Cochrane-GRADE Workshop

Modena, June 2017

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Cochrane

GRADE

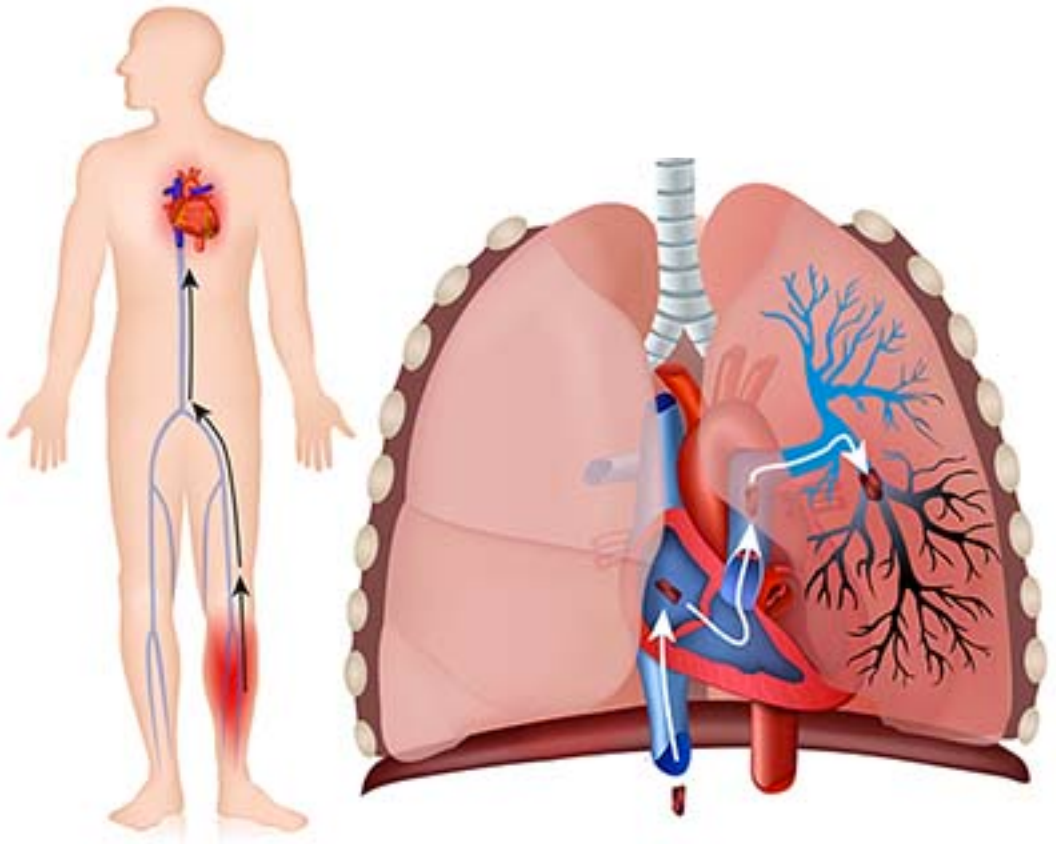
GRADE CERQual

Background / history of GRADE and GRADE CERQual

GRADE

GRADE CERQual

Deep vein thrombosis and pulmonary embolism (VTE)



- The risk of VTE is elevated in cancer (4 – 5% annually)
- Require hospital admission and interventions at end of life
- Associated with impairments in function, pain and increased costs

A clinically sensible question

Population:	In patients with (lung) cancer, what is
the impact of	
Intervention:	heparin
(comparison)	compared with no heparin
Outcomes:	on the risk for venous thromboembolism, death, bleeding, burden…?

PICO

A systematic review of RCTs: heparins in cancer patients

Table 1. Summary of Findings Table Showing the Relative Risks and Absolute Effects over 12 Months for Each Important Outcome after Treatment with a Low-Molecular-Weight Heparin in Patients Receiving Chemotherapy for Cancer.*

Outcome after 12 Months	Participants	Relative Risk (95% CI)	Anticipated Absolute Effect	
			Risk without LMWH	Risk Difference with LMWH (95% CI)
	no. (no. of studies)		*no. of events per 1000 patients*	
Death	6245 (10)	0.94 (0.88–1.00)	501	30 fewer (60 fewer to 0 more)
Symptomatic VTE	5979 (9)	0.57 (0.40–0.81)	46	20 fewer (27 fewer to 9 fewer)
Major bleeding	6518 (11)	1.06 (0.71–1.57)	16	1 more (5 fewer to 9 more)
Minor bleeding	6020 (9)	1.18 (0.89–1.55)	27	5 more (3 fewer to 15 more)

Akl & Schünemann, New Engl J Med, 2012

Do you have confidence in these estimates of effects?

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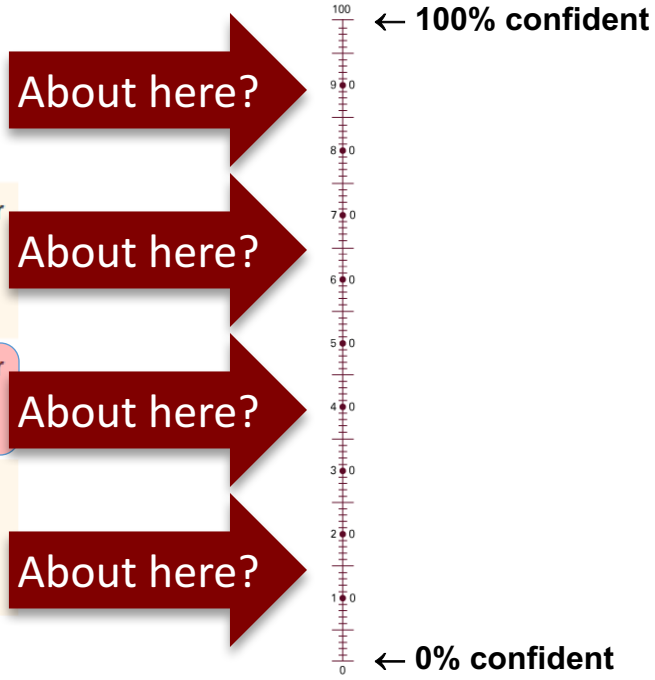


Akl & Schünemann, New Engl J Med, 2012

Certainty of the evidence?

