Dealing with Information Uncertainty

It's an imperfect world but it's the only one we got

"Medicine is a science of uncertainty and an art of probability."
- William Osler

Ignore Media Reports?

Drugs in the News

How well do Canadian newspapers report the good, the bad and the ugly of new prescription drugs?

by Alan Cassels, Merrilee Atina Hughes, Carol Cole,
Barbara Mintzes, Joel Lexchin and James McCormack

April 2003

Canadian Centre for Policy Alternatives

Drugs in the news: an analysis of Canadian newspaper coverage of new prescription drugs

Alan Cassels, Merrilee A. Hughes, Carol Cole, Barbara Mintzes, Joel Lexchin, James P. McCormack

193 articles - 5 selected “new”drugs

100% - mentioned at least one benefit

2/3 - made no mention of possible side effects or harms

1/4 - of mentions of drug benefits and harms presented quantitative information

1/4 - of cases in which drug benefits and harms were quantified, the magnitude was presented only in relative terms

2/3 - of the articles gave no quantification of the benefits or harms

1/5 - reported only surrogate benefits

1/20 - mentioned contraindications - 1/3 mentioned drug costs

After exclusion of industry and government spokespeople, for only 3% was there any mention of potential COI

CMAJ 2003;168:1133-7

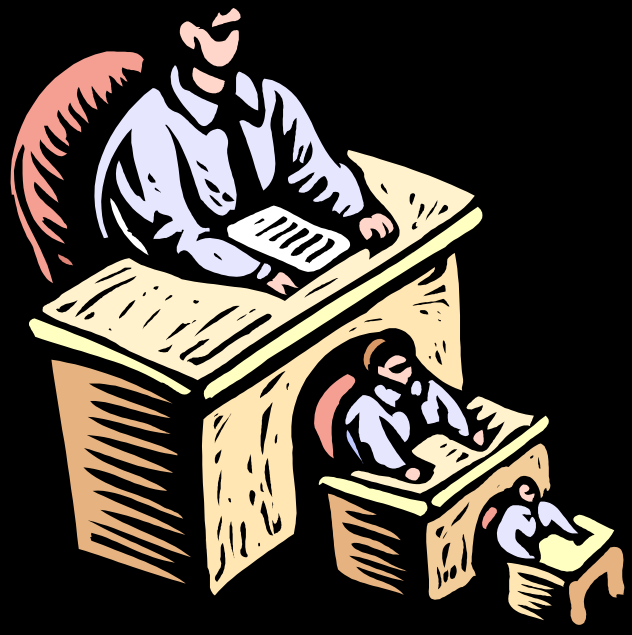
Scorecards we've developed to evaluate medical media. Does the story…

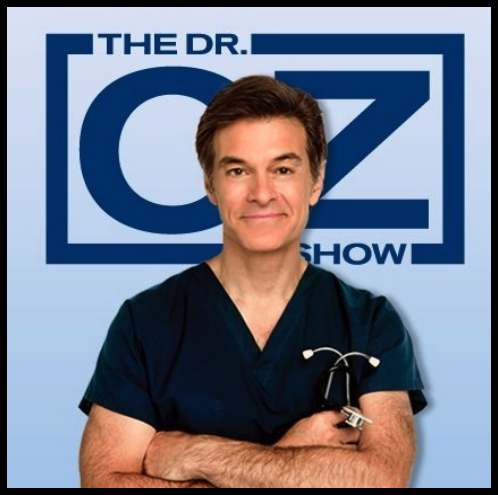
- Adequately discuss costs?
- Quantify potential benefits?
- Quantify potential harms?
- Evaluate quality of the evidence?
- Avoid disease-mongering?
- Establish true novelty of the idea?
- Establish true availability of the idea?
- Use independent sources & identify COI?
- Compare the new idea with existing options?
- Appear to rely on a news release?

media doctor canada

How does a newsroom work? Newsroom Hierarchy

- Managing editor
  - City editor
    - Assignment editor
      - Beat Reporter
        - General Reporter





Ever wonder if the recommendations from these shows are evidence-based?

