78th FIP World Congress of Pharmacy and Pharmaceutical Sciences

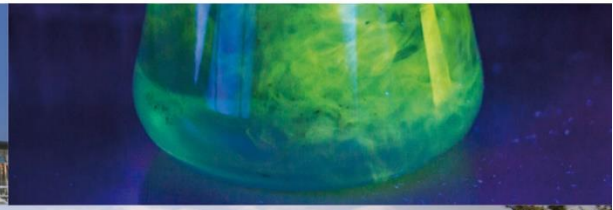
Glasgow, UK
2 - 6 September 2018

Pharmacy:
Transforming outcomes!

Proving the value:
Levels of evidence in Pharmacy Practice

Fernando Fernandez-Llimos, University of Lisbon






GLASGOW 2018
FIP WORLD CONGRESS
2-6 September

Outline

- Levels of evidence
- Strength of a evidence-based recommendation
- Grade: grading the strength
- Implications & take home

Conflict of interest statement:

- No conflict of interest other than being a pharmacist, a researcher in clinical pharmacy services, an author of papers about clinical pharmacy services, and editor-in-chief of Pharmacy Practice.

Lancet. 2014 Jan 11;383(9912):101-4. doi: 10.1016/S0140-6736(13)62329-6. Epub 2014 Jan 8.

Biomedical research: increasing value, reducing waste.

Macleod MR[1], Michie S[2], Roberts I[3], Dirnagl U[4], Chalmers I[5], Ioannidis JP[6], Al-Shahi Salman R[7], Chan AW[8], Glasziou P[9].

Lancet. 2014 Jan 11;383(9912):166-75. doi: 10.1016/S0140-6736(13)62227-8. Epub 2014 Jan 8.

Increasing value and reducing waste in research design, conduct, and analysis.

Ioannidis JP[1], Greenland S[2], Hlatky MA[3], Khoury MJ[4], Macleod MR[5], Moher D[6], Schulz KF[7], Tibshirani R[8].

Milbank Q. 2016 Sep;94(3):485-514. doi: 10.1111/1468-0009.12210.

The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses.

Ioannidis JP[1].

Look at the year!!

“No isolated experiment, however significant in itself, can suffice for the experimental demonstration of any natural phenomenon”

Fisher RA. The design of experiments. 2nd edition. Edinburgh: Oliver and Boyd; 1937.

Evidence based medicine: what it is and what it isn't

It's about integrating individual clinical expertise and the best external evidence

Evidence based medicine, whose philosophical origins extend back to mid-19th century Paris and earlier, remains a hot topic for clinicians, public health practitioners, purchasers, planners, and the public. There are now frequent workshops in how to practice and teach it (one sponsored by the *BMJ* will be held in London on 24 April); undergraduate[1] and postgraduate[2] training programmes are incorporating it[3] (or pondering how to do so); British centres for evidence based practice have been established or planned in adult medicine, child health, surgery, pathology, pharmacotherapy, nursing, general practice, and dentistry; the Cochrane Collaboration and Britain's Centre for Review a
are providing systematic reviews o
new evidence based practice journa
it has become a common topi
enthusiasm has been mixed with
Criticism has ranged from evidenc
hat to it being a dangerous innov

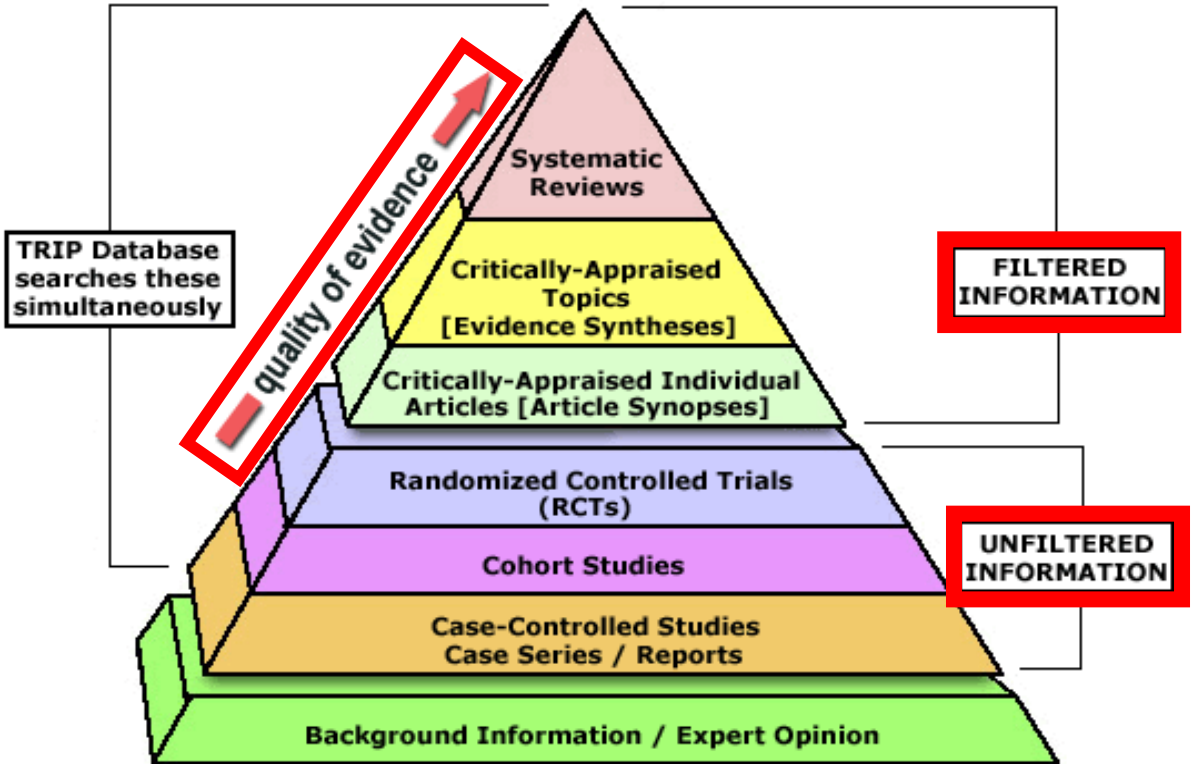
arrogant to serve cost cutters and suppress clinical freedom. As evidence based medicine continues to evolve and adapt, now is a useful time to refine the discussion of what it is and what it is not.

Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from syste-
matic research. By individual clinical expertise we mean the
proficiency and judgment that individual clinicians acquire

Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. BMJ. 1996;312(7023):71-2.

