Can medical guidelines adversely affect the health commons?

James Brophy MD FRCP PhD
Professor, Departments of Medicine and Epidemiology, Biostatistics and Occupational Health, McGill University

MUHC MEDICAL GRAND ROUNDS
Tuesday September 13 2017

Conflicts of Interest

I have no known conflicts associated with this presentation and to the best of my knowledge, am equally disliked by all pharmaceutical and device companies

(and now quite possibly by certain professional societies and their guideline writers)

Guideline Concerns (not just me)

- "Specifically, this concern extends from limitations in the scientific evidence base on which CPGs rely; a lack of transparency of development groups' methodologies; conflict of interest among guideline development group members and funders; and questions regarding how to reconcile conflicting guidelines."

Institute of Medicine (2001) Clinical Practice Guidelines We Can Trust

Outline

- "Specifically, this concern extends from

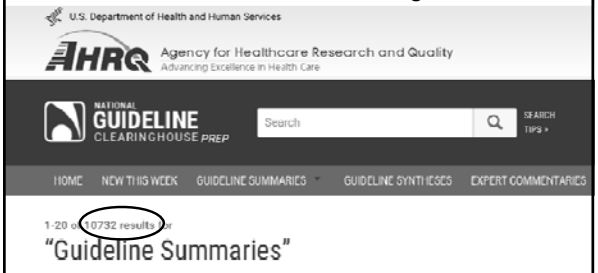
1. limitations in the scientific evidence base on which CPGs rely; a lack of transparency of development groups'
2. methodologies; conflict of interest among guideline development group members and funders; and questions regarding how
3. to reconcile conflicting guidelines."

Institute of Medicine (2001) Clinical Practice Guidelines We Can Trust

Educational Objectives

1. To appreciate the mechanisms (chance, confounding, and bias) whereby guidelines may inadequately interpret & synthesize the evidence
2. To appreciate the adverse health consequences of guidelines
3. To appreciate how the quality of the guideline process may be improved

Guidelines – no shortages



- Clinical and professional society viewpoints hopefully align as a means to provide evidence-based consensus management recommendations to improve patient care
- Integrity, validity, objectivity and independence are paramount

Do guidelines reflect the essentials of EBM?

"Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values."

Sackett D et al. Evidence-Based Medicine: How to Practice and Teach EBM, 2nd edition. Churchill Livingstone, Edinburgh, 2000, p.1

- What are the essentials?
  - Is all the evidence available
  - Critical appraisal of the evidence (avoid biases)
  - Systematic review with incorporation with local expertise and patient values
- If not, guidelines -> marketing tools or for treating diseases, but not for treating patients

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Are the guidelines evidence based?

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1981 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions

Conclusions Recommendations issued in current ACC/AHA clinical practice guidelines are largely developed from lower levels of evidence or expert opinion. The proportion of recommendations for which there is no conclusive evidence is also growing. These findings highlight the need to improve the process of writing guidelines and to expand the evidence base from which clinical practice guidelines are derived.

JAMA. 2009;301(8):831-841 www.jama.com

<20% have level A evidence

And even when the evidence does exist…

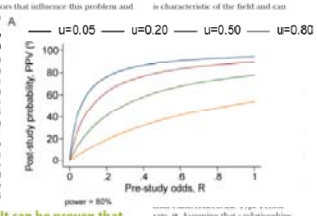
Essay

Why Most Published Research Findings Are False

John P.A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for



It can be proven that most claimed research findings are false.

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A "thought" experiment

- A large (1700) multicenter RCT finds a 6% absolute mortality reduction (P=0.005) with a new therapy (NNT = 16)
- Peer reviewed and published in the NEJM
- What is the probability guidelines will recommend it?
  - 100%, 99.5%, 99%, 98%?
- What is the probability that this drug is useless or even harmful?
  - 50%, 10%, 5%, <0.5 %?

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PROWESS NEJM 3/2001

The New England Journal of Medicine

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

Conclusions Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding. (N Engl J Med 2001;344:699-709.)

Copyright © 2001 Massachusetts Medical Society.