How confident in the research? GRADE

- Are the research studies well done?
- Are the results consistent across studies when they should be?
- How directly do the results relate to our question?
- Is this effect size precise or likely due to random error?
- Are these all of the studies that have been conducted?
- Plus factors that increase certainty – e.g. large intervention effects

Magnitude of effect/association

Likelihood of and certainty in the evidence or effect

Certainty of evidence
Confidence in association/effect

Systematic review process

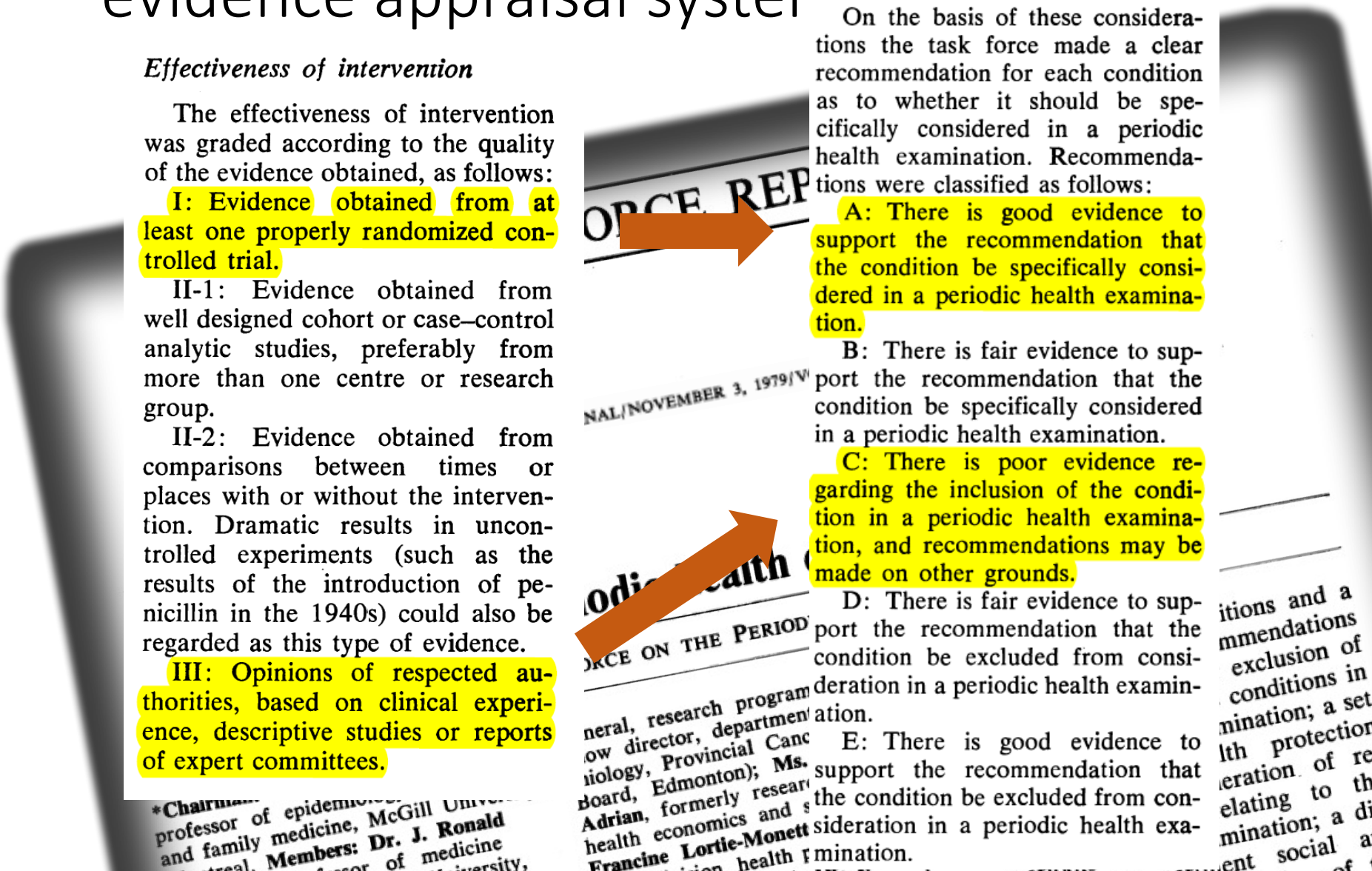
1. define the question
2. plan eligibility criteria
3. plan methods
4. search for studies
5. apply eligibility criteria
6. collect data
7. assess studies for risk of bias
8. analyze and present results
9. **interpret results and draw conclusions**
10. improve and update review

Cochrane reviews….

…interpret results and draw conclusions?

GRADE criteria *(MECIR standards: mandatory)*

Clinical Practice guidelines & the origin of evidence appraisal syster



Effectiveness of intervention

The effectiveness of intervention was graded according to the quality of the evidence obtained, as follows:

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well designed cohort or case–control analytic studies, preferably from more than one centre or research group.