Levels of evidence: Pyramid of evidence



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Levels of evidence: Different approaches

Adapted from Sackett, Straus, Richardson (2000):

Level of Evidence	Type of Study
1a	Systematic reviews of randomized controlled trials (RCTs)
1b	Individual RCTs with narrow confidence interval
2a	Systematic reviews of cohort studies
2b	Individual cohort studies and low-quality RCTs
3a	Systematic reviews of case-control studies
3b	Case-controlled studies
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion

Sackett D, Strauss S, Richardson W, et al. Evidence-Based Medicine: How to Practice and Teach EBM. 2nd ed. Churchill Livingstone; Edinburgh: 2000

Levels of evidence: Different approaches

NHMRC: National Health and Medical Research Council (AU)

Level	Design
I	Systematic reivew of Randomized controlled trials (RCTs)
II	RCT
III- 1	A pseudo-randomised controlled trial
III- 2	A comparative study **with concurrent controls:** ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III- 3	A comparative study **without concurrent controls:** ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes
V	Expert opinion

NHMRC levels of evidence and grades for recommendations for developers of guidelines (2009)

Levels of evidence: Different approaches

National Comprehensive Cancer Network (NCCN)

NCCN Categories of Evidence and Consensus

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

https://www.nccn.org/professionals/physician_gls/categories_of_consensus.aspx

NCCN categories of evidence	Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of evidence		
	Recommendations	Evidence level	Description
Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate	A	1a	Systematic reviews (with homogeneity) of randomized controlled trials
		1b	Individual randomized controlled trials (with narrow confidence interval)
		1c	All or none randomized controlled trials (all patients die before the application of treatment, and some patients survive after treatment; or some patients die before the application of treatment and no patient dies after treatment)
Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate	B	2a	Systematic reviews (with homogeneity) of cohort studies
		2b	Individual cohort study or low quality randomized controlled trials (e.g., <80% follow-up)
Category 2B: based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate		3a	Systematic review (with homogeneity) of case-control studies
		3b	Individual case-control study
Category 3: based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate	C	4	Case-series (and poor quality cohort and case-control studies)
	D	5	Expert opinion or comment

ACP American College of Physicians℠
Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Robert Rich, MD; Linda L. Humphrey, MD, MPH; Jennifer Frost, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians*

Recommendations:

- clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure **persistently at or above 150 mm Hg** to achieve a target systolic **blood pressure of less than 150 mm Hg** to reduce the risk for mortality, stroke, and cardiac events.

STRONG

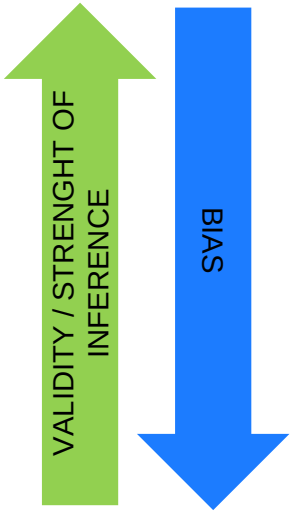
- clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older **with a history of stroke or transient ischemic attack** to achieve a target systolic **blood pressure of less than 140 mm Hg** to reduce the risk for recurrent stroke.

WEAK

LEVELS OF EVIDENCE and Grade of the recommendations

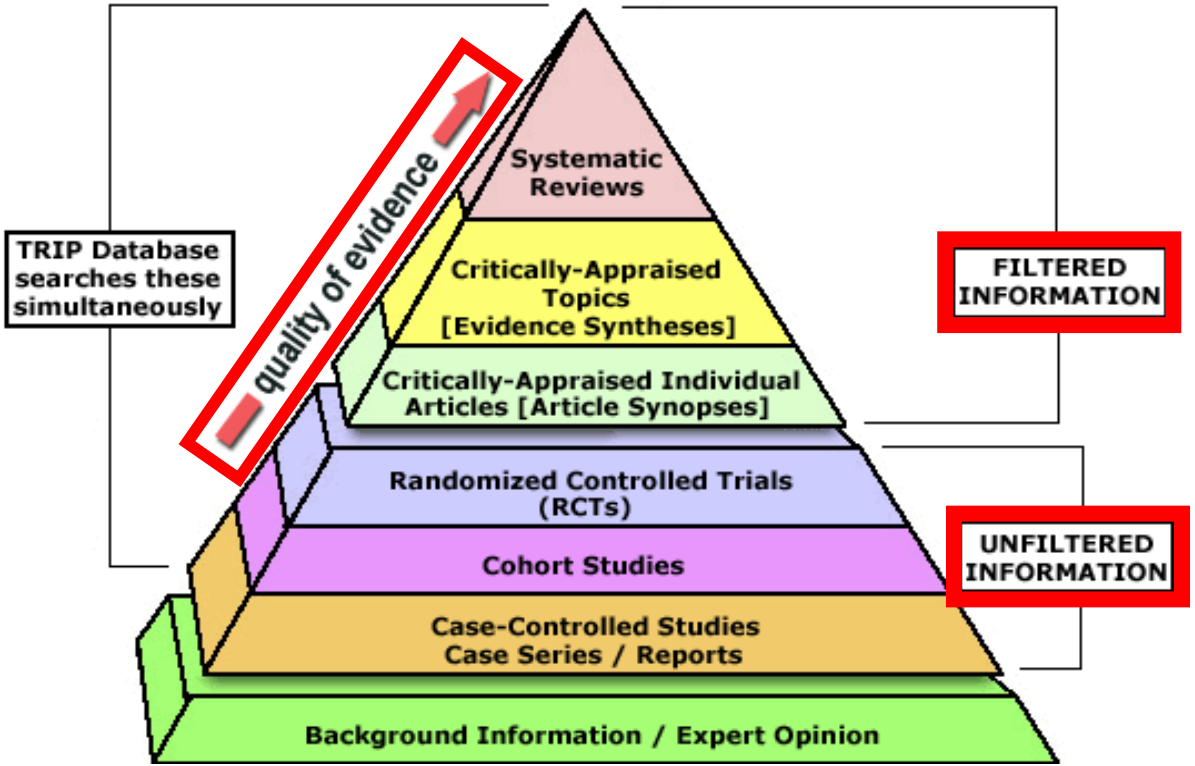
Oxford Centre for Evidence Based Medicine (OCEBM)

