der Qualität der Evidenz und des Empfehlungsgrades zu entwickeln und die Bereiche zu untersuchen, bei denen das System Anwendung finden kann
- Arbeitsgruppe - seit 2000
- Wissenschaftler und Leitlinienentwickler mit Interesse die methodologischen Schwierigkeiten und Ungenauigkeiten aufzuarbeiten
- Evaluierung von vorhandenen Systemen
- GRADE ist **nicht neu**, sondern eine integrative Weiterentwicklung alter Systeme

*www.GradeWorkingGroup.org. CMAJ 2003, BMJ 2004 & 2008, BMC 2004, BMC 2005

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u) Finnish Medical Society Duodecim, Finland

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w) Centers for Disease Control and Prevention, USA

x) University of London, UK

Y) BMJ Clinical Evidence, UK

The GRADE working group

The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care.

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Jacek Mrukowicz	Executive Director	Polish Institute for Evidence Based Medicine, Poland

GRADE Nutzer/Anwender

- World Health Organization
- National Institute Clinical Excellence (NICE)
- Agency for Health Care Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technology in Health (CADTH)
- Cochrane Collaboration
- Allergic Rhinitis in Asthma Guidelines (ARIA)
- American Thoracic Society
- American College of Chest Physicians
- UpToDate
- British Medical Journal
- American College of Physicians
- European Society of Thoracic Surgeons
- Clinical Evidence
- Many other organizations

Was wird beurteilt?

1. Gesamtschau/Qualität der Evidenz für eine Fragestellung
   - Endpunktspezifisch
   - Wahrscheinlichkeit das systematische Fehler vorliegen oder Übertragbarkeit eingeschränkt ist
     - Kein Instrument für die Beurteilung einzelner Studien
     - Bietet aber Ansätze welche Einzelkriterien nützlich sind

2. Stärke/Grad der Empfehlung
   - Stark und schwach/bedingt
   - Qualität nur ein Faktor

Prozess der Leitlinienentwicklung

Einrichtung einer LL-Gruppe

Schlüsselfragen und systematische Reviews

Evidenztabellen/-profile

- Qualität der Evidenz für jeden Endpunkt (inkl. Gesamtqualität der Evidenz)
- Relative Bedeutung der einzelnen Endpunkte
- Abwägung zwischen Nutzen und Schaden // (± Kosten)
- Stärke der Empfehlung

Implementierung und Evaluation

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Schlüsselfragen und systematische Reviews

Evidenztabellen/-profile

Summary of Findings

- Qualität der Evidenz für jeden E
  (inkl. Gesamtqualität der Evidenz)
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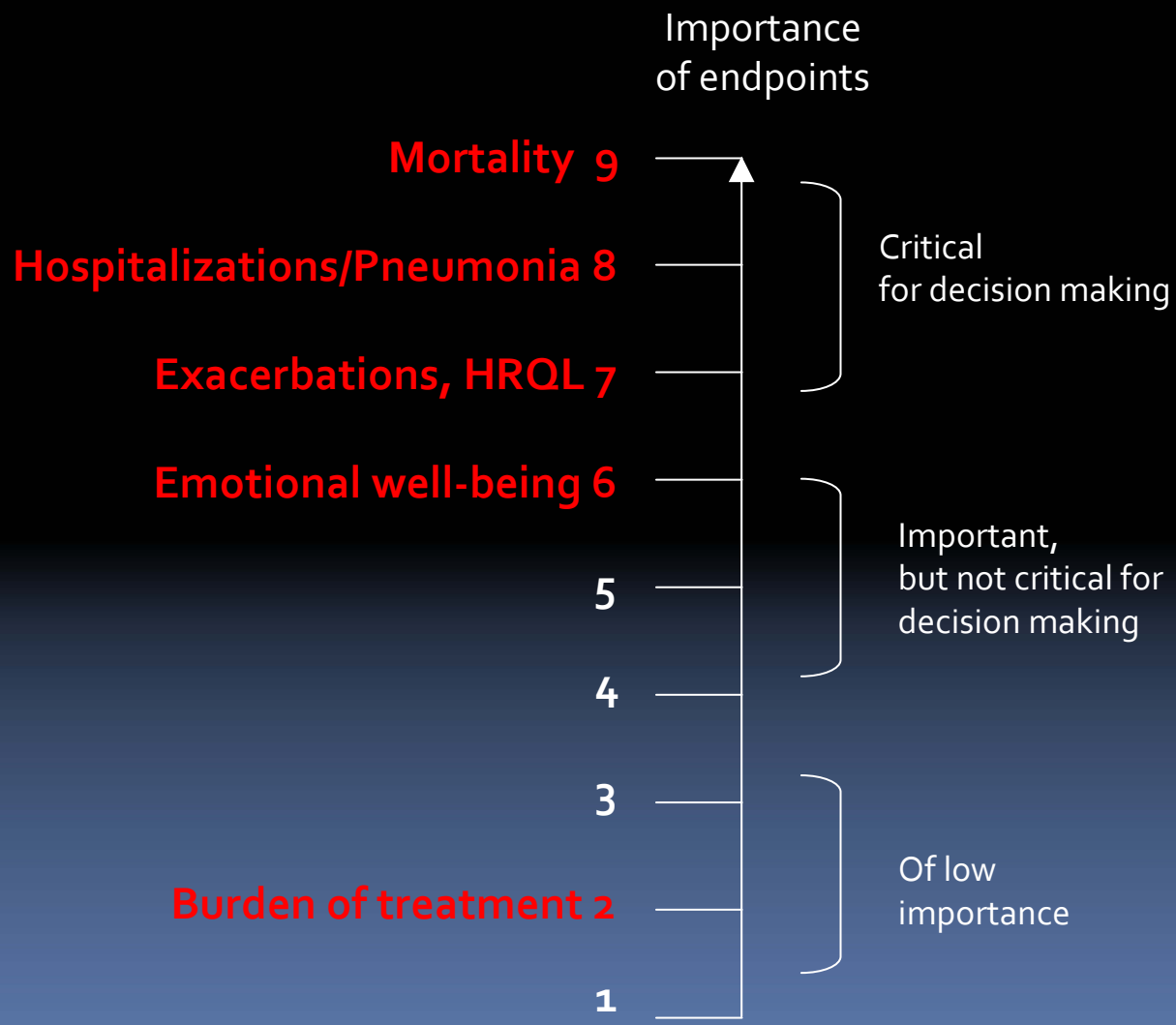
Implementierung und Evaluation