WE DID

Televised medical talk shows— what they recommend and the evidence to support their recommendations: a prospective observational study

Korownyk C, Kolber MR, McCormack J, Lam V, Overbo K, Cotton C, Finley C, Turgeon RD, Garrison S, Lindblad AJ, Banh HL, Campbell-Scherer D, Vandermeer B, Allan GM

Brit Med J 2014;349:g7346 doi: 10.1136/bmj.g7346 (Published 17 December 2014)

CHRISTMAS 2014: MEDIA STUDIES

Televised medical talk shows—what they recommend and the evidence to support their recommendations: a prospective observational study

	No (%) of recommendations	
	The Dr Oz Show **(n=479)**	*The Doctors* **(n=445)**
Benefit of recommendation mentioned	453 (94.6)	402 (90.3)
Benefit was specific	204 (42.6)	184 (41.3)
Magnitude of benefit mentioned	79 (16.5)	49 (11.0)
Possible harms mentioned	47 (9.8)	34 (7.6)
Cost mentioned	60 (12.5)	14 (3.1)
Potential conflict of interest declared or mentioned	1 time	3 times

BMJ 2014;349:g7346

“Believable” Evidence for Recommendations

The Dr Oz Show

evidence supported 46%

contradicted 15%

not found for 39%

believable or somewhat believable evidence 33%

The Doctors

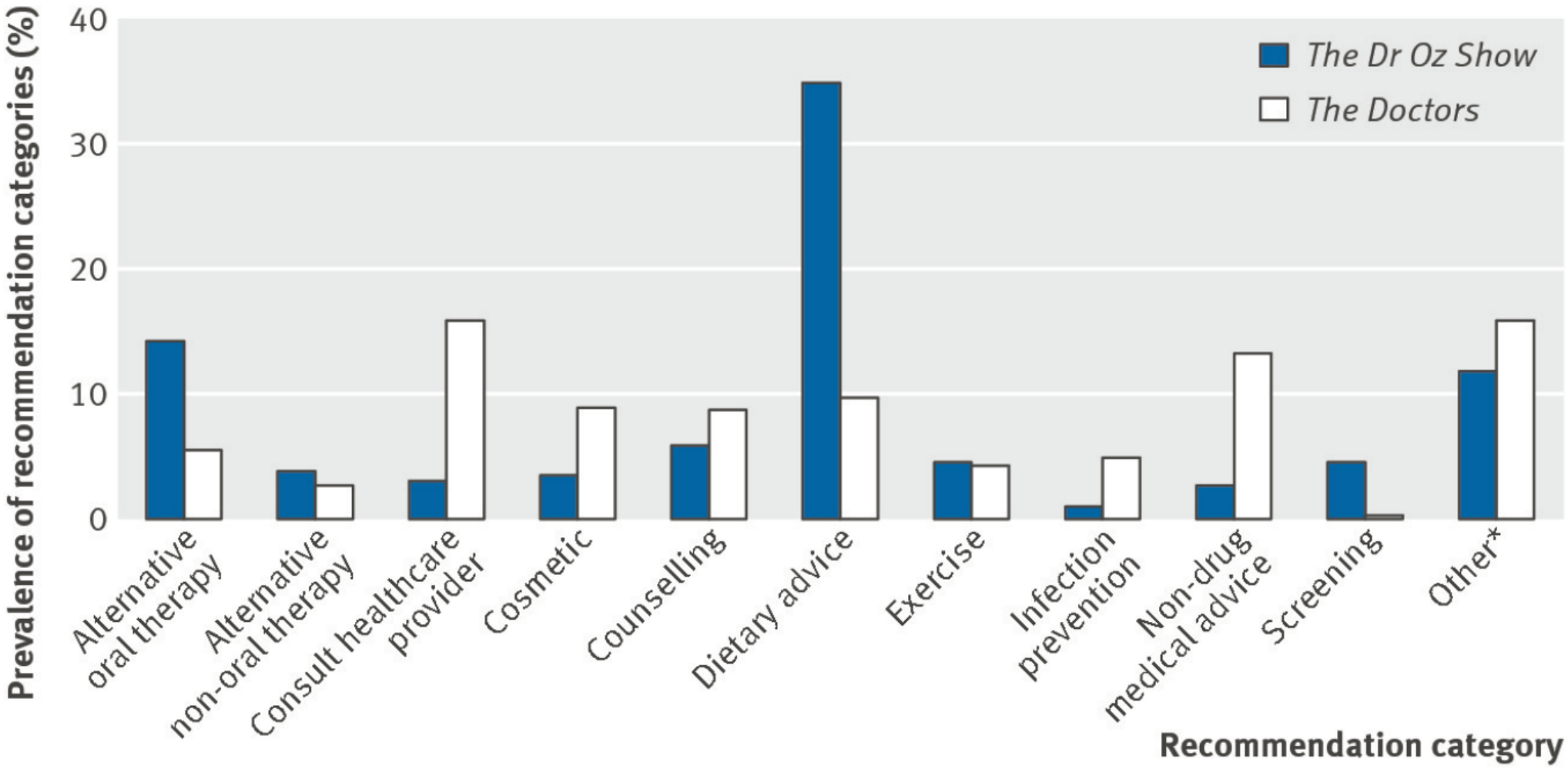
evidence supported 63%

contradicted 14%

not found for 24%

believable or somewhat believable evidence supported 53%

BMJ 2014;349:g7346



* Other includes recommendations pertaining to: medications, drugs of abuse, dental care, diagnosis, lifestyle, motherhood statements, physiotherapy, sex related topics, tests, vitamins and vaccines

BMJ 2014;349:g7346

And then the letters came in…