Results A total of 1690 randomized patients were treated (840 in the placebo group and 850 in the drotrecogin alfa activated group). The mortality rate was 30.8 percent in the placebo group and 24.7 percent in the drotrecogin alfa activated group. On the basis of the prospectively defined primary analysis, treatment with drotrecogin alfa activated was associated with a reduction in the relative risk of death of 19.4 percent (95 percent confidence interval, 6.6 to 30.5) and an absolute reduction in the risk of death of 6.1 percent (P=0.006). The incidence of serious bleeding was higher in the drotrecogin alfa activated group than in the placebo group (3.5 percent vs. 2.0 percent, P=0.06).

Special Articles — Crit Care Med 2004 Vol. 32, No. 3

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australasian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

- Recombinant Human Activated Protein C (rhAPC) recommended in septic shock
- 10 of 15 authors funded directly by Eli Lilly who also sponsored the guideline process

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Guidelines (without COI)

In Favor

CONFIDENTIAL

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Drotrecogin alfa (activated) for severe sepsis

1 Guidance

1.1 Drotrecogin alfa (activated) is recommended for use in adult patients who have severe sepsis that has resulted in multiple organ failure (that is, two or more major organs have failed) and who are being provided with optimum intensive care support.

Not in favor

Technology Assessment Unit (TAU)
McGill University Health Centre (MUHC)

Drotrecogin alfa (activated) in severe sepsis: a systematic review and new cost-effectiveness analysis

Conclusion: The evidence supporting the clinical and economic attractiveness of drotrecogin alfa is not conclusive and further research appears to be indicated.

http://www.nice.org.uk/nicemedia/live/11545/32951/32951.pdf

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So why the difference?

- More information than the NEJM paper
  - FDA submission 1000's of pages so deeper uncertainty exploration e.g. benefit in those with normal APC?
  - Negative trial data in other ("different") populations, (RESOLVE, ENHANCE) "borrowing" some of this information, rather than completely ignoring it, seems reasonable
- Methodological issues
  - Protocol was changed during study
  - Study stopped prematurely ?exaggerated
  - Outcome 28 days, longer term benefits?
- Huge cost -> higher burden of proof of value

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What do you get from guidelines for $2B?

- Replication RCT trial (PROWESS SHOCK - 2011), no benefit, trend for 10% increased mortality (851 APC vs. 845 placebo - 28-day mortality 26.4% vs.24.2% (RR1.09; 0.92, 1.28))
- Drug voluntarily withdrawn Nov 2011
- NICE APC guidance withdrawn (2011)
- Drug sales > $2B ($200 million annual)

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Benefit inflation with early trials –a one off?

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context Controversy and uncertainty ensue when the results of clinical research on the effectiveness of interventions are subsequently contradicted. Controversies are most pronounced when highly inequal research is involved.

- Examined 39 RCTs from 1999-2003 in 3 high impact journals > 1000 citations
- Found that 9 of 39 highly cited RCTs had later contradicted or markedly reduced effects

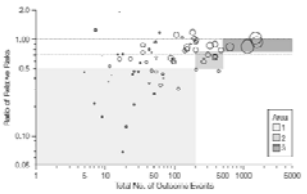
Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

JAMA. 2005;294:218-228 www.jama.com

Benefit inflation with early stopping

Stopping Randomized Trials Early for Benefit and Estimation of Treatment Effects
Systematic Review and Meta-regression Analysis

JAMA. 2010;303(12):1180-1187



Analysis included 91 truncated RCTs asking 63 different questions and 424 matching nontruncated RCTs

Areas (1-3) correspond to very large (RR 37%) in truncated trials < 200 events, large (RR 0.65) 200 -500 events and moderate overestimation (RR 0.88) > 500 events

- CONCLUSION: Truncated RCTs were associated with greater effect sizes than RCTs not stopped early. This difference was independent of the presence of statistical stopping rules and was greatest in smaller studies.

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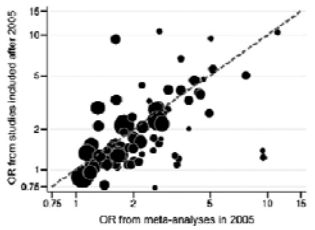
Inflation even with (early) meta-analyses



- 80 MA from Cochrane 2005 – updated 2010
- Effect size on average 15% smaller but 33% smaller in MA with < 300 events
- BIGGER PROBLEM IF THE ADDITIONAL STUDIES ARE NEVER DONE, INFLATION NEVER DETECTED

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Journal of Clinical Epidemiology 64 (2011) 1060e1069

What do you get from guidelines for $20B?