II-2: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Classification of recommendations

On the basis of these considerations the task force made a clear recommendation for each condition as to whether it should be specifically considered in a periodic health examination. Recommendations were classified as follows:

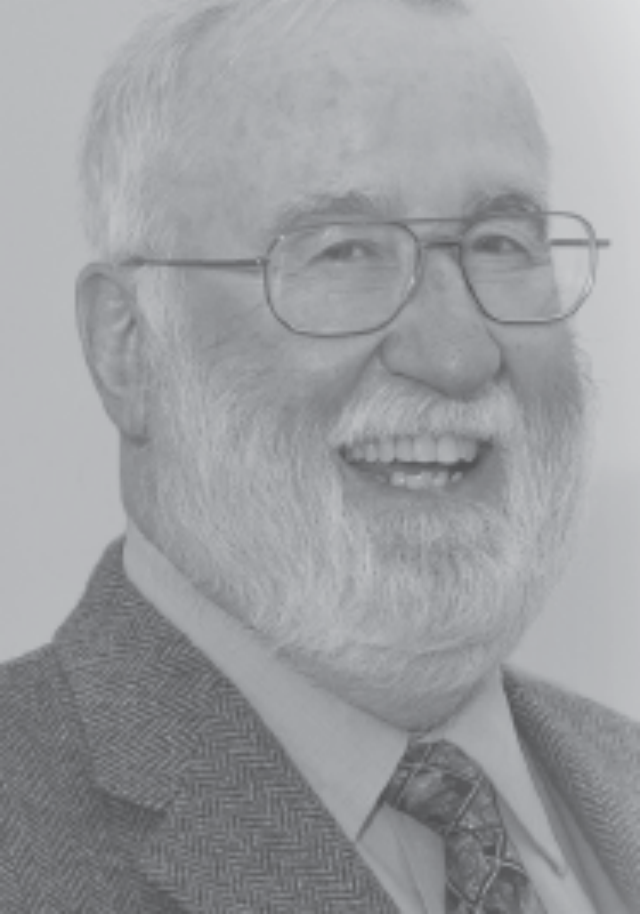
A: There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

B: There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

C: There is poor evidence regarding the inclusion of the condition in a periodic health examination, and recommendations may be made on other grounds.

D: There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

E: There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.



Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents

D. L. Sackett M.D.

Introduction

What rules of evidence ought to apply when expert committees meet to generate recommendations for the clinical management of patients? Should only the thoroughly validated results of randomized clinical trials be admissible to avoid or minimize the application of useless or harmful therapy? Or, to maximize the potential benefits to patients (including those possible from unproved remedies), ought a synthesis of the experiences of seasoned clinicians form the basis for such recommendations?

Ample precedent exists for the latter approach even when attempts are made to replace it.[1] However, for the following three reasons, the nonexperimental evidence that forms the recalled experiences of seasoned clinicians will tend to overestimate efficacy:

1. Favorable treatment responses are more likely to be recognized and remembered by clinicians when their patients comply with treatments and keep follow-up appointments. However, there are already five documented instances in which compliant patients in the *placebo* groups of randomized trials exhibited far more favorable outcomes (including survival) than their noncompliant companions.[2-6] Because high compliance is therefore a marker for better outcomes, even when treatment is useless, our uncontrolled clinical experiences often will cause us to conclude that compliant patients must have been receiving efficacious therapy.

agents in an effort to halt the progression and complications of thromboembolism. For many of the disorders under consideration here, randomized control trials have never been (and, arguably, never could be) carried out, and the only information base for generating some of the recommendations comes from uncontrolled clinical observations.

What this does mean, however, is that it is important, whenever possible, to base firm recommendations (and especially those involving risk to patients) on the results of rigorously controlled investigations and to be much more circumspect when recommendations rest only on the results of uncontrolled clinical observations. This approach was adopted by the conference participants and led to the definition and adoption of both Levels of Evidence and Grades of Recommendations.

Levels of Evidence

The participants in this undertaking, when summarizing what was known about the causes, clinical course, and management of a given clinical entity, specified the level of evidence that was being used in each case, according to the following classification:

Level I: Randomized trials with low false-positive (α) and low false-negative (β) errors (high power)

By "low false-positive (α) error" is meant a "positive" trial that demonstrated a statistically significant benefit from experimental treatment. For example, there have now been two randomized trials in which aspirin produced very large, statistically significant reductions in the risk of stroke and death among patients with transient ischemic attacks.

By "low false-negative (β) error (high power)" is meant a "negative" trial that demonstrated no effect of therapy, yet was large enough to exclude the possibility of a clinically important benefit (*ie*, had very narrow 95% confidence limits

Chest 1986

Clinical Recommendations Using Levels of Evidence for Antithrombotic Agents

Deborah J. Cook, MD, FCCP; Gordon H. Guyatt, MD, Chair; Andreas Laupacis, MD; David L. Sackett, MD; and Robert J. Goldberg, PhD

Expert clinical recommendations on the use of antithrombotic agents should be based on the best available evidence. Ideally, this evidence will come from the results of high-quality systematic reviews of rigorously controlled randomized trials.[1] Weaker evidence comes from observational studies or uncontrolled clinical experience. Timely implementation of recommendations based on strong evidence can save lives.[2] Clinical practice based on the best available literature and recommendations derived from such literature form the foundation of an approach to health care often referred to as evidence-based medicine.[3]

Chest 1995

Table 3—*Levels of Evidence and Grades of Recommendations for Therapy*

Level of Evidence	Grade of Recommendation
Level I	*Grade A*
Level I	Results come from a single RCT in which the lower limit of the CI for the treatment effect exceeds the minimal clinically important benefit
Level I+	Results come from a meta-analysis of RCTs in which the treatment effects from individual studies are consistent, and the lower limit of the CI for the treatment effect exceeds the minimal clinically important benefit
Level I–	Results come from a meta-analysis of RCTs in which the treatment effects from individual studies are widely disparate, but the lower limit of the CI for the treatment effect still exceeds the minimal clinically important benefit
Level II	*Grade B*
Level II	Results come from a single RCT in which the CI for the treatment effect overlaps the minimal clinically important benefit
Level II+	Results come from a meta-analysis of RCTs in which the treatment effects from individual studies are consistent and the CI for the treatment effect overlaps the minimal clinically important benefit
Level II–	Results come from a meta-analysis of RCTs in which the treatment effects from individual studies are widely disparate, and the CI for the treatment effect overlaps the minimal clinically important benefit
Level III	*Grade C*
	Results come from nonrandomized concurrent cohort studies
Level IV	*Grade C*
	Results come from nonrandomized historic cohort studies
Level V	*Grade C*
	Results come from case series

Grades of Recommendation for Antithrombotic Agents

Gordon Guyatt, MD; Holger Schunëmann, MD; Deborah Cook, MD, FCCP; Roman Jaeschke, MD; Stephen Pauker, MD; and Heiner Bucher, MD

Abbreviations: ACCP = American College of Chest Physicians; CI = confidence interval; RCT = randomized, controlled trial; tPA = tissue plasminogen activator

(CHEST 2001; 119:3S–7S)

Treatment decisions involve a trade-off between likely benefits on the one hand, and risks and costs on the other. The Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians (ACCP) has developed guidelines to help clinicians make supporting studies first and the number denoting the clarity of the risk/benefit trade-off second: A1, A2, B1, and so on. In this iteration, we reflect the primacy of the risk/benefit judgment in determining the recommendation and its strength by placing it first: 1A, 1B, 1C+, 1C, 2A, and so on (Table 1).