Klinische Fragestellung

Population:	Patienten mit COPD
Intervention:	kombinierte inhalierbare Medikamente (ICS+LABA)
Comparison:	keine derartige Therapie
Outcomes:	↓ Mortalität und Exazerbationen ↑ Nebenwirkungen/Pneumonien Verbesserung HRQL?

Hierarchie von Endpunkten in der COPD



Evidenzprofile

GRADE Evidence Profile

Author(s): Santesso, Schünemann, Nannini, Cates, Lasserson, Poole
Date: 2007-08-06
Question: Should corticosteroid and long-acting beta-agonist in one inhaler vs no treatment be used for moderate and severe chronic obstructive pulmonary disease?
Bibliography: Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Cochrane Database of Systematic Reviews 2007, Issue 4.

Quality assessment							Summary of findings					Importance for decision making
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroid and long-acting beta-agonist in one inhaler[3]	no treatment	Relative (95% CI)	Absolute		
Exacerbation rate (follow-up 3 years)												
5	randomised trial	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2191	2035	Rate Ratio 0.74 (0.69 to 0.79)	1 less exacerbation per 3 years per patient	⊕⊕⊕O MODERATE	critical
Hospitalisations - not reported												
0	-	-	-	-	-	none	0/0	0/0	-	-		
Mortality (follow-up 3 years)												
7	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	209/2946	255/2806 (9.1%)	RR 0.80 (0.65 to 0.96)	18 fewer per 1000	⊕⊕⊕O MODERATE	critical
Quality of Life (follow-up 3 years; measured with: St. George's Respiratory Questionnaire; range of scores: 0-100; Better indicated by lower scores)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1788	1558	-	MD -2.90 (-3.61 to -2.18)	⊕⊕⊕⊕ HIGH	critical
Pneumonia (follow-up 3 years)												
8	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	333/2927	196/2812 (6.9%)	RR 1.80 (1.51 to 2.21)	55 more per 1000	⊕⊕⊕⊕ HIGH	critical
Any adverse events (follow-up 3 years)												
8	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2215/2808	2116/2685	RR 1.01 (0.96 to 1.27)	0 more per 1000	⊕⊕⊕⊕ HIGH	critical

[1] Withdrawal of participants with severe frequent exacerbations may limit inference for severe patients.
[2] Sparse data.
[3] Both long-acting beta-agonists and inhaled corticosteroids can be used in combination for the treatment of chronic obstructive pulmonary disease. Of the 11 included studies, two evaluated fluticasone/salmeterol at 250 mcg/50 mcg twice daily and seven at 500 mcg/50 mcg twice daily; and two evaluated budesonide/formoterol at 320 mcg/9 mcg twice daily.