- Tamiflu (oseltamivir) FDA approved 1999, based on limited data from two RCTs
- Supportive evidence from MA (Annals 2003) - 10 trials
- Guidelines (Cochrane (2008), CDC (2008), EMA (2009), WHO (2010)) endorsed Tamiflu to reduce influenza complications and maybe mortality
- CDC recommendation to stockpile medication
- WHO adds to list of essential medications
- Estimates that by 2016 $20B spent (50% on stockpiling)

BMJ | 12 december 2009 | Volume 339

BMJ 2017;358:j3266 doi: 10.1136/bmj.j3266 (Published 2017 July 13)

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What do you get from guidelines for $20B?

- MA in Annals (2003) included 10 trials – only 2 published
- Took > 5 years to get the unpublished data
- Cochrane (2014) -> **no** evidence of a reduction in mortality, pneumonia complications or hospital admission (< 1 day reduction in symptoms)
- WHO downgrades essential Rx recommendation (2017)
- Situation described as “multisystem failure” - decisions based on flawed, unpublished evidence
- Complicity of guidelines to this failure “multisystem failure” (?)

BMJ 2017;358:j3266 doi: 10.1136/bmj.j3266 (Published 2017 July 13)

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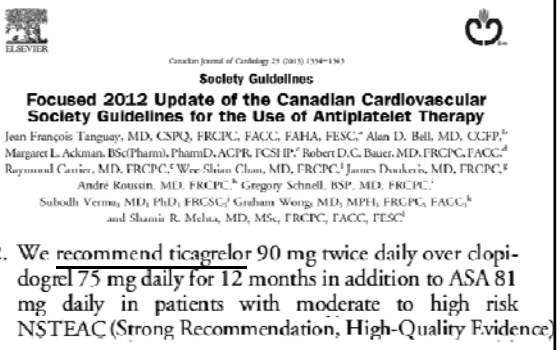
CCS Guidelines 2012



Society Guidelines

Focused 2012 Update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy

Jean François Tanguay, MD, CSPQ, FRCPC, FACC, FAHA, FESC,[a] Alan D. Bell, MD, CCFP,[b] Margaret L. Ackman, BSc(Pharm), PharmD, ACPR, FCSHP,[c] Robert D.G. Bauer, MD, FRCPC, FACC,[d] Raymond Cartier, MD, FRCPC,[e] Wee-Shian Chan, MD, FRCPC,[f] James Douketis, MD, FRCPC,[g] André Roussin, MD, FRCPC,[h] Gregory Schnell, BSP, MD, FRCPC,[i] Subodh Verma, MD, PhD, FRCSC,[j] Graham Wong, MD, MPH, FRCPC, FACC,[k] and Shamir R. Mehta, MD, MSc, FRCPC, FACC, FESC[l]

2. We recommend ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in patients with moderate to high risk NSTEACS (Strong Recommendation, High-Quality Evidence)

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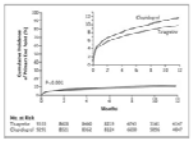
PLATO

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes



RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of

14 of 16 authors received money from the sponsor

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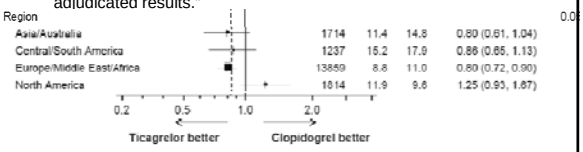
Uncertainty about PLATO

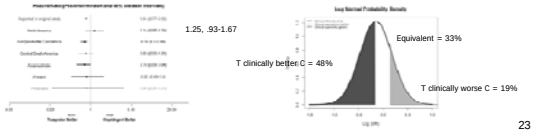
- FDA refused 1st review , accepted 2nd in 2011 dissenting opinions (6-4)
  - “Lack of Robustness of PLATO Superiority with Failure in the US Makes a Confirmatory Study Mandatory.”
  - “Besides failure in the US, superiority was only evident in the adjudicated results.”