The remainder of this article describes the basis of the grading system in more detail. We begin by describing how methodologically strong studies can yield stronger or weaker recommendations depending on the trade-off between risk and benefit.

How Methodologic Quality and Risk Benefit Contribute to Grades of Recommendations

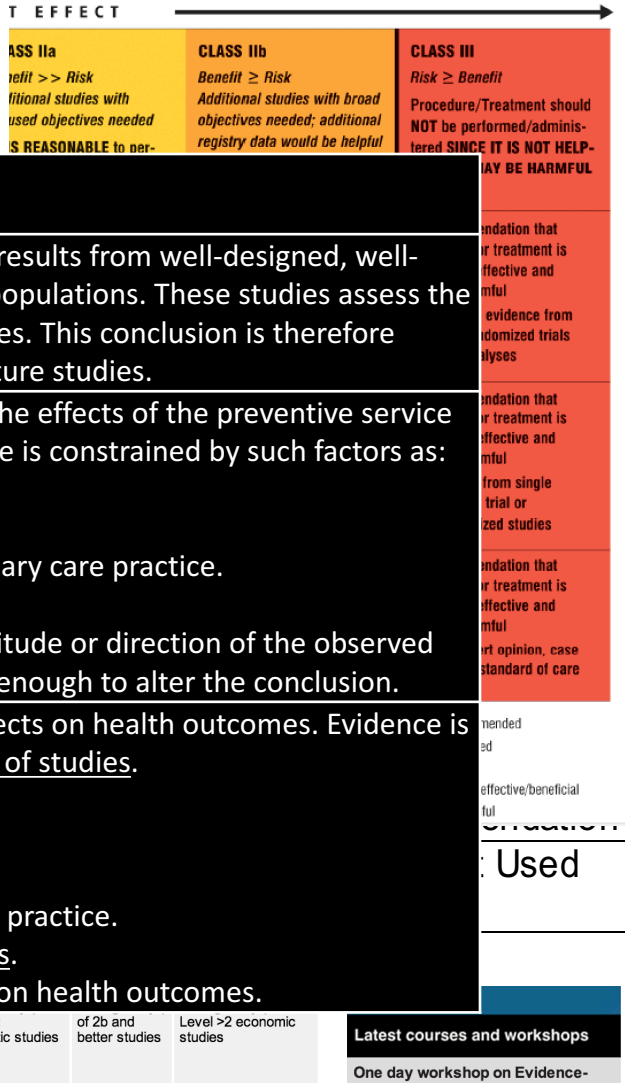
Grade Practice Recommendations*

Study quality	Diagnosis	Treatment/prevention/screening	Prognosis
Level 1—good-quality patient-oriented evidence	Validated clinical decision rule SR/meta-analysis of high-quality studies High-quality diagnostic cohort study†	SR/meta-analysis of RCTs with consistent findings High-quality individual RCT‡ All-or-none study§	SR/meta-analysis of good-quality cohort studies Prospective cohort study with good follow-up
Level 2—limited-quality patient-oriented evidence	Unvali SR/me stud inco Lower stud stud		
Level 3—other evidence	Conse evid prev		

Consistency across studies	
Consistent	Most studies *or* If high-qualit
Inconsistent	Considerable *or* If high-qualit favor of the

Insufficient

Level of Certainty USPSTF	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	•The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: The number, size, or quality of individual studies. •Inconsistency of findings across individual studies. •Limited generalizability of findings to routine primary care practice. •Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	•The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: The limited number or size of studies. •Important flaws in study design or methods. •Inconsistency of findings across individual studies. •Gaps in the chain of evidence. •Findings not generalizable to routine primary care practice. •Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.



Which hierarchy?

Recommendation for use of oral anticoagulation in patients with atrial fibrillation and rheumatic mitral valve disease

Evidence	Recommendation	Organization
• B	Class I	➢ AHA
• A	1	➢ ACCP
• IV	C	➢ SIGN

Simple hierarchies are (too) simplistic

STUDY DESIGN

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations

Expert Opinion

Schünemann & Bone, 2003

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

HULTON/GETTY

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

BMJ, 2003

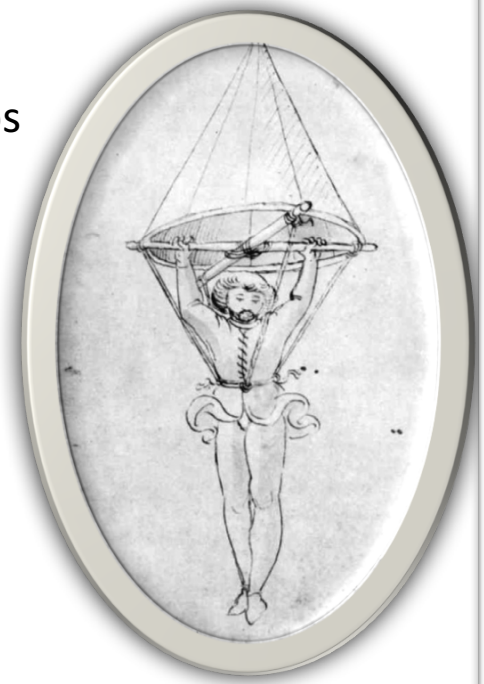
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Relative risk reduction:

….> 99.9 % (1/100,000)

U.S. Parachute Association reported 821 injuries and 18 deaths out of 2.2 million jumps in 2007



Aim: to develop a common, transparent and sensible system for grading the quality of evidence and the strength of recommendations

Proposed acronyms *Meeting minutes London 2002*

GERIC: Grading Evidence and Recommendation International Collaboration (?)

