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Affidabilità Linee Guida

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2011

CLINICAL PRACTICE GUIDELINES WE CAN TRUST

tion is as follows: Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.

To be *trustworthy*, guidelines should

Why do we need clinical guidelines ?

OPEN ACCESS Freely available online

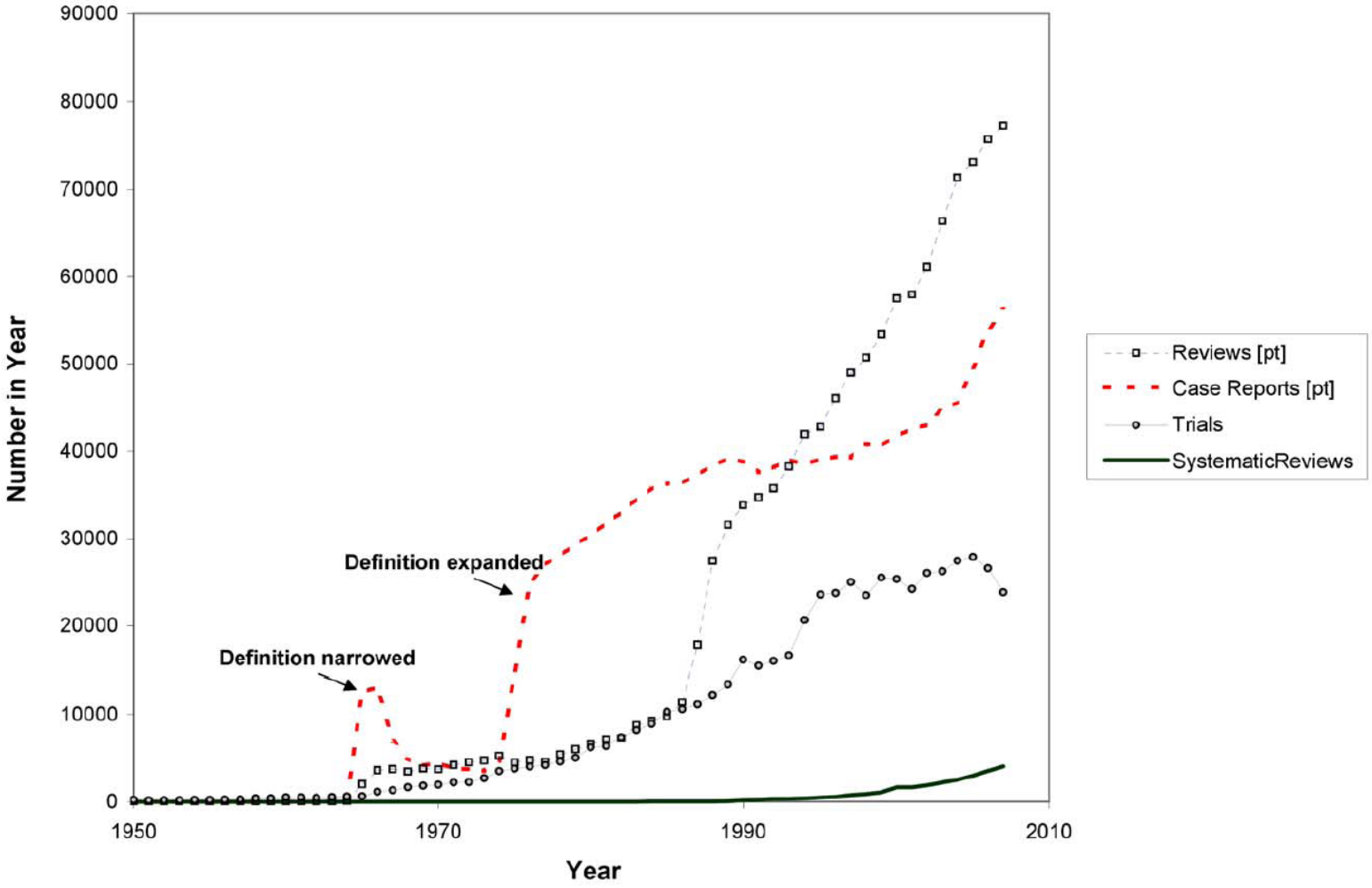
PLoS Med 7(9): e1000326. doi:10.1371/journal.pmed.1000326

Policy Forum

Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?