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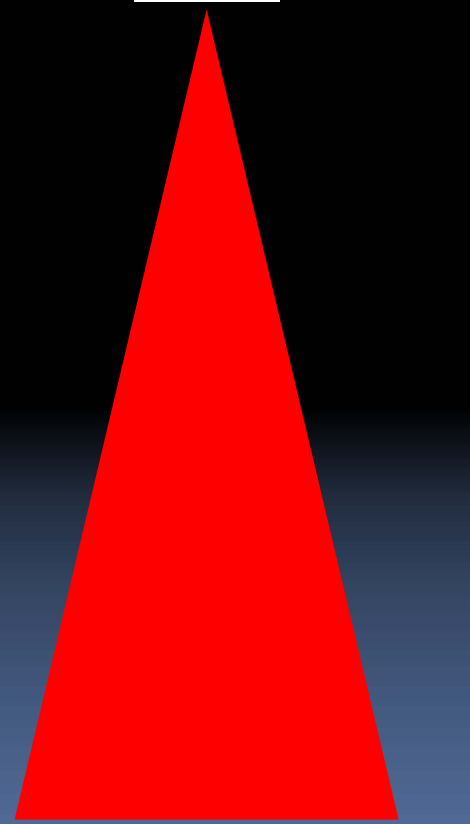
Hierarchie der Evidenz

DESIGN

- Randomisiert kontrollierte Studien (RCTs)
- Kohorten- und Fall-Kontroll-Studien
- Fallbeschreibung/-serien, unsystematische Beobachtungen



Hierarchie der Evidenz

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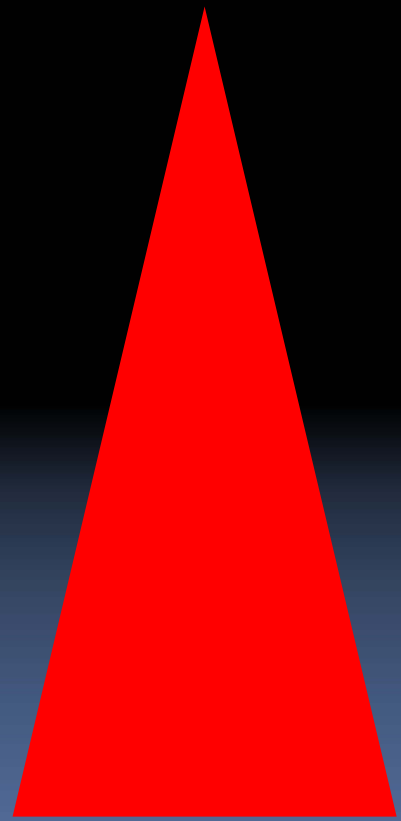
- Randomisiert kontrollierte Studien (RCTs)
- Kohorten- und Fall-Kontroll-Studien
- Fallbeschreibung/-serien, unsystematische Beobachtungen
  Expertenmeinung

BIAS



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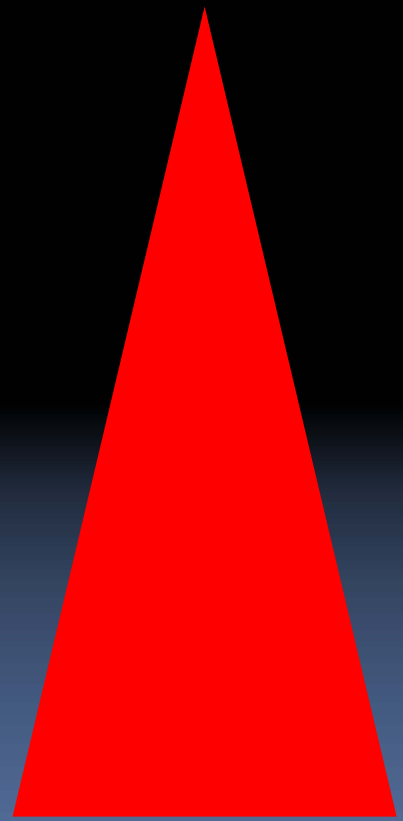


GRADE - Qualität der Evidenz

Gradmesser für die Zuversicht, dass ein ermittelter Effekt korrekt ist.“

Qualität

- Hoch (Randomisierte Studien)
- Mittel
- Niedrig (Beobachtungsstudien)
- Sehr niedrig

“Limitations in Design and Execution”

- Verblindung
- Randomisierung
- Verdeckte Behandlungsfolge “Concealment”
- lack of concealment
- “intention to treat”
- Follow-up
- Studienunterbrechung wg. pos. Effekt
- “selective outcome reporting”

GRADE - Qualität der Evidenz

Herabstufung durch:

1. Bias-anfällige(s) Studiendesign oder Durchführung (RoB)

   → Verblindung, Randomisierung, Concealment, Follow-up, ITT, Studienunterbrechung wg. pos. Effekt, „selective outcome reporting"

2. Heterogenität der Resultate/Evidenz (Inconsistency)

3. Unpräzise Datenlage (imprecise data)

4. „Publication Bias"