- In February 2015, in response to a request from The Dr. Oz Show, we provided the show's producer with the recommendations and the clinical questions created from our review.
- With this data they had enough information to perform their own systematic evidence review of the shows' recommendations.
- "As per standard protocols in the sharing of research data, we would trust that only your office would use this information and it may not be disseminated further without our permission."
- The show then shared our data (without permission) with "4 trusted professionals".
- We contacted The Dr Oz show and they wrote to us saying these individuals included Dr. Steven Woolf, Dr. Adrian Hernandez Diaz, Dr. Cornelius Dyke and Dr. William Li
- All four of these "trusted professionals" proceeded to publish critiques of our research in the BMJ electronic letters section; and some of them actually included some of our research data in their response.
- At the time of our original submission of this response, (May 19), none of these "trusted professionals" declared their association with The Dr. Oz Show as a potential conflict of interest nor that they attained our data from The Dr. Oz Show.

BMJ Open

Representations of the health value of vitamin D supplementation in newspapers: media content analysis

Timothy Caulfield,[1] Marianne I Clark,[1] James P McCormack,[2] Christen Rachul,[3] Catherine J Field[4]

Reviewed Canada, US and UK newspapers for 5 years

294 articles

80% suggested supplementation is or may be necessary for the general population

almost none discussed the potential harms of vitamin D supplementation in any detail

