# A Job for Internists…..

***Guidelines Critical Appraisal***

Call for action!

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IM - ORIGINAL

# Eligibility criteria in heart failure randomized controlled trials: a gap between evidence and clinical practice

**Giorgio Costantino · Anna Maria Rusconi · Pier Giorgio Duca · Stefano Guzzetti · Ilaria Bossi · Marta Del Medico · Giuseppina Pisano · Mara Bulgheroni · Monica Solbiati · Raffaello Furlan · Nicola Montano**

## Question:

How many patients with HF, followed up by the “Outpatient Heart Failure Center” of our Internal Medicine Unit would have been enrolled in the major HF treatment trials?

**Table 4** Percentage of enrollment

| | Treatment | Pharmacological class | Acronym | % of enrollment of our patients |
|---|---|---|---|---|
| 1 | Bisoprolol | β-blocker | CIBIS | 8 |
| 2 | Amiodarone | Antidysrhythmic | GESICA | 29 |
| 3 | Carvedilol | β-blocker | | 38 |
| 4 | Digoxin | Inotrope | DIG | 71 |
| 5 | Ibopamine | Vasodilatator | PRIME II | 21 |
| 6 | Epoprostenol | Vasodilatator | FIRST | 16 |
| 7 | Vesnarinone | Inotrope | | 22 |
| 8 | Spironolactone | Diuretics | RALES | 24 |
| 9 | Dofetilide | Antidysrhythmic | DIAMOND | 48 |
| 10 | Bisoprolol | β-blocker | CIBIS II | 14 |
| 11 | Metoprolol | β-blocker | MERIT-HF | 52 |
| 12 | Mibefradil | Ca-antagonist | MACH-1 | 35 |
| 13 | Carvedilol | β-blocker | COPERNICUS | 38 |
| 14 | Valsartan | Angiotensin-receptor blocker | Val-HeFT | 42 |
| 15 | Bucindolol | β-blocker | BEST | 17 |
| 16 | Candesartan | Angiotensin-receptor blocker | CHARM | 65 |

Mean enrollment 33.8%

**33.8%**

**Table 2** Characteristics of the two populations

| | Trials | Clinical practice |
|---|---|---|
| Patient number | 45,276 | 299 |
| Males (%) | 76.5 | 54.5 |
| Mean age (years) ± SD | 63.5 | 71.9 ± 11.6 |
| Mean ejection fraction (%) ± SD | 25 | 40 ± 16 |
| NYHA class I (%) | 2.2 | 7.6 |
| NYHA class II (%) | 32.0 | 70.2 |
| NYHA class III (%) | 56.7 | 21.0 |
| NYHA class IV (%) | 9.1 | 1.3 |
| Ischemic cause (%) | 61.5 | 39.8 |

***Costantino et al, IEM 2009***

# An updated definition of guideline

the committee believes are defining characteristics. The new definition 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

***Institute of Medicine, 2011***

# Low quality of contemporary guidelines

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*

**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 $\chi^2$ test across all subspecialty areas.

# How good is the quality of the clinical evidence?

- All **1394** systematic reviews published on the Cochrane Database of Systematic Reviews from January 2013 to June, 2014.
- **GRADE** (Grades of Recommendation, Assessment, Development, and Evaluation) summary of findings performed in 608 (43.6%).
- **Quality of the evidence** for the first listed primary outcome: 13.5% high, 30.8% moderate, 31.7% low, 24% very low level.
- Even when all outcomes listed were considered, **only 19.1%** had at least one outcome with high quality of evidence.
- Of the reviews with high quality of evidence, **only 25** had both significant results and a favorable interpretation of the intervention.