Grade of recommendation	Level of evidence	Type of study
A	1a	Systematic review of (homogeneous) randomized controlled trials
	1b	Individual randomized controlled trials (with narrow confidence intervals)
B	2a	Systematic review of (homogeneous) cohort studies of " exposed" and "unexposed" subjects
	2b	Individual cohort study / Low-quality randomized controlled trials
	3a	Systematic review of (homogeneous) case-control studies
	3b	Individual case-control studies
C	4	Case series, low-quality cohort or case-control studies
D	5	Expert opinions based on non systematic reviews of results or mechanistic studies



https://www.cebm.net/2016/05/ocebm-levels-of-evidence/

Levels of evidence: Pyramid of evidence



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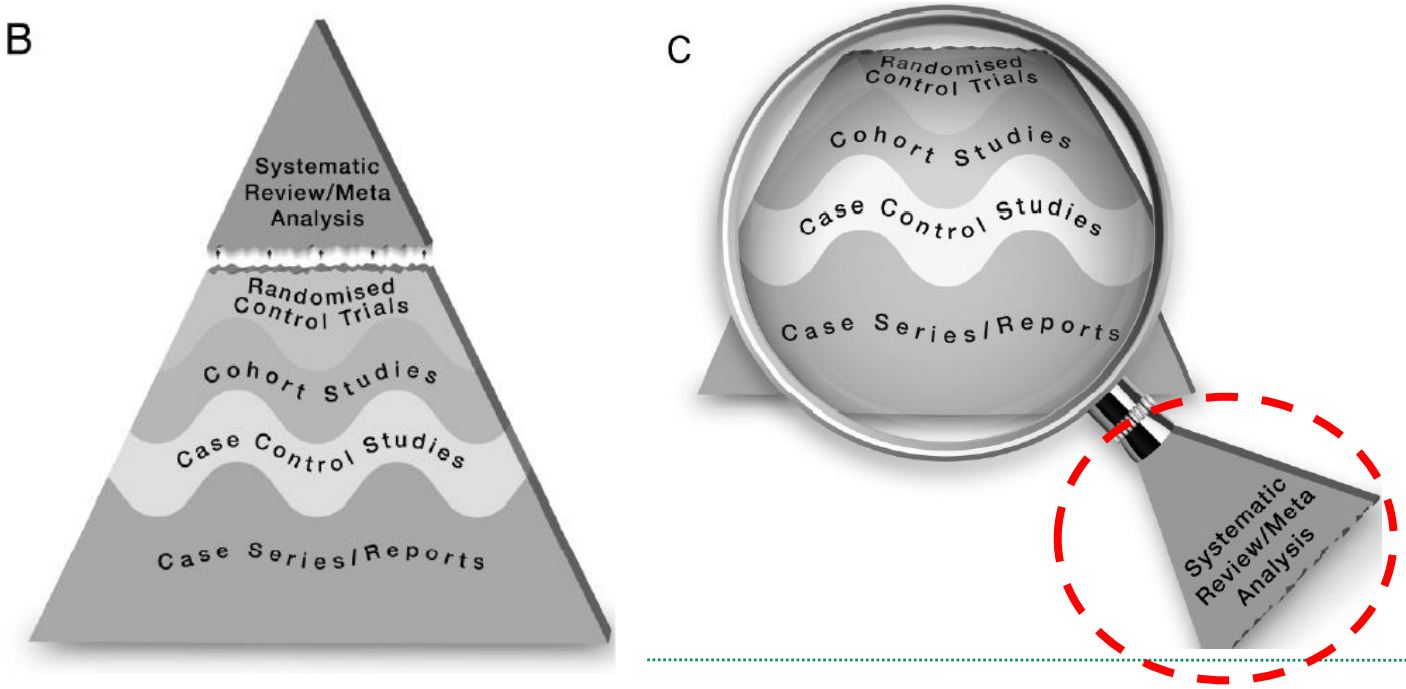
Evid Based Med. 2016 Aug;21(4):125-7. doi: 10.1136/ebmed-2016-110401. Epub 2016 Jun 23.

New evidence pyramid.

Murad MH[1], Asi N[1], Alsawas M[1], Alahdab F[1].



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Rating the Level, Quality, and Strength of the Research Evidence

Katherine R. Jones, PhD, RN, FAAN

Improving patient safety and quality requires more c
on the strongest scientific evidence available. Althou
creasingly being implemented in healthcare settings

Int J Qual Health Care. 2004 Feb;16(1):9-18.

Rating the strength of scientific evidence: relevance for quality improvement programs.

Lohr KN[1].

⊕ **Author information**

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

CONCLUSIONS: Formally grading study quality and rating overall strength of evidence, using sound instruments and procedures, can produce reasonable levels of confidence about the science base for parts of quality improvement programs. With such information, health care professionals and administrators concerned with quality improvement can understand better the level of science (versus only clinical consensus or opinion) that supports practice guidelines, review criteria, and assessments that feed into quality assurance and improvement

GRADE evidence

Grading of Recommendations Assessment, Development and Evaluation

Box 3: Definitions of grades of evidence

High = Further research is unlikely to change our confidence in the estimate of effect.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low = Any estimate of effect is very uncertain.

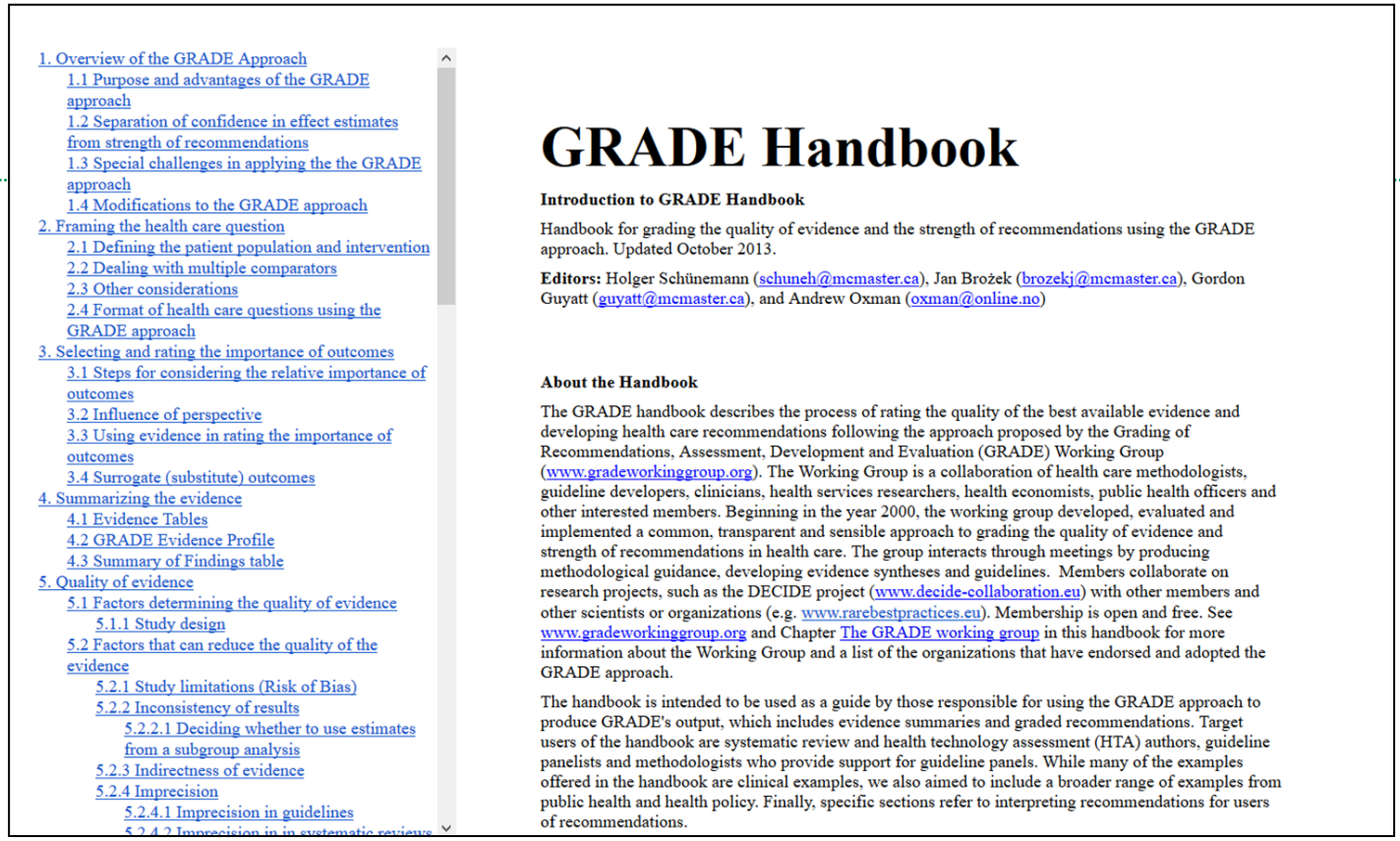
Atkins D et al. BMJ. 2004;328(7454):1490.