BMJ Open 2014;4: e006395. doi:10.1136/ bmjopen-2014-006395

Articles stated supplementation may be beneficial or is necessary

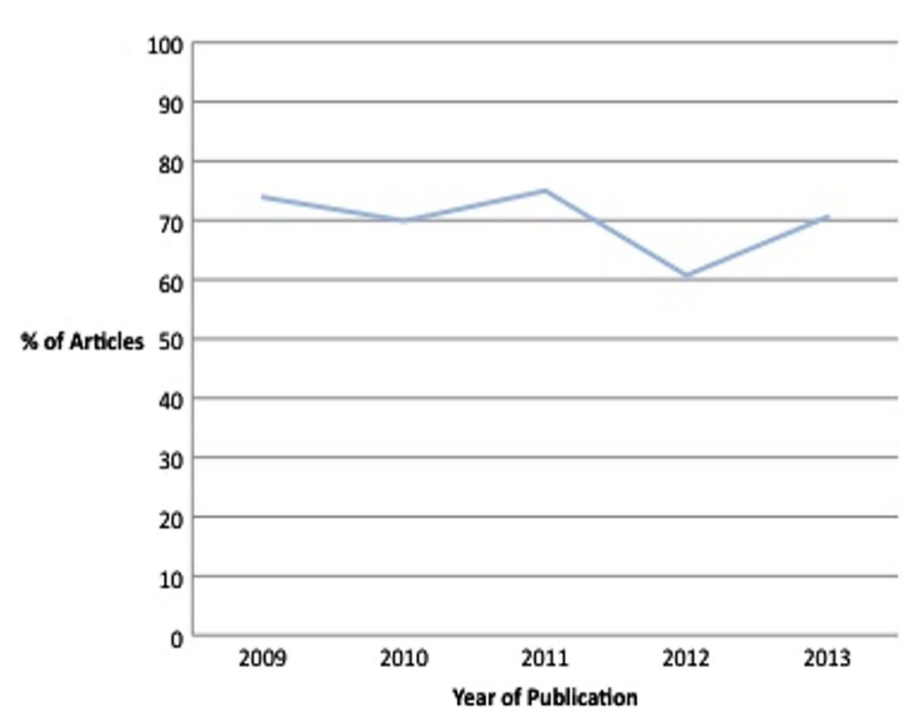


Figure 2 Percentage of articles that utilised one or both of the frames 'supplementation may be beneficial' and/or 'supplementation is necessary' by year.

Articles interpreted research as endorsement of supplementation

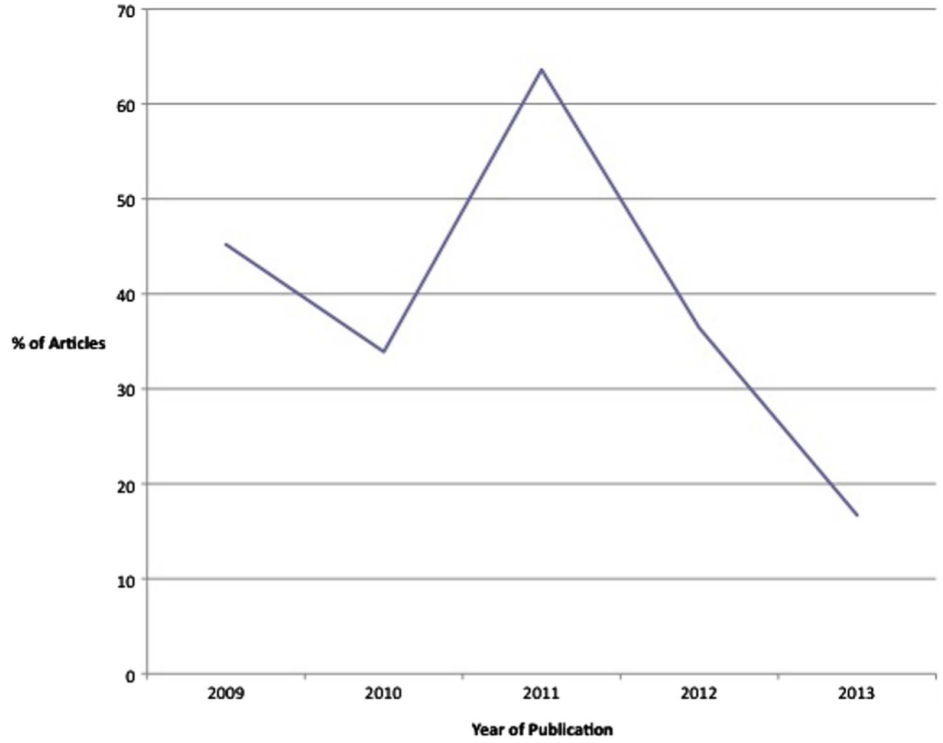


Figure 3 Percentage of articles citing research about vitamin D that interpreted research as endorsement of supplementation by year.