***Fleming et al, J Clin Epidemiol 2016***

# Conflict of interests

**A conflict of interests is a set of conditions in which professional judgment concerning a primary interest (such as the health and well being of a patient or the validity of research), is unduly influenced by a secondary interest - The secondary interests may be financial or nonfinancial.**

**Thompson DF (1993) Understanding financial conflicts of interest. NEJM 329: 573–576.**

- 87% of guideline authors have some form of interaction with pharamceutical industry

- 59% of authors had relationships with companies whose drugs were considered in the guideline they authored

Choudry et Al
JAMA 2002; 287: 612-617

**Industry sponsorship and research outcome (Review)**

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L


**Substantial** relationship

(RR of favorable results for sponsored vs non sponsored trials: 1.32, 95% CI 1.21 to 1.44)

**Citation:** Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: MR000033. DOI: 10.1002/14651858.MR000033.pub2.

# Guidelines as a marketing tool

CLINICAL GUIDELINES

BMJ

2013

## Ensuring the integrity of clinical practice guidelines: a tool for protecting patients

**Jeanne Lenzer**, **Jerome Hoffman**, **Curt Furberg**, and **John Ioannidis** pull together a large expert working group to offer a manifesto for clinical guidelines

Jeanne Lenzer *medical investigative journalist*[1], Jerome R Hoffman *professor of medicine emeritus*[2], Curt D Furberg *professor of public health sciences emeritus*[3], John P A Ioannidis *professor of medicine*[4], On behalf of the Guideline Panel Review working group

**Box 1: Red flags that should raise substantial skepticism among guideline readers (and medical journals)**

- Sponsor(s) is a professional society that receives substantial industry funding;
- Sponsor is a proprietary company, or is undeclared or hidden
- Committee chair(s) have any financial conflict*
- Multiple panel members have any financial conflict*
- Any suggestion of committee stacking that would pre-ordain a recommendation regarding a controversial topic
- No or limited involvement of an expert in methodology in the evaluation of evidence
- No external review
- No inclusion of non-physician experts/patient representative/community stakeholders

*Includes a panelist with either or both a financial relationship with a proprietary healthcare company and/or whose clinical practice/specialty depends on tests or interventions covered by the guideline

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CE - ORIGINAL

# Guidelines on the management of atrial fibrillation in the emergency department: a critical appraisal

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A. Lages, O. M. Reiakvam, F. Savva, J. Schovanek, S. van Bree, I. J. da Silva Chora, G. Privitera, S. Ragozzino, M. von Rotz, and L. Woittiez are participants of the 22nd European Summer School of Internal Medicine.

Most of the references cited by the different guidelines can be found in the Supplementary Appendix.

**Electronic supplementary material** The online version of this article (doi:10.1007/s11739-016-1580-x) contains supplementary material, which is available to authorized users.

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**Table 1** Agreement between guidelines and provisional GRADE based recommendation of the working group