5. Geringe Vergleichbarkeit/Übertragbarkeit der Evidenz (indirekte Evidenz)

   → Vergleich, Population, Intervention, Endpunkte

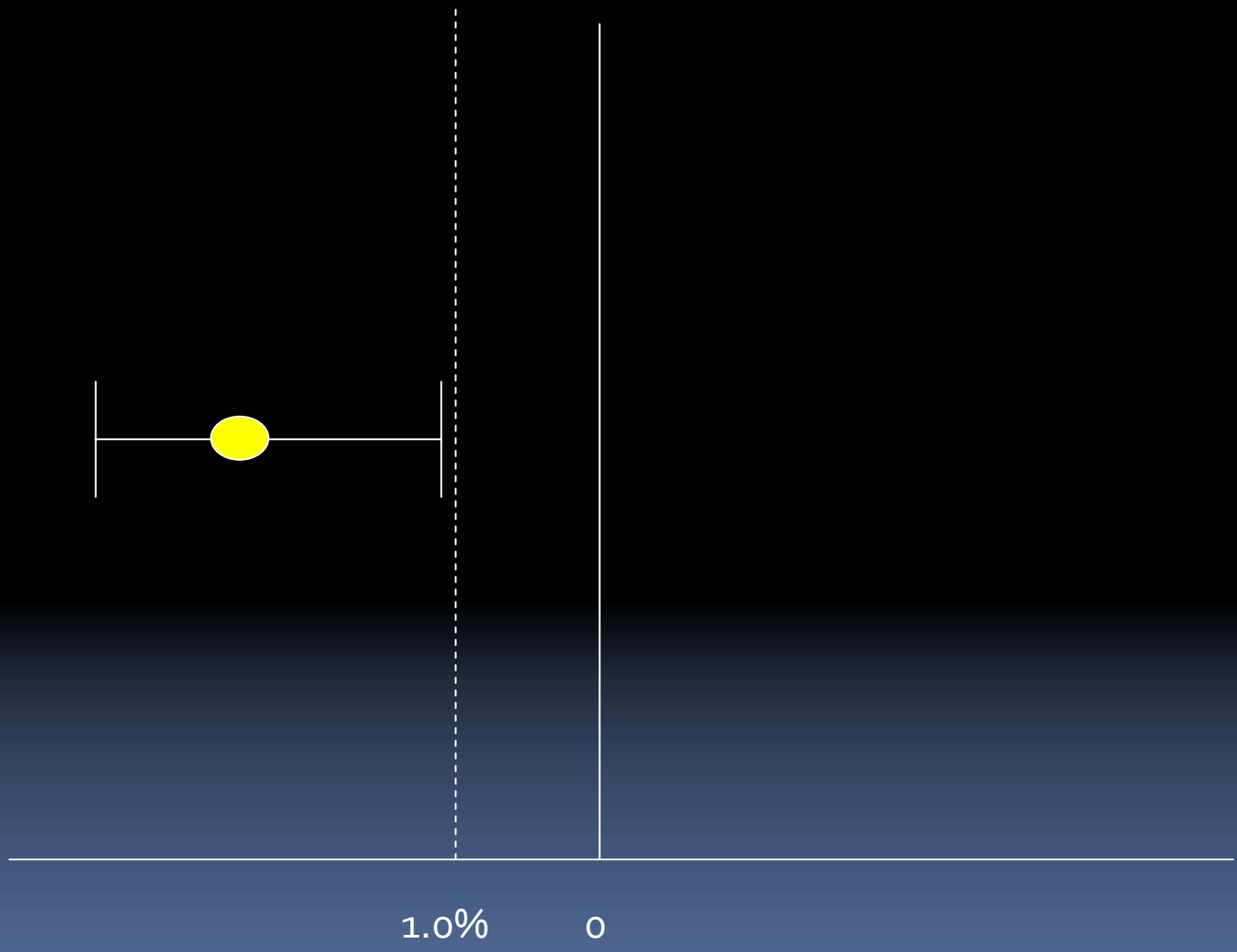
3. Unpräzise Datenlage (imprecise data)