What to do when journalists call?

Answer the phone

Find out their deadline

Find out what the story is about

If you can’t talk to them refer them to someone competent

If you like the piece that is published let them know

Bottom line: Don’t curse the media, become the media

Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data

James McCormack, Trisha Greenhalgh

BMJ 2000;320:1720–3

Summary points

Randomised trials are subject to interpretation bias as shown by the example of the UK prospective diabetes study

The UK prospective diabetes study shows no ben
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study as providing evidence of the benefit of intensive glucose control

Journal editors should be aware of this important potential bias and encourage authors to present their results initially with a minimum of discussion so as to invite a range of comments and perspectives from readers

Table 1 Effect of 10 years' treatment with chlorpropamide, glibenclamide, or insulin on patients with newly diagnosed type 2 diabetes

	Any diabetes related end points* (%)	Microvascular disease (%)	Individual macrovascular disease end points†	Median haemoglobin A_{1c} (%)
Dietary advice plus chlorpropamide, glibenclamide, or insulin	35.3	8.2		Chlorpropamide 6.7; glibenclamide 7.2; insulin 7.1

wer for all drugs compared with

with newly diagnosed type 2

						rovascular ease (%)	Median haemoglobin A_{1c} (%)
						7.0	7.4
Dietary advice plus chlorpropamide, glibenclamide, or insulin	36.8	10.8	20.0	14.6	6.3	7.8	All similar to metformin
Dietary advice only	38.9	13.4	21.7	17.8	5.6	9.2	8.0
Relative risk reduction (metformin *v* dietary advice)	26.2	38.8	32.7	36.0	44.4§	NS	
Absolute risk reduction (metformin *v* dietary advice)	10.2	5.2	7.1	6.4	2.8§	NS	Significantly lower for all drugs compared with dietary advice
No needed to treat for 10 years to prevent one event (metformin *v* dietary advice)	10	19	14	16	36§	NS	

Nevertheless, many authors, journal editors, and the wider scientific community interpreted the study as providing evidence of the benefit of intensive glucose control

"We believe that these cases illustrate the principle that interpretations of clinical trial results are often neither objective nor value-free. Rather, researchers, authors, and editors are highly susceptible to interpretive biases, including:

"We've shown something here" bias

"The result we've all been waiting for" bias

"Just keep taking the tablets" bias

"What the hell can we tell the public?" bias

"If enough people say it, it becomes true" bias

Ignore Most Associations?

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Med: 2005

"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."

What can we study?

Implausible results in human nutrition research

Definitive solutions won't come from another million observational papers or small randomized trials

John P A Ioannidis *professor of medicine, health research and policy, and statistics*

Stanford Prevention Research Center, Stanford, CA 94305, USA

BMJ 2013;347:f6698

Objectively speaking, we can't get definitive answers from more studies because they all have important biases, there are numerous confounders and evaluating surrogate markers is fraught with problems

Single Nutrients

"on the basis of dozens of randomized trials, single nutrients are unlikely to have relative risks less than 0.90 for major clinical outcomes …"

"… most are greater than 0.95"

In other words,if differences exist they are

<10% and may be <5%

"Observational studies and even randomized trials of single nutrients

seem hopeless,

with rare exceptions"

BMJ 2013;347:f6698

Multiple Nutrients and Behaviours

"Larger effect sizes [ie. >10%] are more plausible for complex dietary patterns that sum the effects of multiple nutrients and behaviors"
PREDIMED, Lyon Diet Heart Study