Hilda Bastian[1]*, **Paul Glasziou**[2], **Iain Chalmers**[3]

1 German Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany, **2** Centre for Research in Evidence-Based Practice, Faculty of Health Sciences, Bond University, Gold Coast, Australia, **3** James Lind Library, James Lind Initiative, Oxford, United Kingdom



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

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 systematic research.

David Sackett, 1996

Evidence based medicine

Evidence Based Clinical Guidelines
(Clinical Practice Guidelines)

Requisiti minimi di una CPG

Multidisciplinary development

Studies have shown that the balance of disciplines within a guideline development group has considerable influence on the guideline recommendations

Systematic review of literature

Guidelines based on a consensus of expert opinion or on unsystematic literature surveys have been widely criticised as not reflecting current medical knowledge and being liable to bias.

Graded recommendations

Guideline recommendations are graded to differentiate between those based on strong evidence and those based on weak evidence

Miller J, Petrie J. Development of a practice guideline. Lancet **2000**; 355:82–3.

Certainty
(Level of evidence)

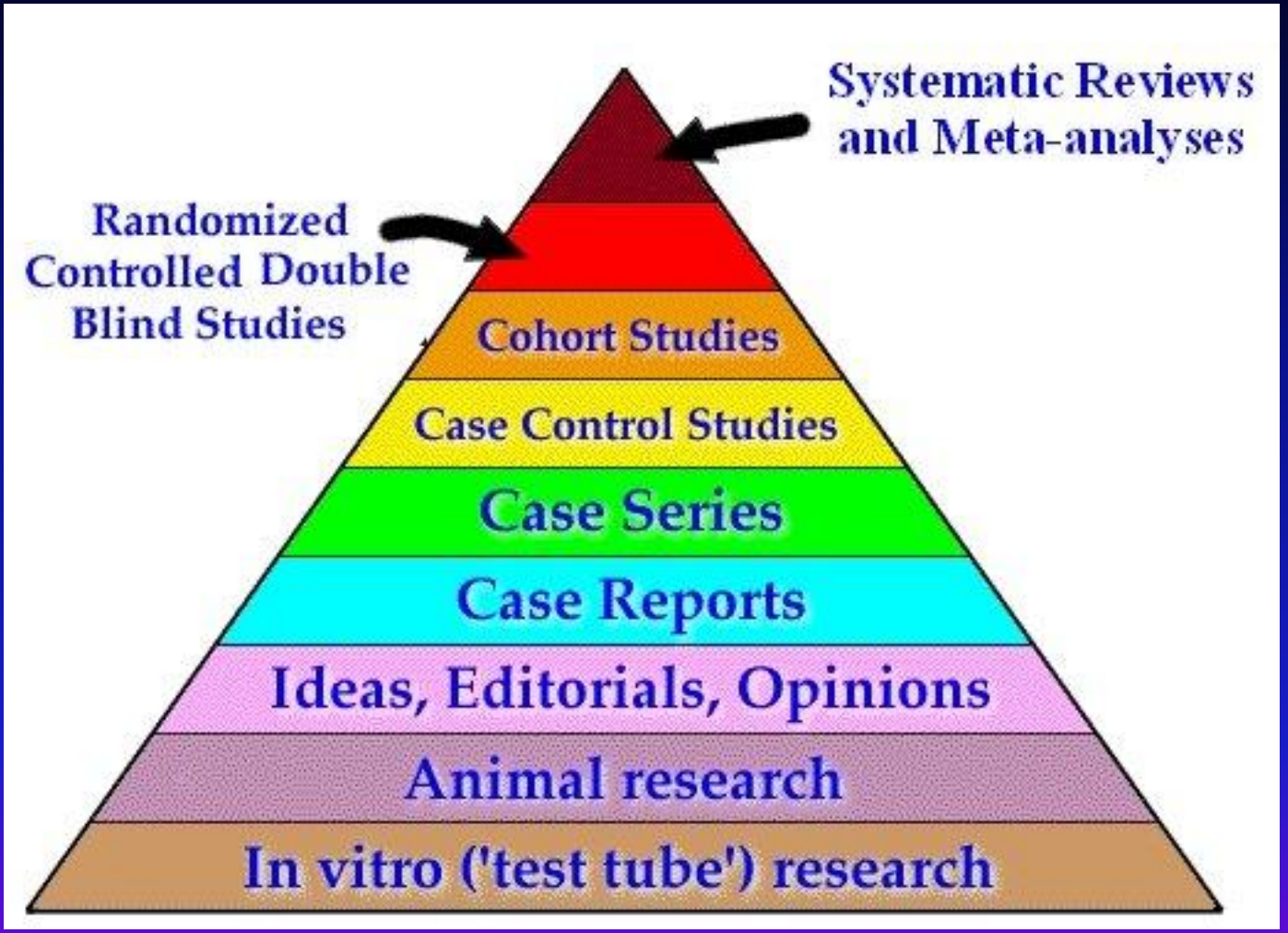
Strenght
of recommendations

high

low

strong

weak



Graded recommendations

Low quality of early guidelines

	1988–91 (n=48)	1992–93 (n=81)	1994–95 (n=125)	1996–98 (n=177)	p for trend
Full description of professionals	6 (12%)	9 (11%)	11 (9%)	27 (15%)	0·99
Search undertaken	1 (2%)	4 (5%)	14 (11%)	32 (18%)	<0·001
Grading of recommendation	3 (6%)	5 (6%)	21 (17%)	48 (27%)	<0·001

Table 2: **Number of guidelines that met the three quality criteria according to year of publication**

Grilli et al : Lancet, **2000**

Problems of CPGs

Many guidelines derive(d) level of evidence almost exclusively from study type

Moreover classification of level of evidences with letters, numbers, or symbols was chaotic

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

ESC/AHA

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

SIGN

C2010 Levels of Evidence for Studies of Therapeutic Interventions

LOE 1: Randomized controlled trials (RCTs) (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomization (eg, "pseudo"-randomized)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (eg, case series)
LOE 5: Studies not directly related to the specific patient/population (eg, different patient/population, animal models, mechanical models, etc)

ERC

And so, no RCT, no strong recommendation?