- A FDA analysis, not reported in NEJM paper found an increased risk among ticagrelor patients undergoing revascularization within 24 hours (HR 1.9, 95%CI 1.3, 2.8)[22]

Accounting for this uncertainty

- Standard analysis treats all patients as independent & identical and make inferences on averages
- Contrary to “personalized” medicine
- Patients are not totally independent as they reside in clusters that can influence outcomes (intensity of other Rx)
- Forces everyone to be a “lumper” or a “splitter”
- Alternative hierarchical model, a statistically justified compromise between these extremes (Efron Sci. Am 1975)



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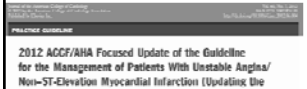
CDN / ACC-AHA / ESC Guidelines

Society Guidelines

Focused 2012 Update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy

2. We recommend ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in patients with moderate to high risk NSTEACS (as defined as PLATO[14]: ≥ 2 or more of (1)

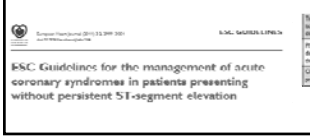
9 of 12 + COI



2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/ Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)

- “This guideline explicitly does not endorse one of the P2Y12 receptor inhibitors over the other.”
- “The writing group does wish to caution clinicians about the potential increased bleeding risks associated with prasugrel and ticagrelor compared with clopidogrel”

9 of 9 NO COI



ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

17 of 17 + COI

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Guideline COI

ALL writers

	COI	No COI	Total
Authors favoring T>C	26	3	29
Authors not favoring T>C	0	9	9

- If there is no association between COI and recommending ticagrelor how likely would chance alone be responsible for observing this data
- Answer, < 1 in 100,000!

NA writers

	COI	No COI	Total
Authors favoring T>C	9	3	12
Authors not favoring T>C	0	9	9

- If there is no association between COI and recommending ticagrelor how likely would chance alone be responsible for observing this data
- Answer, <1 in 1,000!

Different conclusions CDN vs. US correlates with COI

25

Is this a sensible recommendation?

2. We recommend ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in patients with moderate to high risk NSTEACS (Strong Recommendation, High-Quality Evidence)

- PLATO results are not robust
  - Simple change of statistical model nullifies statistical significance
- Totality of the ACS RCT evidence
  - Multiple studies for clopidogrel (credo, cure, commit, caprie, clarity, charisma, oasis-7) > 100,000 pt years
  - 1 study for ticagrelor <7000 pt year with < 1500 NA pt years
- Cost
  - RAMQ Clopidogrel $14.10 vs. Ticagrelor $88.80 / month
  - QC 30,000 PCI annually add $25 MM ($100 MM CDN)

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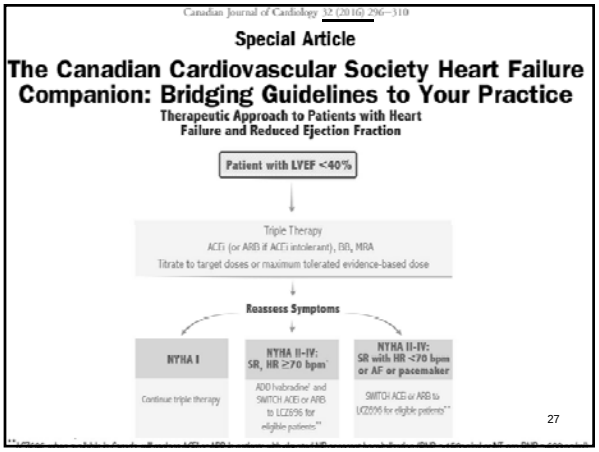
Canadian Journal of Cardiology 32 (2016) 296–310

Special Article

The Canadian Cardiovascular Society Heart Failure Companion: Bridging Guidelines to Your Practice

Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction

Patient with LVEF <40%

Triple Therapy

ACEi (or ARB if ACEi intolerant), BB, MRA

Titrate to target doses or maximum tolerated evidence-based dose

Reassess Symptoms

NYHA I

Continue triple therapy

NYHA II-IV: SR, HR ≥70 bpm

ADD Ivabradine* and SWITCH ACEi or ARB to LCZ696 for eligible patients.**

NYHA II-IV: SR with HR <70 bpm or AF or pacemaker

SWITCH ACEi or ARB to LCZ696 for eligible patients**

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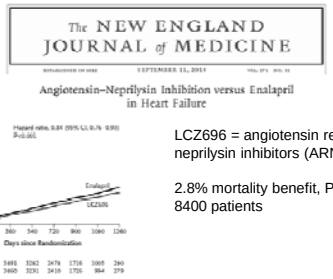
The evidence


The NEW ENGLAND JOURNAL of MEDICINE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

LCZ696 = angiotensin receptor + neprilysin inhibitors (ARNIs)

2.8% mortality benefit, P < 0.001
8400 patients

CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

Cited 1253 times

Soooo good (Google 430,000 hits)


AUG 30, 2014 @ 07:00 AM 7,859

12 Stocks to Buy Now

PARADIGM-HF Establishes a New Paradigm for Heart Failure Treatment

Medical Xpress Topics Conditions

Latest news Week's top Unread news

Home » Cardiology » May 18, 2014

PARADIGM-HF trial stopped early for benefit

May 18, 2014

THE BIGGEST BREAKTHROUGH IN HEART FAILURE TREATMENT IN DECADES: PARADIGM-HF TRIAL

BY DR. KENDRA MARSH-KATES, PREVEA CARDIOLOGIST ON OCTOBER 14, 2014

PARADIGM-HF: A NEW LANDMARK HF TRIAL

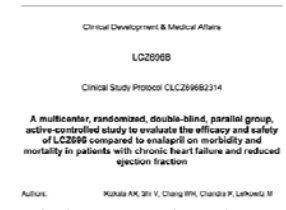
Possible sources of concern (1)

- Is this truly an academic driven trial?


The NEW ENGLAND JOURNAL of MEDICINE

Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure

Research protocol


NOVARTIS

Clinical Development & Medical Affairs

LCZ696B

Clinical Study Protocol CLCZ696B2314

A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction

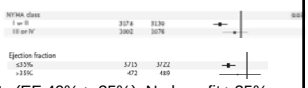
Authors: Kukula AK, Shi Y, Chang WH, Chandra P, Lefkowitz M

7 academic centers (13 p) vs only the sponsor (301 p)

- Independence? –
  - "Data were collected, managed and analyzed by the sponsor"
  - 11/11 NEJM authors received $ from the sponsor (employment,[30] consultation fees, grants)

Possible sources of concern (2)

- Fair comparison? –
  - 320mg valsartan = 40mg enalapril (FDA recommend)
- Overestimate benefit? –
  - Stopped prematurely known to give exaggerated benefits
- If benefit exists is it due to NEPI?
  - OVERTURE (5770 pts) no benefit for ACE +NEPI vs ACE alone
- Generalizability? –
  - 18,071 screened,10,537 run-in (58%), 8442 randomized (47%)
  - Only 600 NA patients, < 15% ICD, 40% not on MRA
- Over extrapolation?
  - Only 60 pts with NYHA IV
  - No benefit NYHA 3-4
- Design issues?
  - Several protocol amendments (EF 40%-> 35%), No benefit >35%
  - Unequal single blinded run-in period complicates data interpretation



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Possible sources of concern (3)

- Quality of life benefits? –
  - KC QoL statistically but not clinically significant
- Safety? –
  - Angioedema (trial) reported same 19 vs. 10 (P = 0.13). But safety not truly confirmed may double risk (RR 1.9, 95% CI 0.9 4.1)
  - Angioedema (run-in) (12 enalapril vs. 10 LCZ696). What if LCZ696 given first could be 22 vs 0? In that scenario, total risk 41 vs. 10 (RR 4.2, 95% CI 2.1, 8.2)
  - NEP breaks down amyloid beta protein, pathological marker for Alzheimer's. What is long term cognitive impact of its inhibition?
- Cost?
  - $ 3.62 per 50 mg, 100 mg, or 200 mg tablet, $7.20/day
  - About $4000 extra / year
  - 150,000 CDN CHF patients -> **$ 600,000,000**