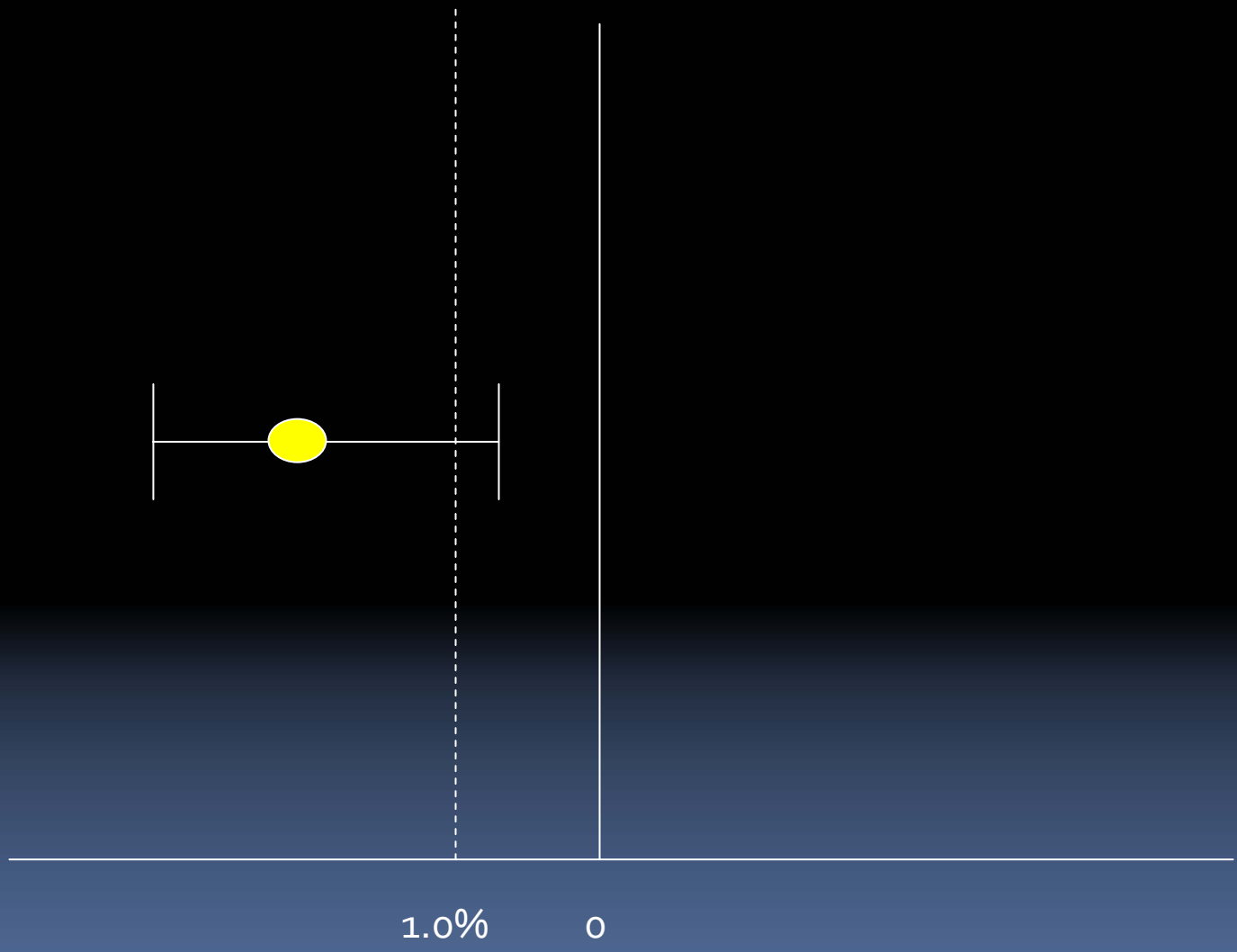
- Kleine Fallzahlen
  - Wenig “events”
- Weite Konfidenzintervalle
  - Unsicherheit über die Grösse des Effekts
- Wie entscheidet man ob die Konfidenzintervalle weit sind?
  - Herunterstufen um eine Stufe?
  - Herunterstufen um zwei Stufen?
- Das Ausmass unseres Vertrauens in den Effekt und eine Entscheidung

Soll man alle effektiven Behandlungen empfehlen?

- Vorhofflimmer und Schlaganfall
- Coumadin erhöht das Blutungsrisiko (Magen)
  - 3 % pro Jahr
- 1,000 Patienten – 1 Schlaganfall
  - 30 Blutungen für jeden verhinderten Schlaganfall
- 1,000 Patienten – 100 weniger Schlaganfälle
  - 3 verhinderte Schlaganfälle für jede Blutung
- Wo ist die Grenze?
  - Wie viele Schlaganfälle muss man verhindern bei einem 3 %igen Blutungsrisiko?