GRASP: Grades of Recommendation ASsessment and Planning group (Andy)

GRADE: Grades of Recommendation Assessement, Development and Evaluation (Working) Group or "GRADE (Working) Group" in short. (Holger)

One could also use DEsign instead of Development

GRADE: Grades of Recommendation Assessement and Development Enterprise (Holger)

GEAR: Grades of Evidence And Recommendations (Andy)

G RADE 2002

Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations

Holger J. Schünemann, Dana Best, Gunn Vist, Andrew D. Oxman, for the GRADE Working Group

CMAJ • SEPT. 30, 2003; 169 (7)

17. National Highway Traffic Safety Administration. Available: www.nhtsa.dot.gov (accessed 2003 Jul 15).
18. DISCERN: Health information on the Internet. Available: www.discern.org.uk/HOTI.htm (accessed 2003 Jul 17).
19. Miller G. The magic number seven plus or minus two: some limits on our capacity for processing information. *Psychol Bull* 1956;63:81-97.

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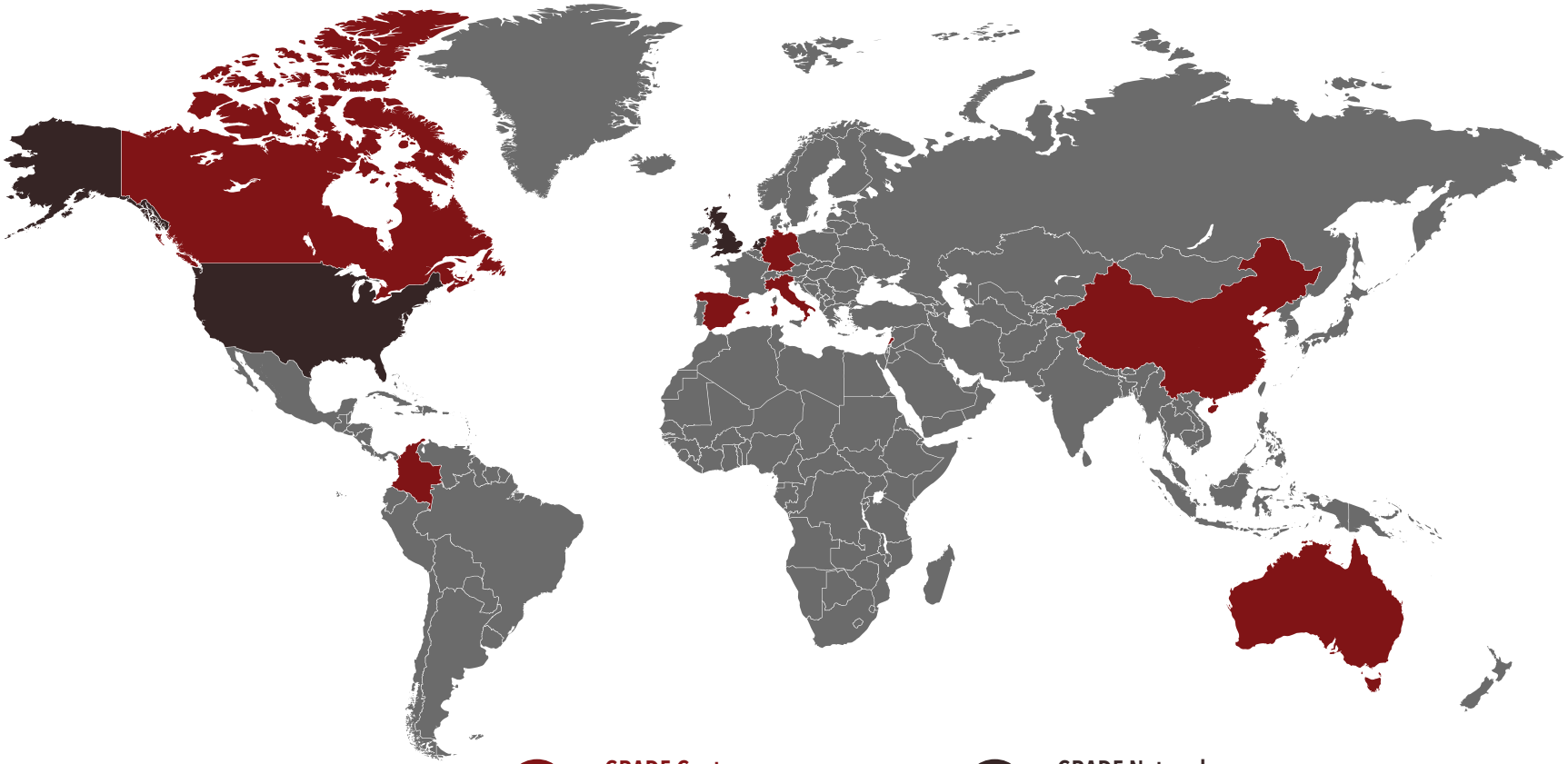
GRADE working group

- Developed a unifying, transparent and sensible system for grading the certainty of evidence and developing recommendations/making decisions
- NICE, WHO, CDC, AHRQ, professional societies, academic institutions
- For systematic reviews, HTA and guidelines
- International contributors (>500) with diversity in background 2008 BMJ series; 2011 JCE series – over 30,000 cites
- Various other publications (incl. GRADE Handbook)
- IT applications GRADEpro | GDT

CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, AJRCCM 2006, Chest 2006, BMJ 2008, JCE 2011-2016

GRADE



GRADE Centers

McMaster University GRADE Center, **Canada**
Lanzhou University GRADE Center, **China**
Barcelona GRADE Center, **Spain**
Freiburg University GRADE Center, **Germany**
American University of Beirut GRADE Center, **Lebanon**
Lazio Region-ASL Rome GRADE Center, **Italy**
Javeriana Bogota GRADE Center, **Colombia**
JBI Adelaide GRADE Center, **Australia**

GRADE Networks

U.S. GRADE Network, **United States**
Dutch GRADE Network, **Netherlands**
UK GRADE Network, **United Kingdom**

GRADE working group

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GRADE


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Certainty of the evidence?