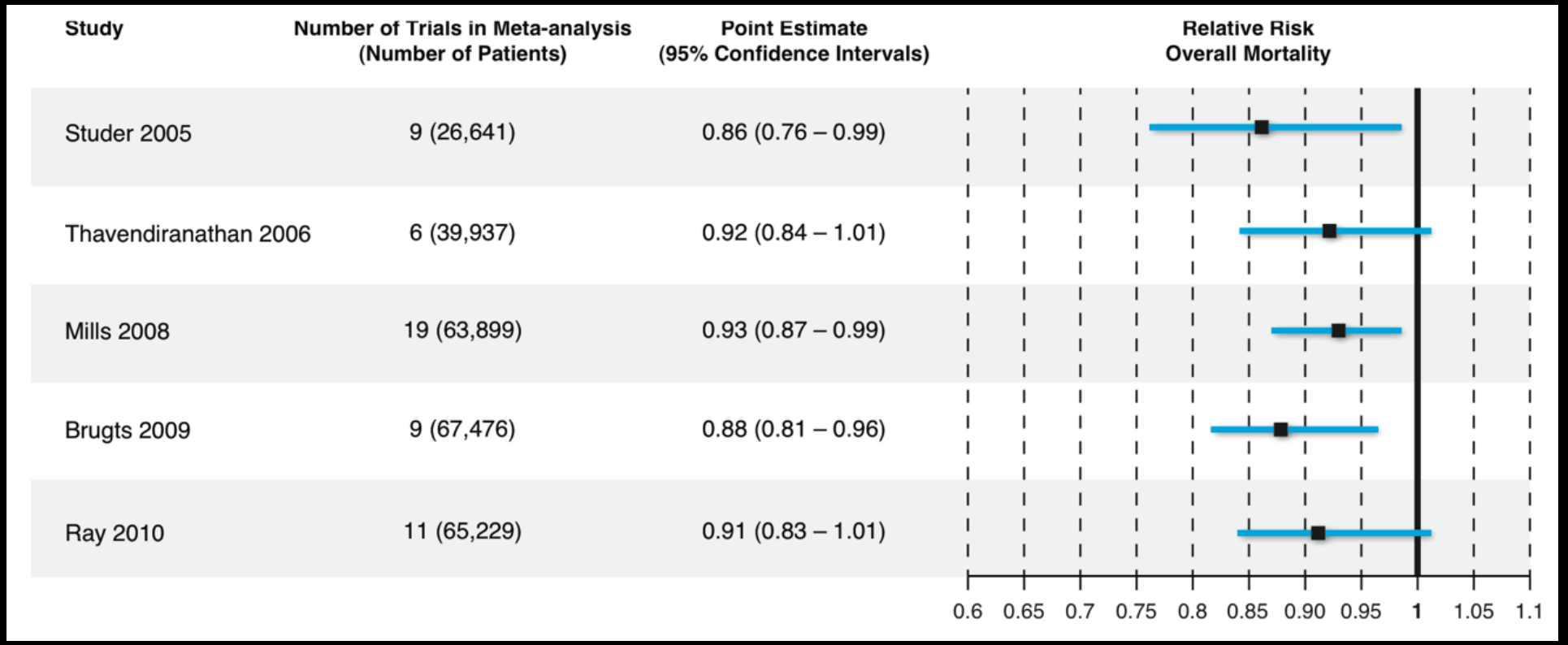
Now, it is possible to *"identify nutrition related interventions that produce a 5-10% relative risk reduction in overall mortality in the general population"*

However, this would require
>10 times the sample size of PREDIMED
(n = 80,000 and 4,000 endpoints)