| Questions | Agreement | Grade |
|---|---|---|
| Question 1: When do you choose rate control or rhythm control strategy? | | |
| Question 1a: In haemodynamically unstable patients affected by acute-onset non-valvular atrial fibrillation is rhythm control preferable to a rate-control strategy? | Agreement on rhythm control strategy | Strong recommendation, low-quality evidence<br>Outcome: survival |
| Question 1b: In haemodynamically stable patients affected by acute-onset (less than 48 hours) non-valvular atrial fibrillation for which patients rhythm control is preferable to a rate-control strategy ? | No agreement | |
| Question 1c: In haemodynamically unstable patients affected by acute-onset non-valvular atrial fibrillation and WPW syndrome is rhythm control preferable to a rate-control strategy? | Not available (ESC not covered) | |
| Question 1d: In haemodynamically stable patients affected by acute-onset non-valvular atrial fibrillation and WPW syndrome is rhythm control preferable to a rate-control strategy? | Not available (ESC not covered) | |
| Question 2: When do you choose electrical or pharmacological cardioversion? | | |
| Question 2a: In haemodynamically unstable patients affected by acute-onset non-valvular atrial fibrillation is electrical cardioversion preferable to pharmacological cardioversion? | Agreement on electrical cardioversion | Strong recommendation, low-quality evidence<br>Outcome: survival |
| Question 2b: In haemodynamically unstable patients affected by acute-onset non-valvular atrial fibrillation and WPW is electrical cardioversion preferable to pharmacological cardioversion? | Agreement on electrical cardioversion | Strong recommendation, low-quality evidence<br>Outcome: survival |
| Question 2c: In haemodynamically stable patients affected by acute-onset (less than 48 hours) non-valvular atrial fibrillation is electrical cardioversion preferable to pharmacological cardioversion? | No agreement | |
| Question 2d: In haemodynamically stable patients affected by acute-onset non-valvular atrial fibrillation and WPW syndrome is electrical cardioversion preferable to pharmacological cardioversion? | Not available)<br>(ESC not covered) | |
| Question 3: In case of pharmacological cardioversion which drug would you use? | | |
| Question 3a: In haemodynamically stable patients affected by acute-onset (less than 48 hours) non-valvular atrial fibrillation and no structural heart disease which drug is preferable for pharmacological cardioversion? | Partial agreement: agreement on Flecainide and Propafenone; less consensus regarding ibutilide | Weak recommendation, low quality of evidence<br>Outcome: restoring sinus rhythm |
| Question 3b: In haemodynamically stable patients affected by acute-onset (less than 48 hours) non-valvular atrial fibrillation and structural heart disease which drug is preferable for pharmacological cardioversion? | No agreement | |
| Question 3c: In haemodynamically stable patients affected by paroxysmal non-valvular atrial fibrillation and no structural heart disease would you recommend the pill in the pocket approach with flecainide or propafenone? | Agreement on pill-in-the-pocket strategy | Weak recommendation, low quality of evidence<br>Outcomes: emergency room visits, hospitalization, quality of life |
| Question 4: In case of rate control strategy which drug would you use? | | |
| Question 4a: In patients affected by acute-onset non-valvular atrial fibrillation and no hypotension or heart failure which therapy would you recommend in order to obtain rate control? | Agreement on beta blockers or non-dihydropyridine calcium channel antagonists | Strong recommendation, low quality of evidence<br>Outcome: rate control, quality of life |
| Question 4b: In patients affected by acute-onset non-valvular atrial fibrillation with hypotension or heart failure which drug would you recommend? | Agreement on digitalis | Strong recommendation, low quality of evidence<br>Outcome: rate control, worsening of heart failure |

# Guidelines on the management of atrial fibrillation in the emergency department: a critical appraisal

**Abstract** Several guidelines often exist on the same topic, sometimes offering divergent recommendations. For the clinician, it can be difficult to understand the reasons for this divergence and how to select the right recommendations. The aim of this study is to compare different guidelines on the management of atrial fibrillation (AF), and provide practical and affordable advice on its management in the acute setting. A PubMed search was performed in May 2014 to identify the three most recent and cited published guidelines on AF. During the 1-week school of the European School of Internal Medicine, the attending residents were divided in five working groups. The three selected guidelines were compared with five specific questions. The guidelines identified were: the European Society of Cardiology guidelines on AF, the Canadian guidelines on emergency department management of AF, and the American Heart Association guidelines on AF. Twenty-one relevant subquestions were identified. For five of these, there was no agreement between guidelines; for three, there was partial agreement; for three data were not available (issue not covered by one of the guidelines), while for ten, there was complete agreement. Evidence on the management of AF in the acute setting is largely based on expert opinion rather than clinical trials. While there is broad agreement on the management of the haemodynamically unstable patient and the use of drugs for rate-control strategy, there is less agreement on drug therapy for rhythm control and no agreement on several other topics.

Original Investigation

# Reanalyses of Randomized Clinical Trial Data

Shanil Ebrahim, PhD; Zahra N. Sohani, MSc; Luis Montoya, DDS; Arnav Agarwal, BSc; Kristian Thorlund, PhD; Edward J. Mills, PhD; John P. A. Ioannidis, MD, DSc

**IMPORTANCE** Reanalyses of randomized clinical trial (RCT) data may help the scientific community assess the validity of reported trial results.