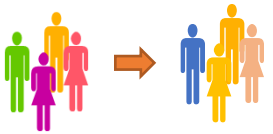
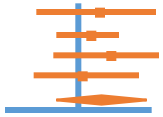
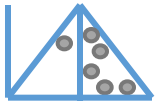
How confident in the research? GRADE

- Are the research studies well done?
- Are the results consistent across studies when they should be?
- How directly do the results relate to our question?
- Is this effect size precise or likely due to random error?
- Are these all of the studies that have been conducted?
- Plus factors that increase certainty – e.g. large intervention effects

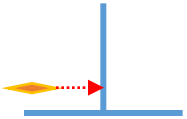
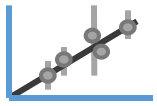
Determinants of certainty of evidence


- **RCTs ⊕⊕⊕⊕ | high**
- **observational studies ⊕⊕◯◯ | low**

- **5 factors that can lower quality**
  1. limitations in detailed study design and execution *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision
  5. Publication bias

- **3 factors can increase quality**
  1. large magnitude of effect
  2. opposing plausible residual bias or confounding
  3. dose-response gradient

Assessing Certainty in Evidence
by Outcome

For each outcome based on a systematic review and across outcomes (lowest certainty across the outcomes critical for decision making)

1. Establish initial level of certainty

Study design	*Initial certainty of evidence*
Randomized trials ➔	**High certainty**
Observational studies ➔	**Low certainty**

2. Consider lowering or raising level of certainty

Reasons for considering lowering or raising certainty	
⬇ **Lower if**	⬆ **Higher if***
Risk of Bias	**Large effect**
Inconsistency	**Dose response**
Indirectness	**All plausible confounding & bias**
Imprecision	• would reduce a demonstrated effect **or**
Publication bias	• would suggest a spurious effect if no effect was observed

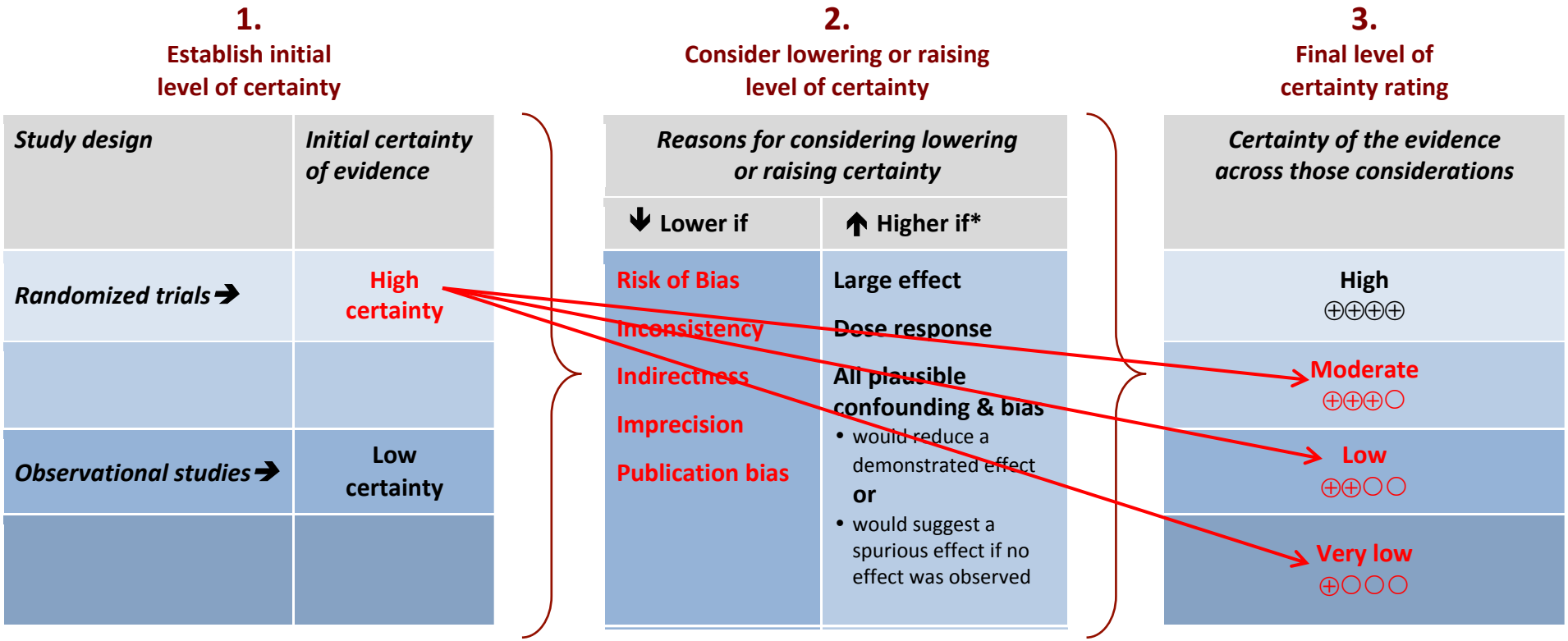
3. Final level of certainty rating

Certainty of the evidence across those considerations
High ⨁⨁⨁⨁
Moderate ⨁⨁⨁◯
Low ⨁⨁◯◯
Very low ⨁◯◯◯

*upgrading criteria are usually applicable to observational studies only.