GRADE evidence

Grading of Recommendations Assessment, Development and Evaluation

Quality level	Current definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Guyatt G et al. J Clin Epidemiol. 2011;64: 383-394



GRADE Handbook

Introduction to GRADE Handbook

Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013.

Editors: Holger Schünemann (schuneh@mcmaster.ca), Jan Brożek (brozekj@mcmaster.ca), Gordon Guyatt (guyatt@mcmaster.ca), and Andrew Oxman (oxman@online.no)

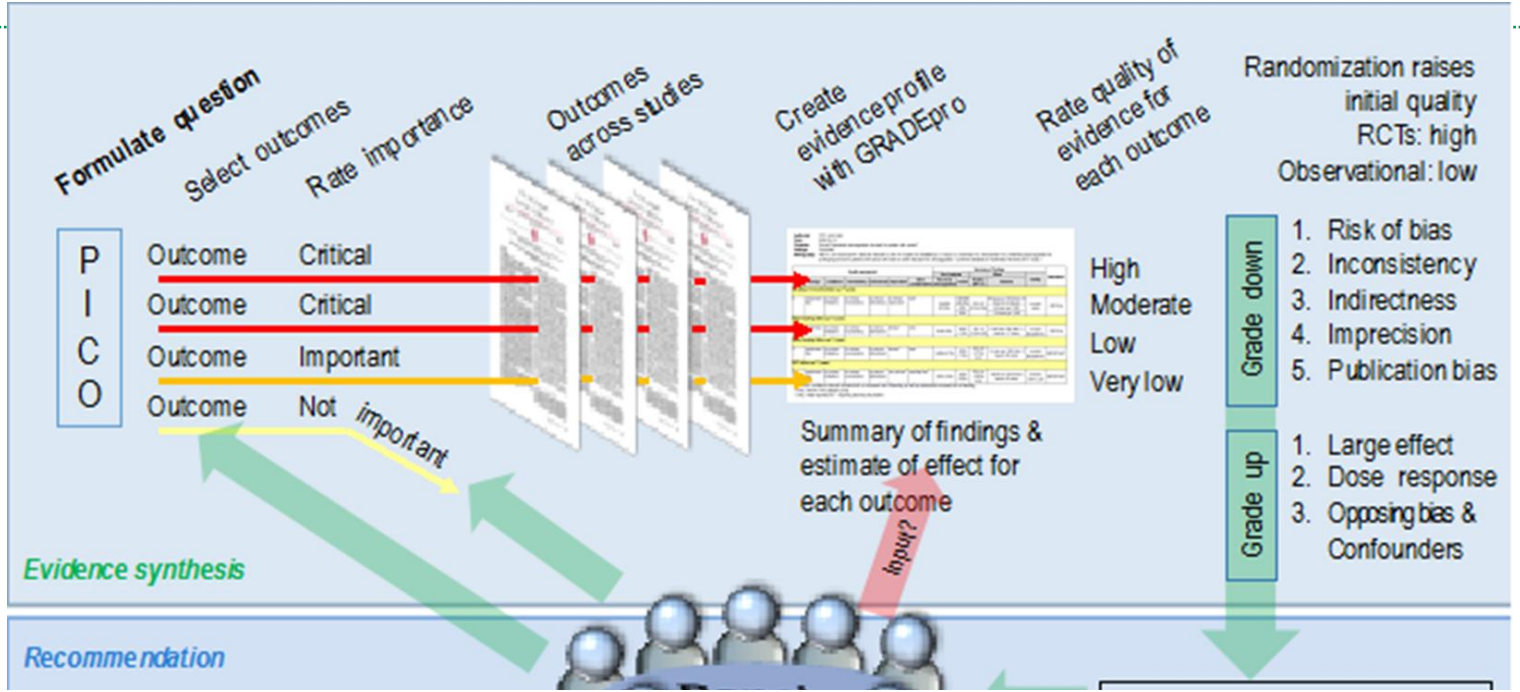
About the Handbook

The GRADE handbook describes the process of rating the quality of the best available evidence and developing health care recommendations following the approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (www.gradeworkinggroup.org). The Working Group is a collaboration of health care methodologists, guideline developers, clinicians, health services researchers, health economists, public health officers and other interested members. Beginning in the year 2000, the working group developed, evaluated and implemented a common, transparent and sensible approach to grading the quality of evidence and strength of recommendations in health care. The group interacts through meetings by producing methodological guidance, developing evidence syntheses and guidelines. Members collaborate on research projects, such as the DECIDE project (www.decide-collaboration.eu) with other members and other scientists or organizations (e.g. www.rarebestpractices.eu). Membership is open and free. See www.gradeworkinggroup.org and Chapter The GRADE working group in this handbook for more information about the Working Group and a list of the organizations that have endorsed and adopted the GRADE approach.

The handbook is intended to be used as a guide by those responsible for using the GRADE approach to produce GRADE's output, which includes evidence summaries and graded recommendations. Target users of the handbook are systematic review and health technology assessment (HTA) authors, guideline panelists and methodologists who provide support for guideline panels. While many of the examples offered in the handbook are clinical examples, we also aimed to include a broader range of examples from public health and health policy. Finally, specific sections refer to interpreting recommendations for users of recommendations.

http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

making health care recommendations



http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

Box 2: Criteria for assigning grade of evidence

Type of evidence
Randomised trial = high
Observational study = low
Any other evidence = very low

Decrease grade if:

- Serious (−1) or very serious (−2) limitation to study quality
- Important inconsistency (−1)
- Some (−1) or major (−2) uncertainty about directness
- Imprecise or sparse data (−1)
- High probability of reporting bias (−1)

Increase grade if:

- Strong evidence of association—significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)[46]
- Very strong evidence of association—significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)[46]
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

- **Study Design**
- **Quality**
- **Inconsistency**
- **Indirectness**
- **Imprecision**
- **Other factors**

Atkins D et al. BMJ. 2004;328(7454):1490.