Grenze von 1%

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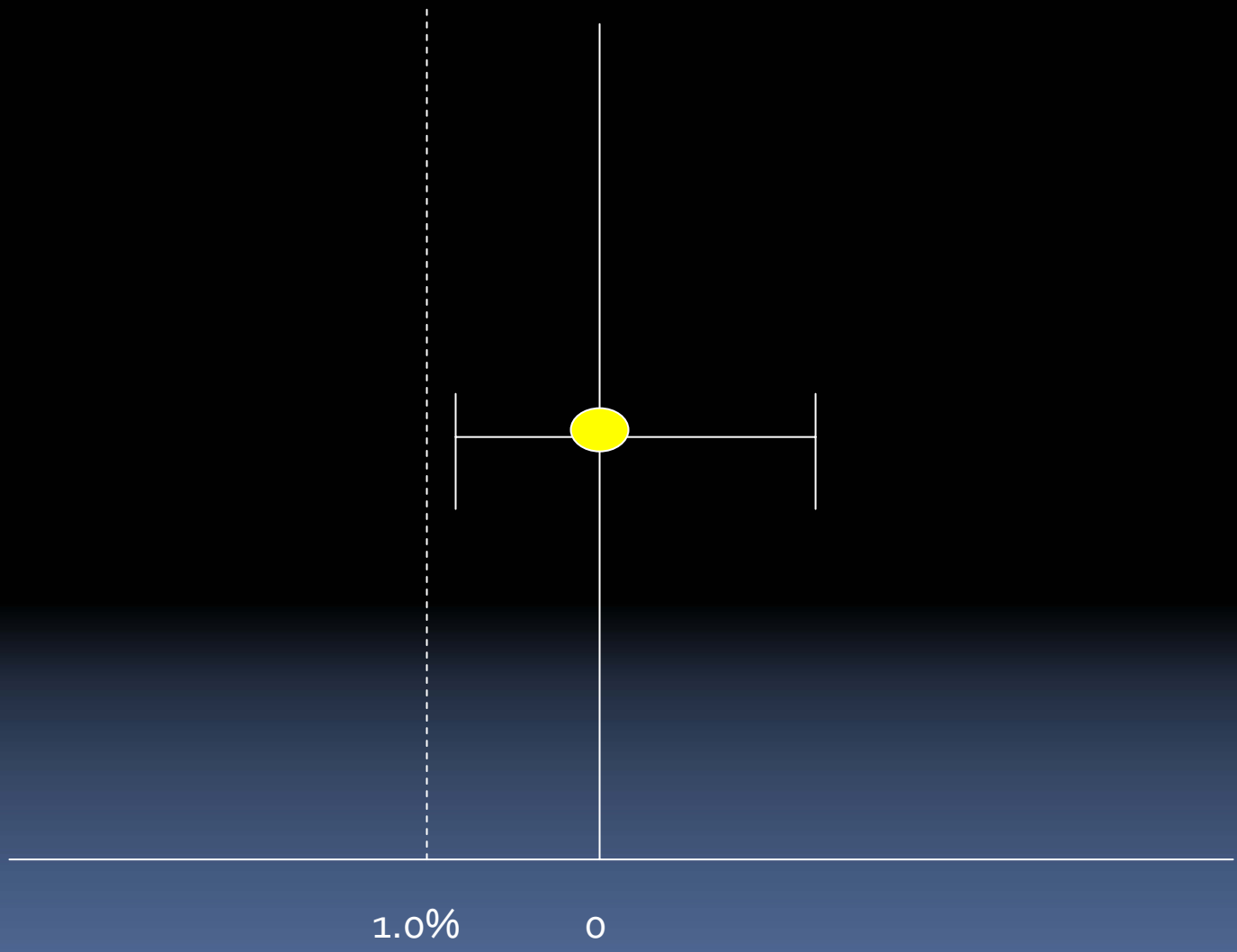
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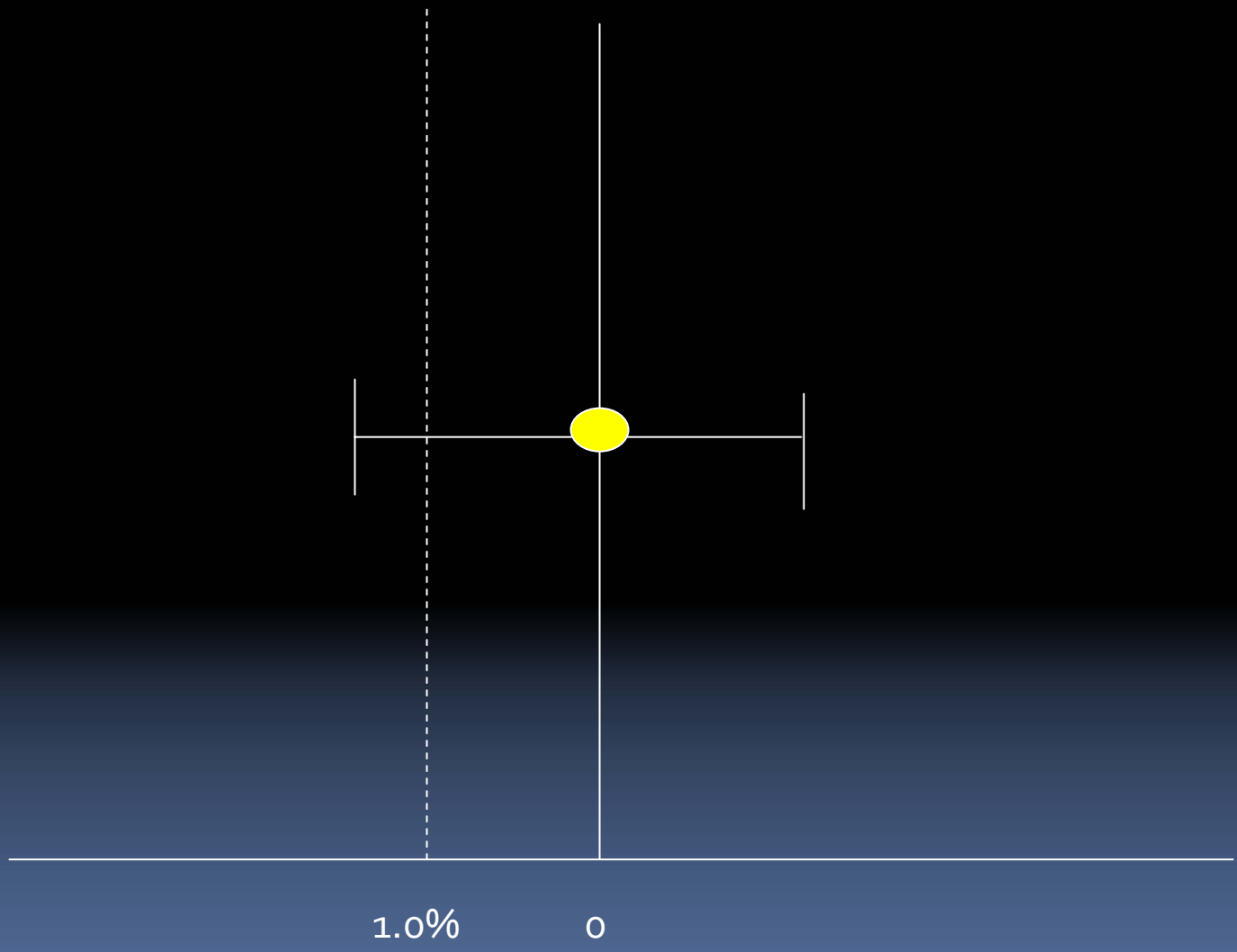
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Geringe Vergleichbarkeit/ Übertragbarkeit der Evidenz