BMJ 2003;327:1459–61

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

Sometimes trials are unethical or impossible

yet some treatments are quite effective

Type of study

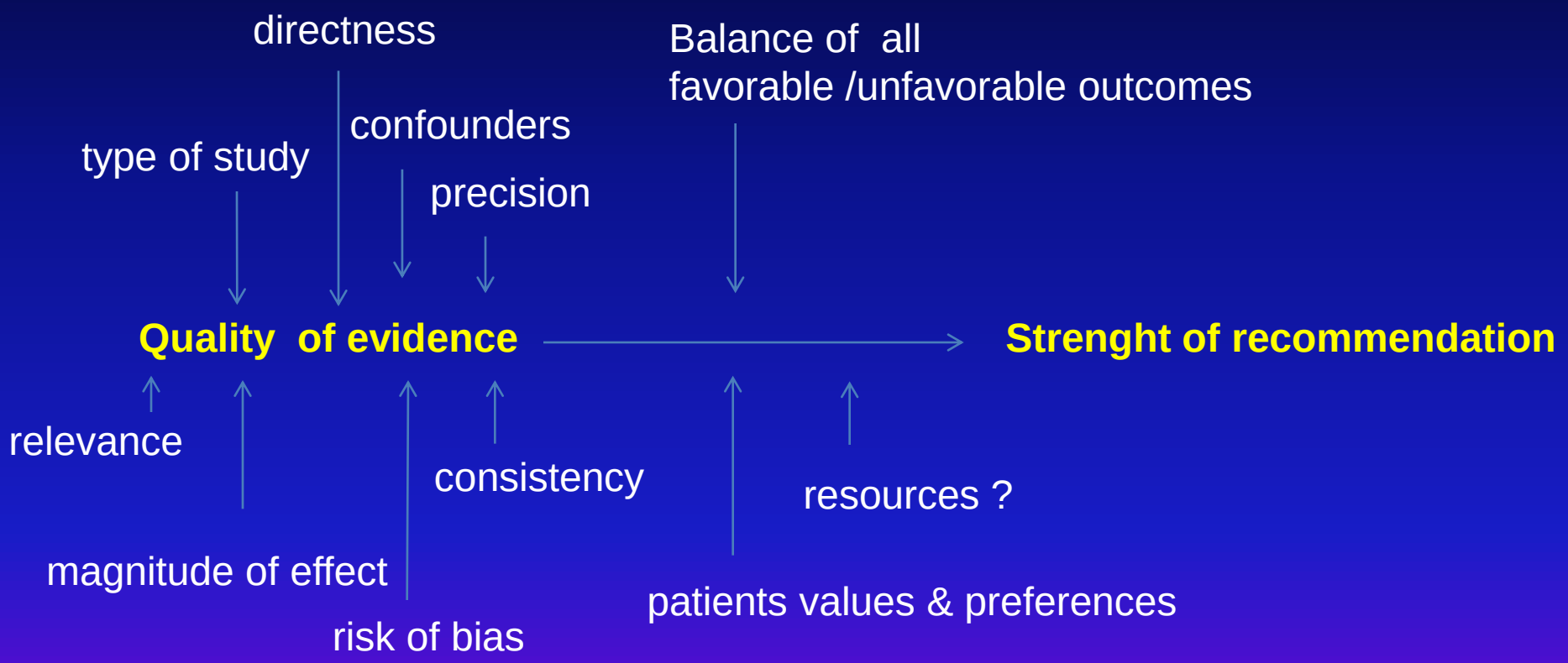
↓

Quality of evidence → **Strength of recommendation**

↑

Other factors ?

a more complex approach is needed



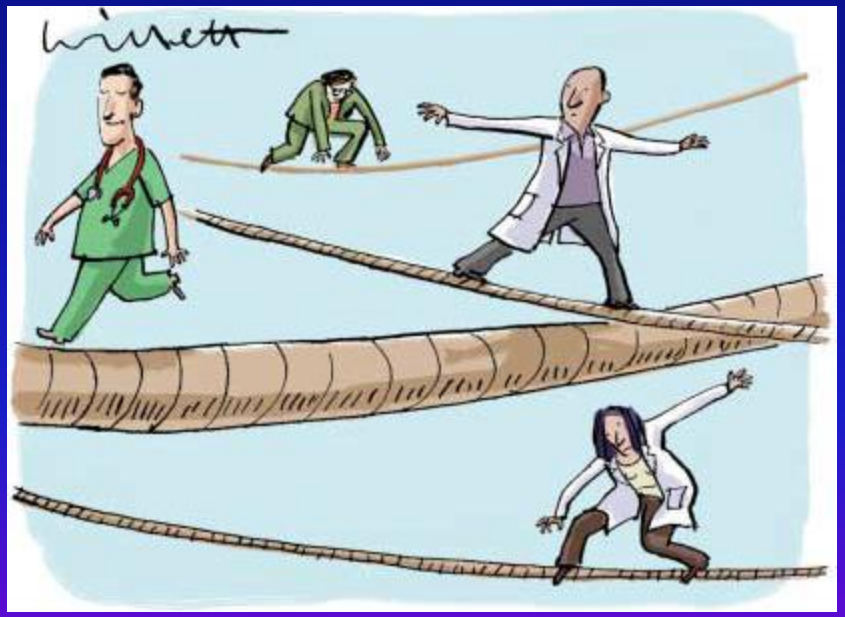
Grading quality of evidence and strength of recommendations

Grades of Recommendation, Assessment, Development, and Evaluation (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

BMJ 2004;328:1490–4

GRADE



http://www.gradeworkinggroup.org/

According to GRADE
Quality of evidence must be summarized in a table

Table 3. Summary of Evidence: Dronedarone vs Placebo

Outcome	No. of Studies	Presence of Serious Quality Flaws				Absolute Effect With Dronedarone per 1000 Patients Treated, No. of Events (95% CI)	Overall Quality of Evidence[d]	Importance
		Risk of Bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]			
Mortality	5[e,f,g,h,i]	No	Yes[j]	No	Yes	13 (−15 to 61)	Low	Critical
Adverse events necessitating suspension	3[e,h,i]	No	No	No	No	46 (27 to 68)	High	Critical
Hospitalization	3[e,g,h]	Yes[k]	No	No	Yes	−30 (−91 to 34)	Low	Important
Recurrence rate	3[g,h,i]	No	Yes[l]	No	No	−137 (−220 to −59)	Moderate	Important
Any adverse event	4[e,f,g,h]	No	Yes[m]	No	No	32 (−19 to 76)	Moderate	Important
Cardiac adverse events	3[e,g,h]	No	No	No	No	24 (8 to 42)	High	Important