Lowering certainty in RCTs

For each outcome based on a systematic review and across outcomes (lowest certainty across the outcomes critical for decision making)



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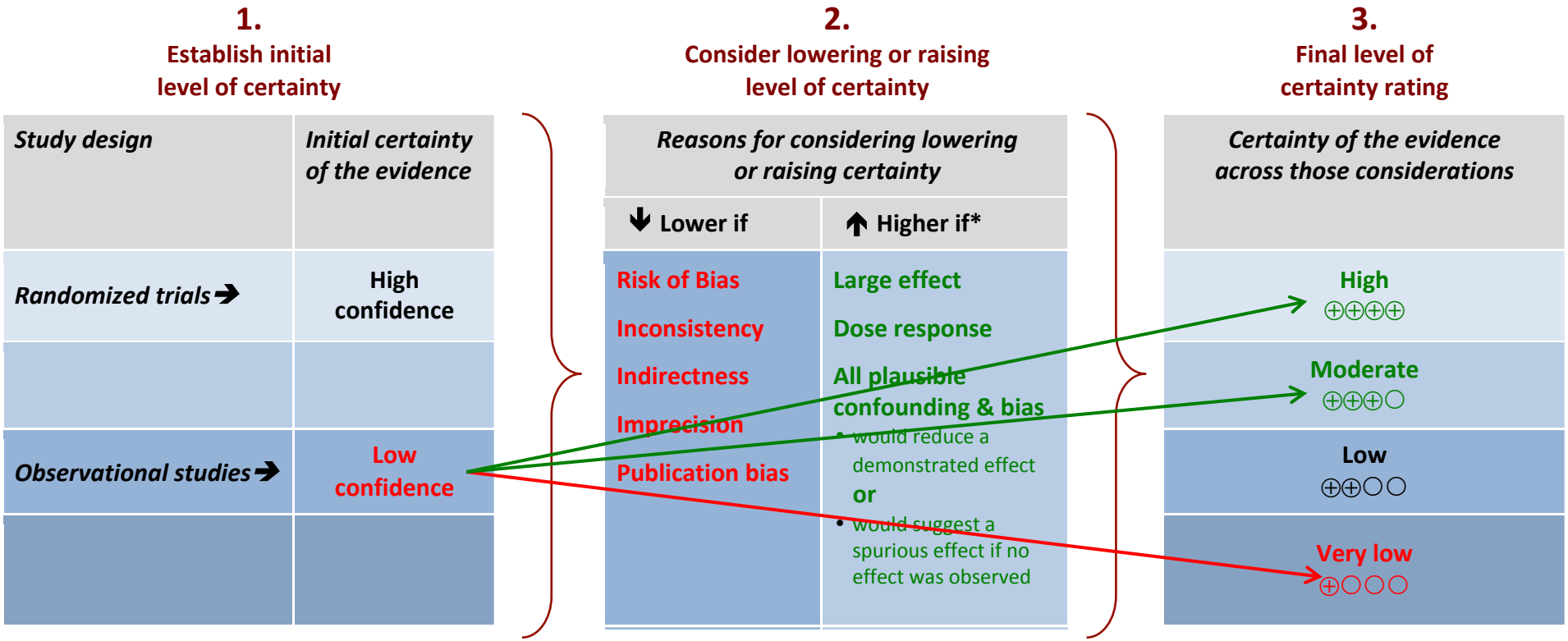
Altering certainty of non-randomized studies

For each outcome based on a systematic review and across outcomes (lowest certainty across the outcomes critical for decision making)



*upgrading criteria are usually applicable to observational studies only.

GRADE

2 principles

- **Certainty of evidence**
  - Assess evidence transparently across all domains
  - Confidence in an estimate?
  - Starts with single research studies
  - Ends with a body of evidence by health outcome
    - high, moderate, low, very low certainty
- **Recommendations/Decisions**
  - Involves making judgments and decisions transparent
  - Evidence to Decision (EtD) frameworks
    - Comprehensive list of criteria that influence a decision or recommendation
  - Clearly developed & formulated action message
    - Strong or conditional recommendations for or against an option

GRADE working group

Formulate question

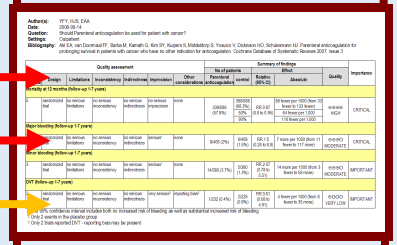
Select outcomes

Rate importance

Outcomes across studies

P	Outcome	Critical
I/E	Outcome	Critical
C	Outcome	Important
O	Outcome	Not important

Create **evidence profile/SoF** Table with GRADEpro



Summary of findings & estimate of effect for each outcome

Rate quality of evidence for each outcome

High
Moderate
Low
Very low

Randomization raises initial quality
RCTs: high
Observational: low

Grade down

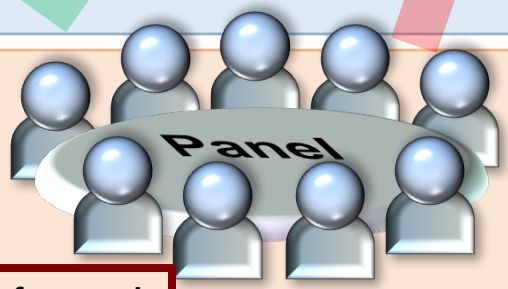
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Opposing bias & Confounders

Evidence synthesis (systematic review/HTA)

Input?



Recommendation/Decision

Grade recommendations (Evidence to Recommendation)

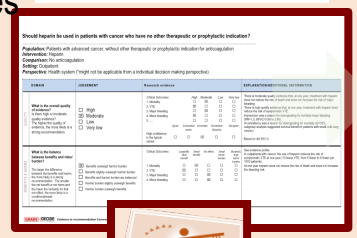
- For or against (direction) ↓↑
- Strong or conditional/weak (strength)

By considering balance of consequences (evidence to recommendations):

- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences (equity)
- ❑ Resource use (cost, feasibility)
- ❑ Acceptability

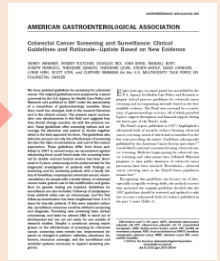
EtD framwork

GRADEpro GDT



Grade overall quality of evidence across outcomes based on lowest quality of ***critical*** outcomes

Guideline/Decision



Formulate Recommendations (↓↑ | ⊕…)

"The panel recommends that ….should..."