Scoring GRADE

		Score
Study Design		
RCTs		+4
Observational studies		+2
Other designs		+1
Quality (Risk of Bias or limitations)		
Not serious		0
Serious		-1
Very serious		-2
Inconsistency		
Not serious		0
Serious		-1
Very serious		-2
Indirectness		
Not serious		0
Serious		-1
Very serious		-2
Imprecision		
Not serious		0
Serious		-1
Very serious		-2
Other factors		
	Publication bias detected	-1
	Large effect size	+1
	Very large effect size	+2
	Plausible confounders	+1
	Dose respond gradient	+1

Quality of a body of evidence
High (four plus: ⊕⊕⊕⊕)
Moderate (three plus: ⊕⊕⊕◯)
Low (two plus: ⊕⊕◯◯)
Very low (one plus: ⊕◯◯◯)

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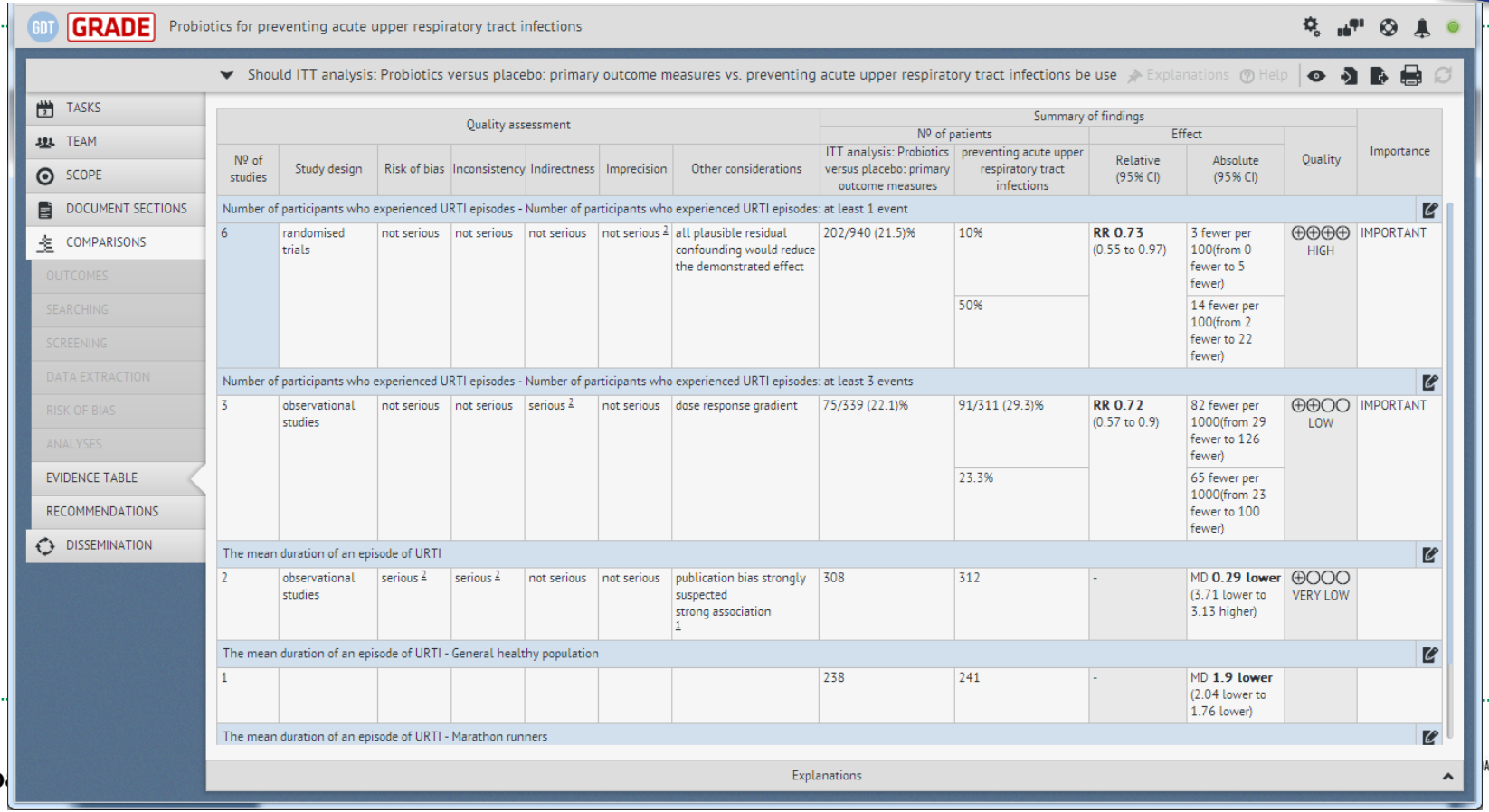
GRADE pro



GDT GRADE Probiotics for preventing acute upper respiratory tract infections

Should ITT analysis: Probiotics versus placebo: primary outcome measures vs. preventing acute upper respiratory tract infections be use

Explanations Help

TASKS
TEAM
SCOPE
DOCUMENT SECTIONS
COMPARISONS
OUTCOMES
SEARCHING
SCREENING
DATA EXTRACTION
RISK OF BIAS
ANALYSES
EVIDENCE TABLE
RECOMMENDATIONS
DISSEMINATION

Quality assessment							Summary of findings					
							Nº of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ITT analysis: Probiotics versus placebo: primary outcome measures	preventing acute upper respiratory tract infections	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Number of participants who experienced URTI episodes - Number of participants who experienced URTI episodes: at least 1 event												
6	randomised trials	not serious	not serious	not serious	not serious [2]	all plausible residual confounding would reduce the demonstrated effect	202/940 (21.5)%	10%	**RR 0.73** (0.55 to 0.97)	3 fewer per 100(from 0 fewer to 5 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
								50%		14 fewer per 100(from 2 fewer to 22 fewer)		
Number of participants who experienced URTI episodes - Number of participants who experienced URTI episodes: at least 3 events												
3	observational studies	not serious	not serious	serious [2]	not serious	dose response gradient	75/339 (22.1)%	91/311 (29.3)%	**RR 0.72** (0.57 to 0.9)	82 fewer per 1000(from 29 fewer to 126 fewer)	⨁⨁◯◯ LOW	IMPORTANT
								23.3%		65 fewer per 1000(from 23 fewer to 100 fewer)		
The mean duration of an episode of URTI												
2	observational studies	serious [2]	serious [2]	not serious	not serious	publication bias strongly suspected strong association [1]	308	312	-	MD **0.29 lower** (3.71 lower to 3.13 higher)	⨁◯◯◯ VERY LOW	
The mean duration of an episode of URTI - General healthy population												
1							238	241	-	MD **1.9 lower** (2.04 lower to 1.76 lower)		
The mean duration of an episode of URTI - Marathon runners												