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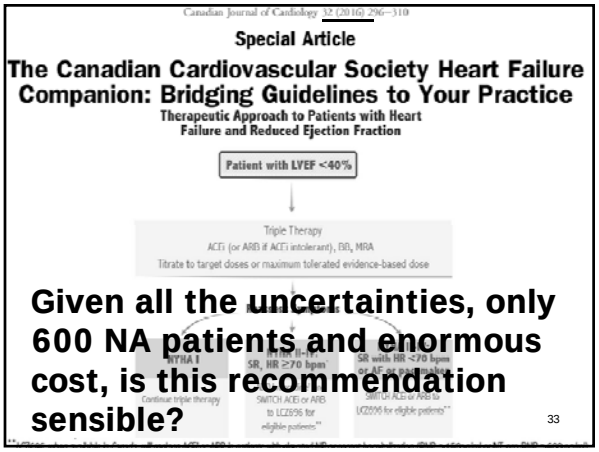

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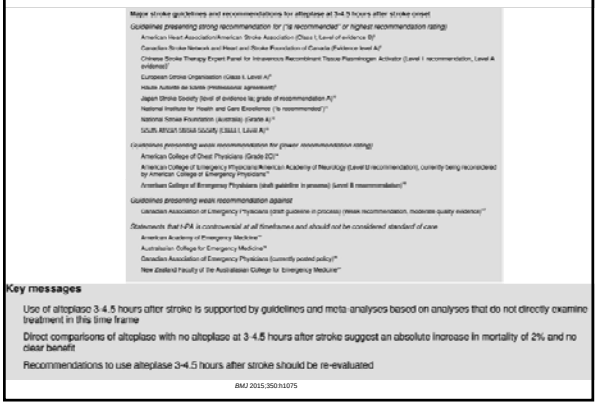
Stroke - Inconsistencies & Overtreatment



Cochrane - Inconsistencies & Overtreatment

- **2012 -** Reductions in all-cause mortality, major vascular events and revascularisations were found ... Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk. (RR 0.84, 95% CI 0.73 to 0.96) - mortality
- **2013 -** Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins. Caution in the use of statins in people at low risk of cardiovascular events is no longer tenable. (OR 0.86, 95% CI 0.79 to 0.94) - mortality

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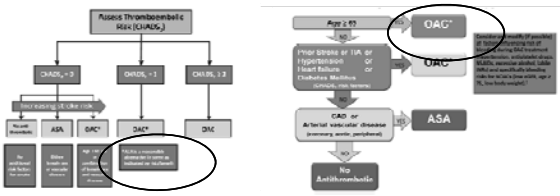
http://onlinelibrary.wiley.com.proxy3.library.mcgill.ca/wol1/doi/10.1002/14651858.CD004816.pub5/full

CCS - Inconsistencies & Overtreatment



- In 2012 , CDN guidelines ASA was reasonable for low risk patients. 2014 ASA no longer reasonable
- Yet no new compelling data were available (2014 US guidelines CHA_2DS_2-VASc score of 1, uncertainty still acknowledged - no antithrombotic therapy or oral anticoagulant or aspirin may be considered)

J Am Coll Cardiol 2014;64:2246–80

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Industry influences

Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review

Emmanuel Stamatakis[1,*], Richard Weiler[2] and John P.A. Ioannidis[3,*] Eur J Clin Invest 2013; 43 (5): 469–475

- Conclusion: industry masterfully influences evidence base production, evidence synthesis, understanding of harms issues, cost-effectiveness evaluations, clinical practice guidelines and healthcare professional education and also exerts direct influences on professional decisions and health consumers. There is an urgent need for regulation and other action towards redefining the mission of medicine towards a more objective and patient-, population- and society-benefit direction that is free from conflict of interests.