**OBJECTIVES** To identify published reanalyses of RCT data, to characterize methodological and other differences between the original trial and reanalysis, to evaluate the independence of authors performing the reanalyses, and to assess whether the reanalysis changed interpretations from the original article about the types or numbers of patients who should be treated.

***".....35% of published reanalyses led to changes in findings that implied conclusions different from those of the original article".***

**RESULTS** We identified 37 eligible reanalyses in 36 published articles, 5 of which were performed by entirely independent authors (2 based on publicly available data and 2 on data that were provided on request; data availability was unclear for 1). Reanalyses differed most commonly in statistical or analytical approaches (n = 18) and in definitions or measurements of the outcome of interest (n = 12). Four reanalyses changed the direction and 2 changed the magnitude of treatment effect, whereas 4 led to changes in statistical significance of findings. Thirteen reanalyses (35%) led to interpretations different from that of the original article, 3 (8%) showing that different patients should be treated; 1 (3%), that fewer patients should be treated; and 9 (24%), that more patients should be treated.

**CONCLUSIONS AND RELEVANCE** A small number of reanalyses of RCTs have been published to date. Only a few were conducted by entirely independent authors. Thirty-five percent of published reanalyses led to changes in findings that implied conclusions different from those of the original article about the types and number of patients who should be treated.

*JAMA*. 2014;312(10):1024-1032. doi:10.1001/jama.2014.9646

# Peer review: a still dark side

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IM - ORIGINAL

**Errors in medical literature: not a question of impact**

**Giorgio Costantino · Giovanni Casazza · Giulia Cernuschi · Monica Solbiati · Simone Birocchi · Elisa Ceriani · Piergiorgio Duca · Nicola Montano**

- 100 articles from NEJM
- 50 articles from JAMA
- 50 articles from Lancet
- published from October 2010 to April 2011
- consecutive articles with at least two tables allowing reanalysis of the data

## Errors classification:

- *methodological* (abstract, results or discussion not coherent with the method section)
- *numerical* (the counts do not match)
- *severe* (if numbers in the abstract were completely different from numbers reported in the full text)
- *slip* (likely miswriting)

**Table 1** Errors retrieved in the analyzed articles

| | Total | Non structured abstract | Structured abstract |
|---|---|---|---|
| Number of articles analysed | 200 | 100 | 100 |
| Number of articles included | 125 | 74 | 51 |
| Number of articles with errors (%, CI 95 %) | 102 (82, 74–88) | 57 (77, 66–86) | 45 (88, 76–96) |
| At least one slip (%, CI 95 %) | 9 (7, 3–13) | 4 (5, 1–13) | 5 (10, 3–21) |
| At least one methodological error (%, CI 95 %) | 22 (18, 11–25) | 17 (23, 14–34) | 5 (10, 3–21) |
| At least one numerical error (%, CI 95 %) | 92 (74, 65–81) | 47 (64, 52–74) | 45 (88, 76–96) |
| At least one severe error (%, CI 95 %) | 5 (4, 1–9) | 4 (5, 1–13) | 1 (2, 0–10) |
| Rounding errors (%, CI 95 %) | 56 (45, 36–54) | 25 (34, 23–46) | 12 (24, 13–37) |
| Article with errors excluding rounding (%, CI 95 %) | 85 (68, 59–76) | 52 (70, 59–80) | 33 (65, 50–78) |

***Costantino G et al, IEM 2013***

# In conclusion…..

- Bad doctors are ignorant about guidelines
- Mediocre doctors follow guidelines
- Good doctors know when to deviate from guidelines…….and thus perform a personalized therapy

#EvidenceLive

# A Tribute

"The worst enemy of knowledge is not ignorance, but the illusion to know"

*Stephen Hawking (1942-2018)*