Explanations

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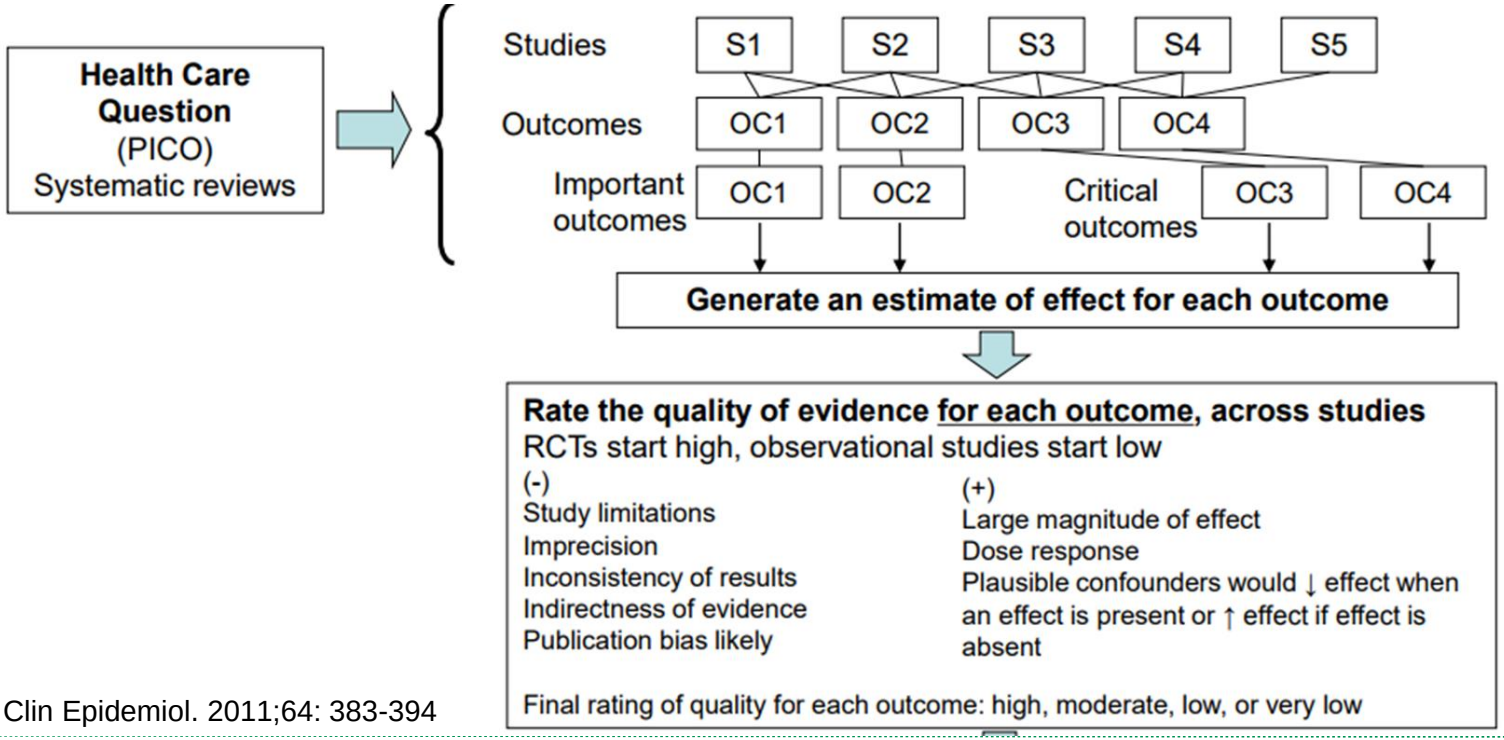
How to grade with GRADE



Guyatt G et al. J Clin Epidemiol. 2011;64: 383-394

GRADE's output

	Quality assessment					Summary of findings					
						No of patients		Effect			
No of studies	Design	Quality	Consistency	Directness	Other modifying factors*	SSRIs	Tricyclics	Relative (95% CI)	Absolute	Quality	Importance
Depression severity (measured with Hamilton Depression Rating Scale after 4 to 12 weeks)											
Citalopram (8) Fluoxetine (38) Fluvoxamine (25) Nefazodone (2) Paroxetine (18) Sertraline (4) Venlafaxine (4)	Randomised controlled trials	No serious limitations	No important inconsistency	Some uncertainty about directness (outcome measure)†	None	5044	4510	WMD 0.034 (–0.007 to 0.075)	No difference	Moderate	Critical
Transient side effects resulting in discontinuation of treatment											
Citalopram (8) Fluoxetine (50) Fluvoxamine (27) Nefazodone (4) Paroxetine (23) Sertraline (6) Venlafaxine (5)	Randomised controlled trials	No serious limitations	No important inconsistency	Direct	None	1948/7032 (28%)	2072/6334 (33%)	RRR 13% (5% to 20%)	5/100	High	Critical

Atkins D et al. BMJ. 2004;328(7454):1490.

Drugs Aging
DOI 10.1007/s40266-015-0290-9

SYSTEMATIC REVIEW

Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis

Monica Teng[1] · Liang Lin[1] · Ying Jiao Zhao[1] · Ai Leng Khoo[1] · Barry R. Davis[2] · Quek Wei Yong[3] · Tiong Cheng Yeo[4] · Boon Peng Lim[1]

Reduction of risk of major adverse cardiovascular event (i.e. myocardial infarction, stroke, coronary revascularization, cardiac sudden death, and angina)

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)							12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)												
Simvastatin (1)												
Rosuvastatin (1)												
SCORE												

*Imprecise or sparse data, a strong or very strong association, high risk of reporting bias, evidence of a dose-response gradient, effect of plausible residual confounding.