Iannone et Al,
JAMA Intern Med, 2014

Box 1. Organizations That Have Adopted the Grade System

Agency for Healthcare Research and Quality (USA)
Agenzia Sanitaria Regionale (Italy)
American College of Chest Physicians (USA)
American College of Physicians (USA)
American Thoracic Society (USA)
Ärztliches Zentrum für Qualität in der Medizin (Germany)
British Medical Journal (United Kingdom)
BMJ Clinical Evidence (United Kingdom)
COMPUS at The Canadian Agency for Drugs and Technologies in Health (Canada)
The Cochrane Collaboration (International)
EMB Guidelines (Finland/International)
The Endocrine Society (USA)
European Respiratory Society (Europe)
European Society of Thoracic Surgeons (International)
Evidence-based Nursing Südtirol (Italy)
German Center for Evidence-based Nursing "sapere aude" (Germany)
Infectious Diseases Society of America (USA)
Japanese Society for Temporomandibular Joint (Japan)
Journal of Infection in Developing Countries (International)
Kidney Disease: Improving Global Outcome (International)
Ministry for Health and Long-Term Care, Ontario (Canada)
National Board of Health and Welfare (Sweden)
National Institute for Health and Clinical Excellence (United Kingdom)
Norwegian Knowledge Centre for the Health Services (Norway)
Polish Institute for EBM (Poland)
Society for Critical Care Medicine (USA)
Society for Vascular Surgery (USA)
Spanish Society for Family and Community Medicine (Spain)
Surviving Sepsis Campaign (International)
University of Pennsylvania Health System Center for Evidence-Based Practice (USA)
UpToDate (USA)
World Health Organization (International)

There are good guidelines

Yet many medical specialty societies haven't adopted GRADE

ONLINE FIRST | HEALTH CARE REFORM

Failure of Clinical Practice Guidelines to Meet Institute of Medicine Standards

Two More Decades of Little, If Any, Progress

Justin Kung, MD; Ram R. Miller, MD; Philip A. Mackowiak, MD

20 anni dopo ….

Table 1. Frequency of Adherence to Institute of Medicine Standards by Organization Type and Subspecialty Area

Organization Type (No. of Guidelines)	Standards Met, Median	Guidelines Meeting >50% of Standards, No. (%)
All (114)	8 (44.0)	56 (49.1)
United States (68)	8 (44.0)	34 (50.0)
Non-US (46)	9 (50.0)	22 (47.8)
US government agency (15)	9 (50.0)	10 (66.7)
Subspecialty societies (41)	8 (44.0)[a]	16 (39.0)[b]
Subspecialty area		
Infectious diseases (21)	9 (50.0)	11 (52.4)
Oncology (17)	9.5 (52.8)	9 (52.9)
OB/GYN (12)	8 (44.0)	3 (25.0)
All other (64)	8 (44.0)	36 (56.2) [c]

Abbreviation: OB/GYN, obstetrics/gynecology.
[a] $P = .34$ by Mann-Whitney test compared with all other organization types.
[b] $P = .11$ by Fisher exact test compared with all other organization types.
[c] $P = .40$ by χ^2 test across all subspecialty areas.

We have also another problem….

Conflict of interests

Is not a source of a random error

COI generates BIAS

Bias almost always
results in an overestimation of benefit
and an underestimation of
harm

Managing COI within a guideline panel is of paramount importance to warrant trustworthy recommendations

RESEARCH

Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study

Jennifer Neuman *instructor*[1], Deborah Korenstein *associate professor*[2], Joseph S Ross *assistant professor*[3], Salomeh Keyhani *assistant adjunct professor*[4 5]

What is already known on this topic

Conflicts of interest (COI) among panel members are common in guidelines issued by certain specialty organisations

What this study adds

The prevalence and under-reporting of COI are high and transparency is incomplete among a wide range of guideline producing organisations

An association exists between the source of sponsorship of guidelines and the presence of COI

BMJ 2011;343:d5621 doi: 10.1136/bmj.d5621

JAMA®

Online article and related content current as of January 28, 2009.