1) Indirekter Vergleich
2) Population, Intervention, Outcome/Endpunkt

Geringe Vergleichbarkeit/ Übertragbarkeit der Evidenz

1) Indirekter Vergleich

   Thromboseprophylaxe im Krankenhaus

   2 x versus 3 x tägliche Gabe von Heparin

   Viele Studien, die 2 x oder 3 x tägliche Gabe mit Placebo verglichen haben, aber kein direkter Vergleich

   Verringert unser Vertrauen in den direkten Vergleich

Geringe Vergleichbarkeit/ Übertragbarkeit der Evidenz

2) Population, Outcome

Fragestellung	**Indirekte Evidenz**
Oseltamivir zur Behandlung der Vogelgrippe durch Influenza A(H5N1) Virus	Population: Randomisierte Studien mit Oseltamivir sind vorhanden, aber für die gewöhnliche Grippe, nicht für die Vogelgrippe
Heparin zur Thromboseprophylaxe	Indirekte “outcomes”: asymptomatische versus symptomatische tiefe Venenthrombose

GRADE - Qualität der Evidenz

Heraufstufung durch:

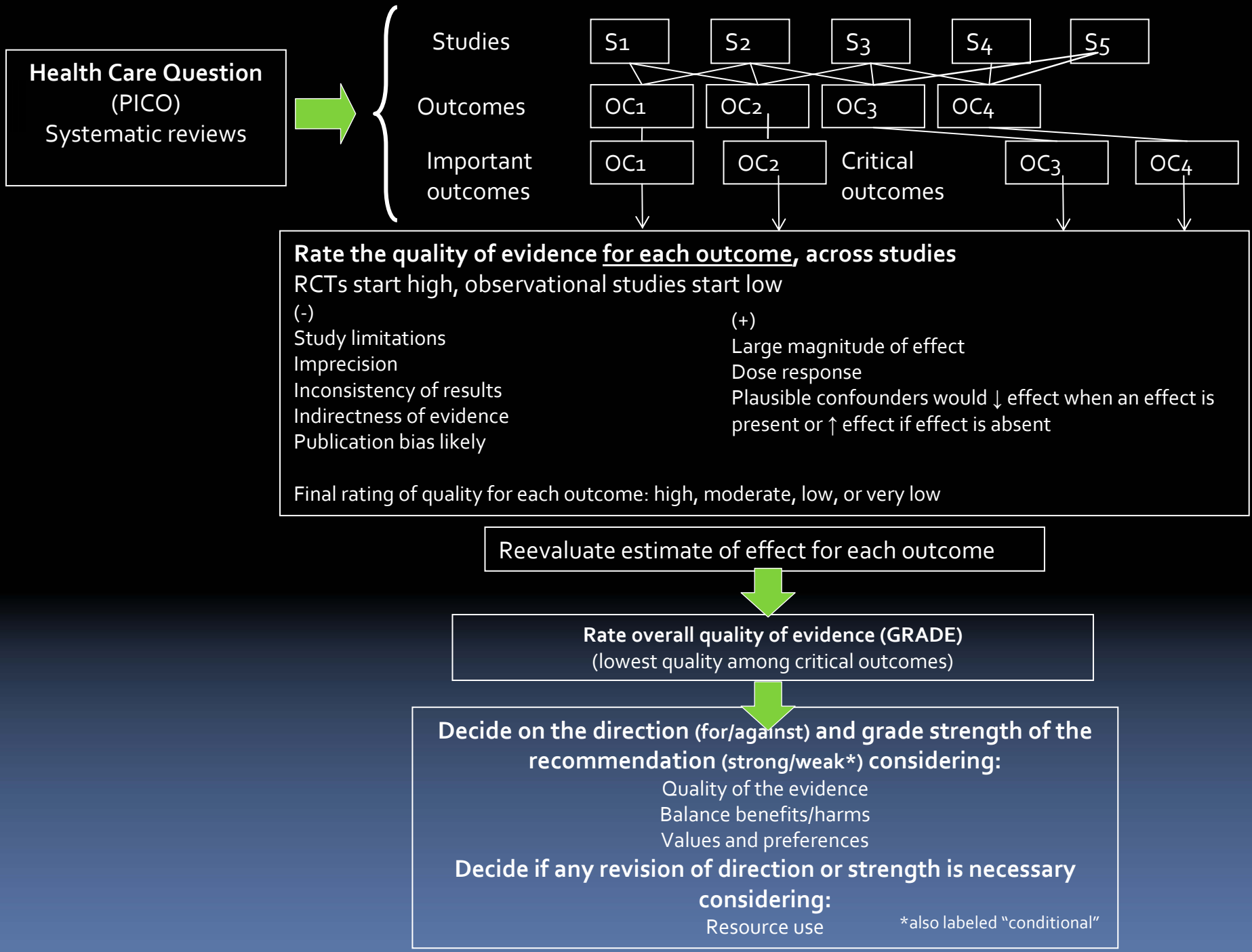
- Vorhandensein einer starken Assoziation
  - RR > 2 (< 0,5), wenn mehr als zwei Studien ohne plausible Confounder und mit konsistenten Ergebnissen vorliegen
  - RR > 5 (< 0,2)
- Vorhandensein einer Dosis-Wirkungs-Beziehung
- Alle verbleibenden, plausiblen „Confounder" haben den beobachteten Effekt bereits reduziert oder einen abwesenden Effekt möglicherweise verstärkt