GRADE: Study Design

Drugs Aging
DOI 10.1007/s40266-015-0290-9

SYSTEMATIC REVIEW

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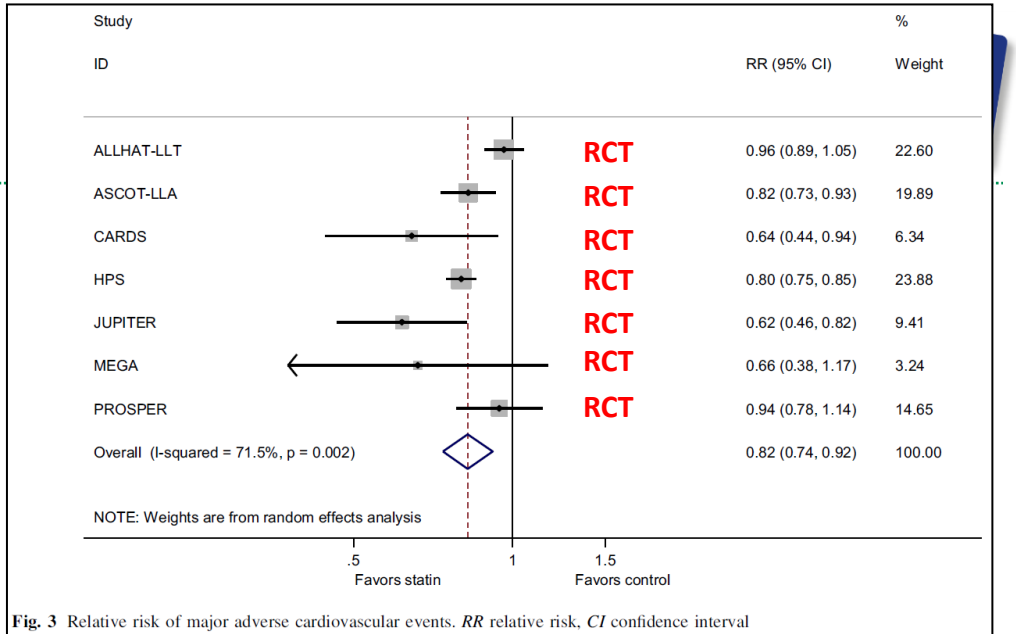

Fig. 3 Relative risk of major adverse cardiovascular events. *RR* relative risk, *CI* confidence interval

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)	RCTs						12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)	RCTs											
Simvastatin (1)	RCT											
Rosuvastatin (1)	RCT											
SCORE	+4											

*Imprecise or sparse data, a strong or very strong association, high risk of reporting bias, evidence of a dose-response gradient, effect of plausible residual confounding.

GRADE: Quality

Drugs Aging
DOI 10.1007/s40266-015-0290-9

SYSTEMATIC REVIEW

Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis

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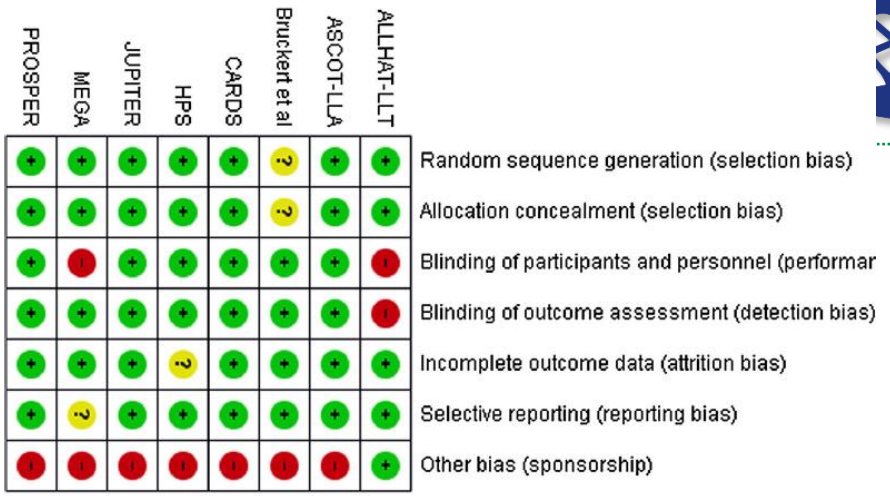

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)	RCTs	Serious: Two studies are not blinded, but sensitivity analyses were done. Other methodological concerns: sponsorship (almost all studies)					12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)	RCTs											
Simvastatin (1)	RCT											
Rosuvastatin (1)	RCT											
SCORE	+4	-1										

*Imprecise or sparse data, a strong or very strong association, high risk of reporting bias, evidence of a dose-response gradient, effect of plausible residual confounding.

GRADE: Inconsistency

Drugs Aging
DOI 10.1007/s40266-015-0290-9

SYSTEMATIC REVIEW

Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis

Monica Teng[1] · Liang Lin[1] · Ying Jiao Zhao[1] · Ai Leng Khoo[1] · Barry R. Davis[2] · Quek Wei Yong[3] · Tiong Cheng Yeo[4] · Boon Peng Lim[1]

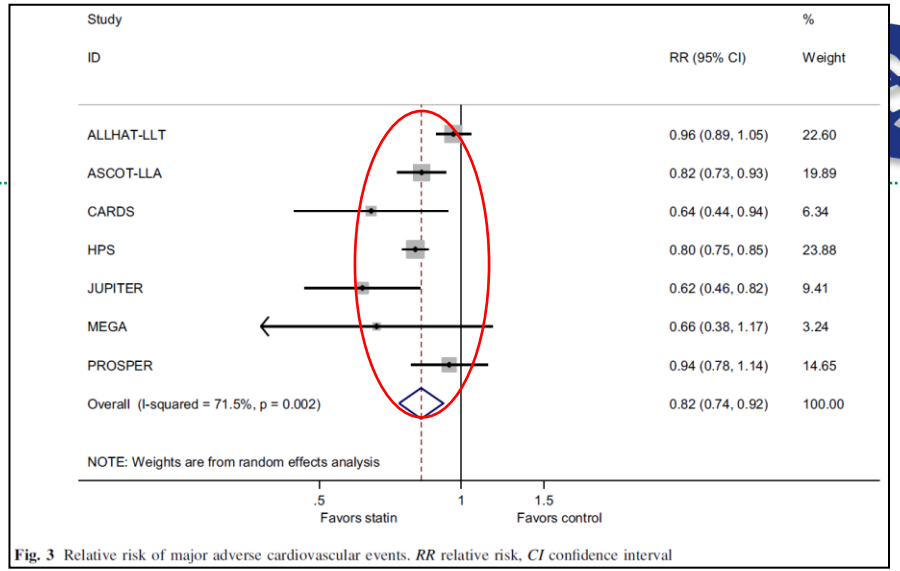

Fig. 3 Relative risk of major adverse cardiovascular events. *RR* relative risk, *CI* confidence interval

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	**Quality assessment**						**Summary of findings**					
							N. patients		**Effect size**		**Final assessment**	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)	RCTs	**Serious:** Two studies are not blinded, but sensitivity analyses were done. Other methodological concerns: sponsorship (almost all studies)	**Not Serious:** Almost all studies show similar results. For two of the statins there is only one included study.				12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)	RCTs											
Simvastatin (1)	RCT											
Rosuvastatin (1)	RCT											
SCORE	+4	-1	0									

*Imprecise or sparse data, a strong or very strong association, high risk of reporting bias, evidence of a dose-response gradient, effect of plausible residual confounding.