Why Guideline-Making Requires Reform

Allan D. Sniderman; Curt D. Furberg

JAMA. 2009;301(4):429-431 (doi:10.1001/jama.2009.15)

http://jama.ama-assn.org/cgi/content/full/301/4/429

HEALTH CARE REFORM

Conflicts of Interest in Cardiovascular Clinical Practice Guidelines

Todd B. Mendelson, MD, MBE; Michele Meltzer, MD, MBE; Eric G. Campbell, PhD; Arthur L. Caplan, PhD; James N. Kirkpatrick, MD

Arch Intern Med. 2011;171(6):577-584

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Impugning the Integrity of Medical Science

The Adverse Effects of Industry Influence

Catherine D. DeAngelis, MD, MPH

Phil B. Fontanarosa, MD, MBA

to note that for some of the referenced publications listed in the Table of the article by Ross et al,[1] some of the authors either did not actually receive financial support from the company; were

An so, how to decide whether a guideline is trustworthy ?

«Traditional» approach

- Evaluation frameworks (AGREE, GIN, IOM standards)
- Concordance between guidelines

2011

CLINICAL PRACTICE GUIDELINES WE CAN TRUST

1. Establishing Transparency
2. Management of Conflict of Interest (COI)
3. Guideline Development Group Composition
4. Clinical Practice Guideline–Systematic Review Intersection
5. Establishing Evidence Foundations for and Rating Strength of Recommendations
6. Articulation of Recommendations
7. External Review
8. Updating

Evaluation frameworks explore the quality of producing and reporting guidelines

NOT

the trustworthiness of their recommendations

a case study…

Can dronedarone be recommended for preventing recurrences of Atrial Fibrillation ?

- Three renowned medical specialty societies (AHA, ESC, CCS)
- Three guidelines on the same disease (**why ?**)
- Same evidence base (6 RCTs) about dronedarone
- One guideline declared to comply with GRADE
- disclosure of conflict of interests
- One of these guideline declared to comply with AGREE criteria
- Substantial agreement among them about the effectiveness of dronedarone

~~yes~~

However applying GRADE methods to the same evidence base considered by these three guidelines….

We didn't find any relevant favorable outcome, we found unexplained heterogeneity of results, and we could not exclude an unfavorable effect of dronedarone on mortality, with an excess of 13 (95%CI, −15 to 61) deaths per 1000 patients treated with it

Special Communication

Dronedarone for Atrial Fibrillation
The Limited Reliability of Clinical Practice Guidelines

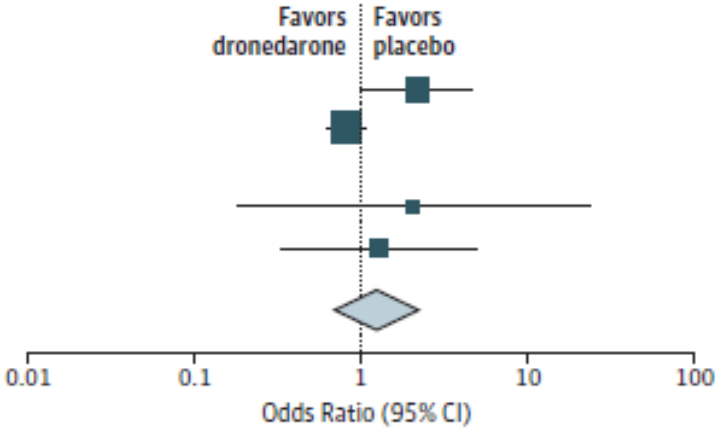
Primiano Iannone, MD; Enrico Haupt, MD; Gaddo Flego, MD; Paola Truglio, MD; Monica Minardi, MD; Simon Clarke, MD; Nicola Magrini, MD

JAMA Internal Medicine

Figure. Results of the Meta-analysis (Outcome: All-Cause Mortality) Excluding and Including the PALLAS Study

A

	Odds Ratio (95% CI)
ANDROMEDA	2.23 (1.10-4.52)
ATHENA	0.84 (0.65-1.08)
DAFNE	Not estimable
ERATO	2.12 (0.19-23.83)
EURIDIS-ADONIS	1.32 (0.35-5.00)
Total	**1.30 (0.67-2.51)**