Alle verbleibenden, plausiblen „Confounder“ haben einen abwesenden Effekt möglicherweise verstärkt

- Diabetes Medikament “Fenformin” verursacht “lactic acidosis”
- Ein verwandtes Medikament wurde verdächtigt die gleiche Nebenwirkung zu haben
- Gross Beobachtungsstudien haben das nicht gezeigt
  - Kliniker sind gegenüber dieser Nebenwirkung aber sehr aufmerksam gewesen

GRADE - Kriterien zur Bewertung der Qualität

Qualität der Evidenz	Studiendesign	Herabstufen falls*	Hinaufstufen falls *
Hoch	Randomisierte Studie	Studienqualität: **Schwerwiegende Einschränkungen ……. -1** **Sehr schwerwiegende Einschränkungen ..... -2** Widersprüchliche Effekte **Wesentl. inkonsistente Effekte ..... -1 oder -2** Direktheit** **Einige Unsicherheit ..... -1** **Große Unsicherheit ….. -2** Vorhandene Daten **Wenige oder ungenaue Daten ..... -1 oder -2** Reporting Bias **Hohe Wahrscheinlichkeit für Reporting Bias ..... -1 oder -2**	die Assoziation **.... stark, ohne plausible Confounder, konsistente u. direkte** Evidenz ..... +1** **.... sehr stark, ohne Einschränkung d. Validität, konsistente und direkte** Evidenz..... +2** Dosis-Wirkungsbeziehung **Evidenz für eine** Dosis-Wirkungsbeziehung**.... +1** Confounder **Alle plausiblen Confounder hätten den beobachteten Effekt verringert oder einen abwesenden Effekt verstaerkt..... +1**
Mittel			
Niedrig	Beobachtungs-Studie		
Sehr niedrig			


Health Care Question
(PICO)
Systematic reviews
Studies
Outcomes
Important outcomes
S1
S2
S3
S4
S5
OC1
OC2
OC3
OC4
OC1
OC2
Critical outcomes
OC3
OC4
Rate the quality of evidence for each outcome, across studies
RCTs start high, observational studies start low
(-)
Study limitations
Imprecision
Inconsistency of results
Indirectness of evidence
Publication bias likely
(+)
Large magnitude of effect
Dose response
Plausible confounders would ↓ effect when an effect is present or ↑ effect if effect is absent
Final rating of quality for each outcome: high, moderate, low, or very low
Reevaluate estimate of effect for each outcome
Rate overall quality of evidence (GRADE)
(lowest quality among critical outcomes)
Decide on the direction (for/against) and grade strength of the recommendation (strong/weak*) considering:
Quality of the evidence
Balance benefits/harms
Values and preferences
Decide if any revision of direction or strength is necessary considering:
Resource use
*also labeled "conditional"

Zusammenfassung

Integrative Beurteilung der Evidenz ist nötig, aber ein komplexer Vorgang

Herausforderungen beim Zuweisen der Gradmesser

- Beurteilungen sind immer nötig

Untertrennung von Handlungsempfehlung und Qualitätsbeurteilung

Abwägen von Nutzen und Schaden/Kosten

Grösse der Effekte, Präzision, Werte

GRADE Working Group aktiv in Verbreitung und Dialog zur Methodenverbesserung