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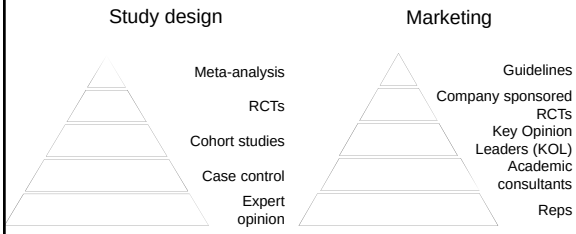
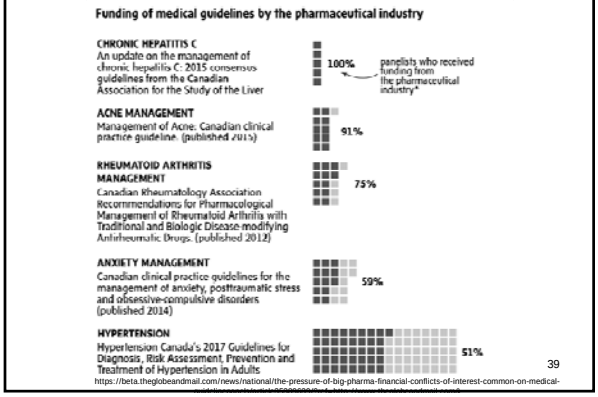
Two Pyramids of "evidence based medicine"



COI are pervasive



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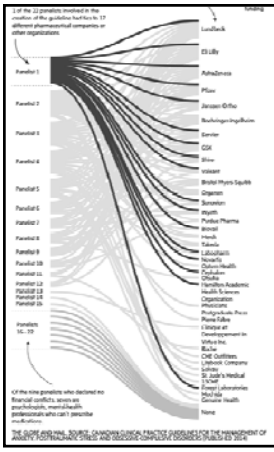
https://beta.theglobeandmail.com/news/national/the-pressure-of-big-pharma-financial-conflicts-of-interest-common-on-medical-



Anxiety

- Anxiety Disorders Association of Canada - CMAJ 2014
- 9 antidepressants drug makers, Prozac, Zoloft and Paxil, paid $205,000 for flights, meals and hotel rooms for the meeting and paid 2 medical writers to research and draft the final guideline paper.
- One of the 10 most-frequently accessed of 1,200 CPG in CMAJ database

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Red flags for COI in guidelines

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 panellist 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

Ensuring the integrity of clinical practice guidelines

BMJ 2013;347:f5535 doi: 10.1136/bmj.f5535
(Published 17 September 2013)

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Mechanisms leading to low quality guidelines

- Poor estimation of evidence quality
  - Uncritical evaluation -> provides veneer of study integrity, objectivity, scientific validity and independence to sometimes questionable evidence
  - Unrecognized hazards of early adoption, "exaggerated" initial results, esp. with early stopping
  - Large effect sizes – if it is too good to be true, it probably isn't true
  - Lack of recognition of potential role of bias (even with RCTs)
  - Have meaningful outcomes been measured?
  - Inability to accumulate scientifically in presence of uncertainty
  - Ignoring importance of study publication, replication and data sharing made available for independent reanalysis -> AllTrials (http://www.alltrials.net/)

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Mechanisms leading to low quality guidelines(2)

- Propagates cult of presumption of benefit allowing + studies to get disproportionate support
  - Over-confidence bias
  - Discount negative studies, side effects (harm)
- Cognitive biases & subjectivity of the guideline process
  - "Stacking the deck" -> Belief bias
  - Group bias
  - Vociferous champions can dominate the guideline process (ad hominem attacks)
- Conflicts of interest (financial and non-financial) may favor a different agenda than improving patient care
  - Industry viewpoint of guidelines may be potential marketing tool
  - Most guideline chairpersons and panel members in CDN have COI[43]

Adverse health consequences of guidelines

- Can encourage acceptance of marginal or ineffective therapies as "standard of care"
- Can encourage overtreatment
- Can divert limited funds to ineffective treatments – no consideration of cost effectiveness (societal viewpoint)
  - Money wasted is money not spent on other public health priorities.
- Can inhibit local critical assessment of the evidence
- Can inhibit clinical judgement and patient preferences in routine decision making
- Can inhibit the scientific process as provides false certainty -> removes impetus for replication studies & data sharing to resolve residual uncertainty
- Ultimately -> less research to find and confirm truly effective drugs

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Improving the process

- Enhance multidisciplinary committee composition (methodologists, multi-stakeholder, multi-disciplinary)
- Expand mandate to include the domains of economics, meaningful patient outcomes
- Enhance transparency of the process
- More critical appraisal process with SR & better reasoning under uncertainty
- Better COI management (remove all COI from decision making – declaration alone insufficient)

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Thank you!

"Everybody gets so much information all day long that they lose their common sense" – Gertrude Stein

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