B

	Odds Ratio (95% CI)
ANDROMEDA	2.23 (1.10-4.52)
ATHENA	0.84 (0.65-1.08)
DAFNE	Not estimable
ERATO	2.12 (0.19-23.83)
EURIDIS-ADONIS	1.32 (0.35-5.00)
PALLAS	1.94 (0.99-3.80)
Total	**1.43 (0.81-2.52)**

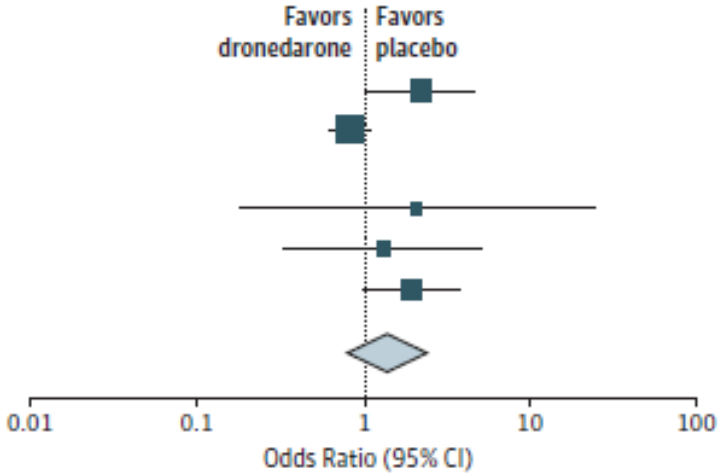


Table 2. Quality Assessment of Dronedarone Guidelines According to the Institute of Medicine Standards[1]

No.	Quality Domain	Fulfillment of the Standard (No. Fulfilled/Total Items)		
		ESC Guideline	AHA Guideline	CCS Guideline
1	Transparency	Yes (1/1)	Yes (1/1)	Yes (1/1)
2	Management of conflict of interest	Partial (2/8)	Partial (5/8)	Partial (4/8)
3	Guideline development group composition	No (0/3)	No (0/3)	No (0/3)
4	Clinical practice guideline-systematic review intersection	No (0/2)	No (0/2)	No (0/2)
5	Evidence foundations for and rating strength of recommendations	Partial (2/4)	Partial (2/4)	Partial (2/4)
6	Articulation of recommendations	Yes (2/2)	Yes (2/2)	Yes (2/2)
7	External review	Partial (1/4)	Partial (1/4)	Partial (1/4)
8	Updating	Yes (3/3)	Yes (3/3)	Yes (3/3)

How to decide whether a guideline is trustworthy

in presence of

- flawed methods (no GRADE guidelines)
- uncontrolled conflict of interests
- restricted panel compositions

Concordance of recommendations between guidelines and declared adherence to quality standards do not warrant their trustworthiness

How to decide whether a guideline is trustworthy

A roadmap I would suggest…

(a very modest & weak recommendation…)

Have You a clinical problem ?

PICO framing

Search whether a guideline addressing relevant outcomes does exsist

NO

YES

No/Negligible conflict of Interest ?

NO

YES

IOM criteria helpful

Sound methodology ?
(GRADE fully exploited)

NO

Search for other evidences

YES

Multidisciplinary involvement ?

NO

YES

Low risk of untrustworthiness

Evaluate primary evidences carefully in case of any doubt

Consider temporal gaps

Follow GRADE

- Overall quality of evidences
  - Relevance of outcomes
  - Type of studies
  - Precision
  - Consistency
  - Directness
  - Risk of bias
  - Modifiers/Confounders
- Balance across all favourable and unfavourable outcomes
- Patients' values and preferences
- Resources' use

I didn’t mean to confuse You

But Evidence Based Medicine is
an eminently creative
methodology which emphasizes
critical reasoning
and not the robotic application of
rules and recommendations…

Bogathy & Brophy, Lancet 2003

VIEWPOINT

The Connection Between Evidence-Based Medicine and Shared Decision Making

Hoffman et Al

JAMA October 1, 2014 Volume 312, Number 13 1295

Figure. The Interdependence of Evidence-Based Medicine and Shared Decision Making and the Need for Both as Part of Optimal Care