"The panel suggests that ….should..."

"The panel suggests to **not** ..."

"The panel recommends to **not**..."

Transparency, clear, actionable

A clinically sensible question

Population: In patients with (lung) cancer, what is the impact of

Intervention: heparin
(comparison) compared with no heparin

Outcomes: on the risk for venous thromboembolism, death, bleeding, burden…?

PICO

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Anticoagulation for the long-term treatment of venous thromboembolism in patients with **cancer**
Elie A Akl , Lara A Kahale , Maddalena Barba , Ignacio Neumann , Nawman Labedi , Irene Terrenato , Francesca Sperati , Paola Muti and Holger **Schünemann**
Online Publication Date: July 2014

Review

Parenteral anticoagulation in ambulatory patients with **cancer**
Elie A Akl , Lara A Kahale , Rami A Ballout , Maddalena Barba , Victor E D Yosuico , Frederiek F van Doormaal , Saskia Middeldorp , Andrew Bryant and Holger **Schünemann**
Online Publication Date: December 2014

Review

Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with **cancer**
Elie A Akl , Lara A Kahale , Francesca Sperati , Ignacio Neumann , Nawman Labedi , Irene Terrenato , Maddalena Barba , Elena V Sempos , Paola Muti , Deborah Cook and Holger **Schünemann**
Online Publication Date: June 2014

Review

Oral anticoagulation in patients with **cancer** who have no therapeutic or prophylactic indication for anticoagulation
Elie A Akl , Lara Kahale , Irene Terrenato , Ignacio Neumann , Victor E D Yosuico , Maddalena Barba , Francesca Sperati and Holger **Schünemann**
Online Publication Date: July 2014

Ns Review

Anticoagulation for the initial treatment of venous thromboembolism in patients with **cancer**
Elie A Akl , Lara A Kahale , Ignacio Neumann , Maddalena Barba , Francesca Sperati , Irene Terrenato , Paola Muti and Holger **Schünemann**
Online Publication Date: June 2014

Review

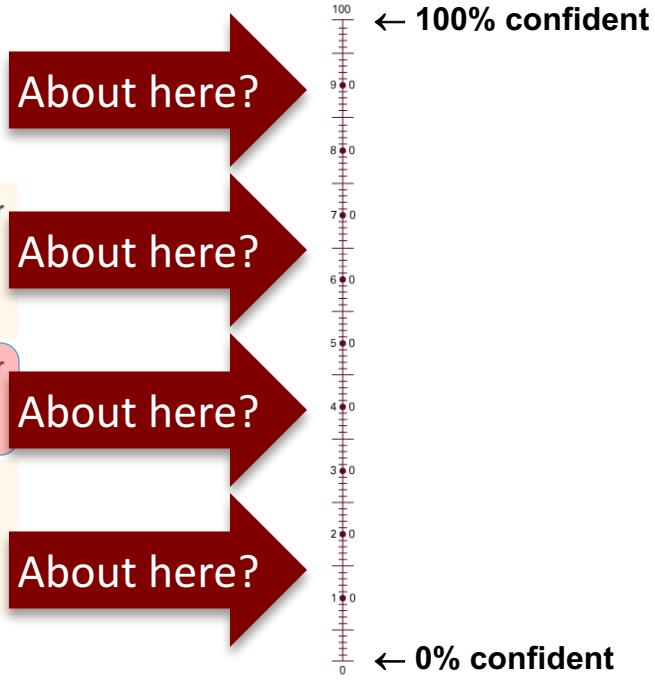
Anticoagulation for people with **cancer** and central venous catheters
Elie A Akl , Elie P Ramly , Lara A Kahale , Victor E D Yosuico , Maddalena Barba , Francesca Sperati , Deborah Cook and Holger **Schünemann**
Online Publication Date: October 2014

Ns Review

Do you have confidence in these estimates of effects?

Table 1. Summary of Findings Table Showing the Relative Risks and Absolute Effects over 12 Months for Each Important Outcome after Treatment with a Low-Molecular-Weight Heparin in Patients Receiving Chemotherapy for Cancer.*

Outcome after 12 Months	Participants	Relative Risk (95% CI)	Anticipated Absolute Effect	
			Risk without LMWH	Risk Difference with LMWH (95% CI)
	no. (no. of studies)		*no. of events per 1000 patients*	
Death	6245 (10)	0.94 (0.88–1.00)	501	30 fewer (60 fewer to 0 more)
Symptomatic VTE	5979 (9)	0.57 (0.40–0.81)	46	20 fewer (27 fewer to 9 fewer)
Major bleeding	6518 (11)	1.06 (0.71–1.57)	16	1 more (5 fewer to 9 more)
Minor bleeding	6020 (9)	1.18 (0.89–1.55)	27	5 more (3 fewer to 15 more)

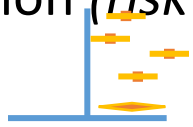


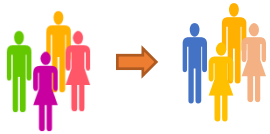
Akl & Schünemann, New Engl J Med, 2012

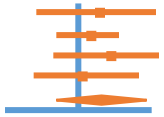
Determinants of quality/certainty of a body of evidence

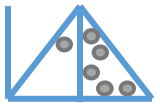
- **RCTs ⊕⊕⊕⊕**
- **observational studies (NRS) ⊕⊕◯◯**

- **5 factors that can lower quality**
  1. limitations in detailed study design and execution *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision
  5. Publication bias

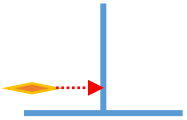


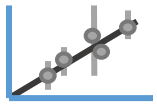






- **3 factors can increase quality**
  1. large magnitude of effect
  2. opposing plausible residual bias or confounding
  3. dose-response gradient





Risk of bias – within & across