FACULDADE DE FARMÁCIA
Universidade de Lisboa

GRADE: Indirectness

Drugs Aging
DOI 10.1007/s40266-015-0290-9

SYSTEMATIC REVIEW

Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis

Monica Teng[1] · Liang Lin[1] · Ying Jiao Zhao[1] · Ai Leng Khoo[1] · Barry R. Davis[2] · Quek Wei Yong[3] · Tiong Cheng Yeo[4] · Boon Peng Lim[1]

Mean age, years (range)	Women (%)	Statin and dose	Diabetes (%)	HTN (%)	Smoking (%)	Mean baseline lipid levels (mmol/l)			
						TC	LDL-C	HDL-C	TG
72 (65–111)	47.8	Pravastatin 40 mg/day	38.3	100	41.3	5.77	3.75	1.24	3.84
NA	19.6	Atorvastatin 10 mg/day	100	26.7	23.7	5.48	3.44	1.33	1.73
75.5 (69–92)	74.9	Fluvastatin XL 80 mg/day	7	55.9	16.2	7.28	5.18	1.36	1.53
69 (65–77)	31.4	Atorvastatin 10 mg/day	100	NR	15.6	5.3	3.06	1.44	1.53
NA	24.7	Simvastatin 40 mg/day	100	NR	NR	NR	NR	NR	NR
74 (70–97)	51.6	Rosuvastatin 20 mg/day	0	65.6	8.4	NR	NR	NR	NR
NA	51.9	Pravastatin 10–20 mg/day	52	21	14	NR	NR	NR	NR
75 (70–82)	58.5	Pravastatin 40 mg/day	12.2	71.6	33	5.69	3.78	1.31	1.52

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)	RCTs	Serious: Two studies are not blinded, but sensitivity analyses were done. Other methodological concerns: sponsorship (almost all studies)	Not Serious: Almost all studies show similar results. For two of the statins there is only one included study.	Not Serious: Population and outcomes broadly generalisable			12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)	RCTs											
Simvastatin (1)	RCT											
Rosuvastatin (1)	RCT											
SCORE	+4	-1	0	0								

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GRADE: Imprecision

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SYSTEMATIC REVIEW

Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis

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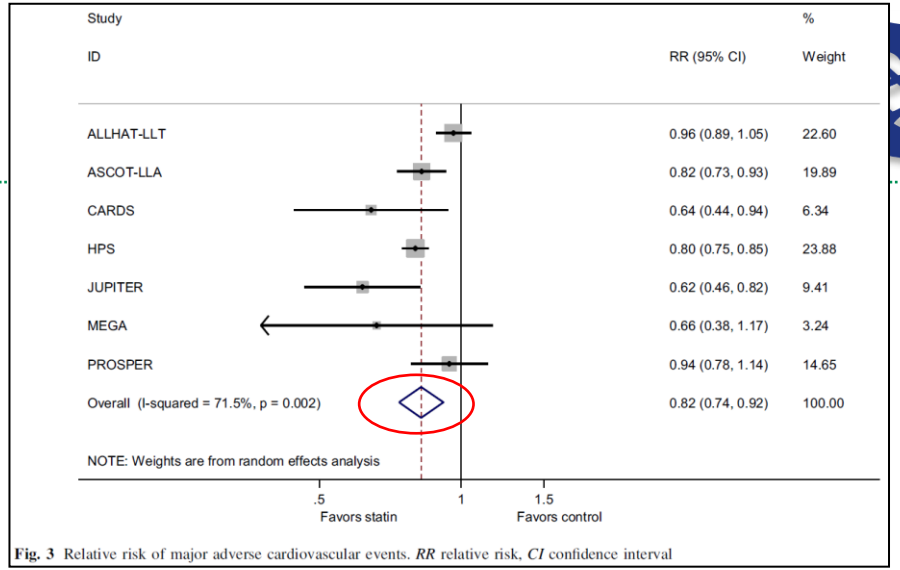

Fig. 3 Relative risk of major adverse cardiovascular events. *RR* relative risk, *CI* confidence interval

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)	RCTs	Serious: Two studies are not blinded, but sensitivity analyses were done. Other methodological concerns: sponsorship (almost all studies)	Not Serious: Almost all studies show similar results. For two of the statins there is only one included study.	Not Serious Population and outcomes broadly generalisable	Not Serious: 95%CI symmetric and not large		12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)	RCTs											
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Rosuvastatin (1)	RCT											
SCORE	+4	-1	0	0	0							

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FACULDADE DE FARMÁCIA Universidade de Lisboa

GRADE: Other

Drugs Aging
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SYSTEMATIC REVIEW

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Publication bias
Large effect size
Very large effect size
Plausibel confounders
Dose respond gradient

Outcome: Major adverse cardiovascular events												
Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolute	Quality	Importance
Pravastatin (3)	RCTs	**Serious:** Two studies are not blinded, but sensitivity analyses were done. Other methodological concerns: sponsorship (almost all studies)	**Not Serious:** Almost all studies show similar results. For two of the statins there is only one included study.	**Not Serious:** Population and outcomes broadly generalisable	**Not Serious** 95%CI symmetric and not large	**None**	12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	????	Critical
Atorvastatin (2)	RCTs											
Simvastatin (1)	RCT											
Rosuvastatin (1)	RCT											
SCORE	+4	-1	0	0	0	0						

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GRADE: Final Score

+4 -1 +0 +0 +0 +0 = 3

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Quality of a body of evidence
High (four plus: ⊕⊕⊕⊕)
Moderate (three plus: ⊕⊕⊕◯)
Low (two plus: ⊕⊕◯◯)
Very low (one plus: ⊕◯◯◯)

We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Outcome: Major adverse cardiovascular events

Drugs (n. studies)	Quality assessment						Summary of findings					
							N. patients		Effect size		Final assessment	
	Study Design	Quality	Inconsistency	Indirectness	Imprecision	Other modifying factors*	Statins	Control	Relative (95% CI)	Absolut	Quality	Importance
Pravastatin (3)	RCTs	**Serious:** Two studies are not blinded, but sensitivity analyses were done. Other methodological concerns: sponsorship (almost all studies)	**Not Serious:** Almost all studies show similar results. For two of the statins there is only one included study.	**Not Serious:** Population and outcomes broadly generalisable	**Not Serious:** 95%CI symmetric and not large	**None**	12367	12356	RR 0.82 (0.74–0.92) Favors statins	2347 events / 18,914 patients	**Moderate**	Critical
Atorvastatin (2)	RCTs											
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SCORE	+4	-1	0	0	0	0						

*Imprecise or sparse data, a strong or very strong association, high risk of reporting bias, evidence of a dose-response gradient, effect of plausible residual confounding.

Implications & Take home

- **Frequent incorrect use of the term ‘evidence’**
  - **Evident ideas are not evidence**
  - **One study does not produce evidence**
  - **Several positive studies may not create evidence of a positive effect**
- **Evidence generation needs high quality primary studies**
- **Evidence generation high quality synthetizing process**
- **Not all the recommendations emerging from a systematic review are equal**
- **We should get used to always evaluate the strength of each recommendation**