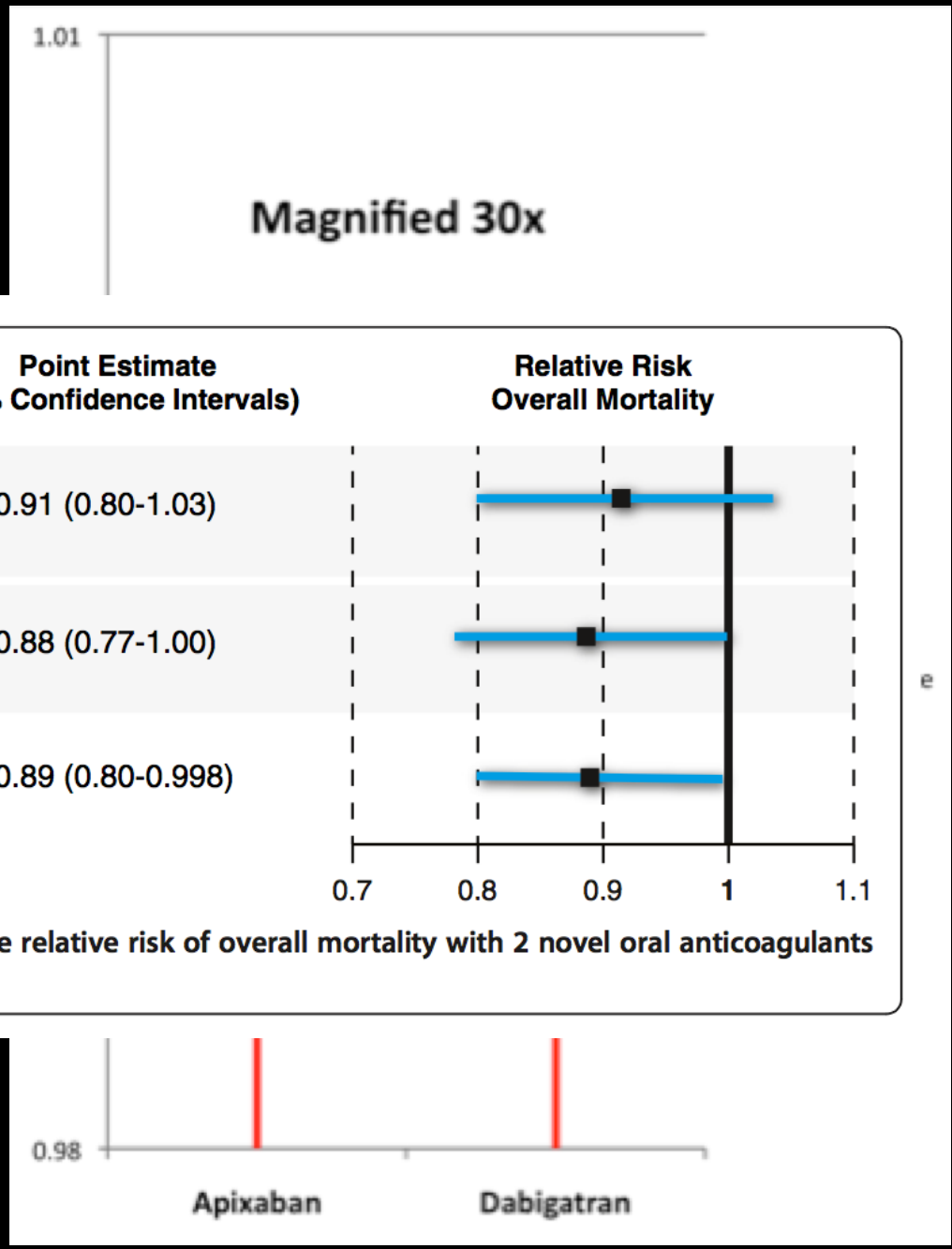
BMJ 2013;347:f6698

Ignore Many Conclusions?

Comparison of 5 meta-analyses examining relative risk of overall mortality with statin use in primary prevention



Novel Anti-Coagulants



Study	Medication	Point Estimate (95% Confidence Intervals)	Relative Risk Overall Mortality
Connolly 2009	110 mg dabigatran	0.91 (0.80-1.03)	
	150 mg dabigatran	0.88 (0.77-1.00)	
Granger 2011	Apixaban	0.89 (0.80-0.998)	

Figure 2 Comparison of 2 randomized controlled trials examining the relative risk of overall mortality with 2 novel oral anticoagulants versus warfarin in atrial fibrillation.

http://www.theheart.org/article/1268723.do, Dabigatran (150mg): N Engl J Med 2009;361:1139-51. Apixaban: N Engl J Med. 2011;365(11):981-92

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

Diabetes Care

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

January 2015 Volume 38, Supplement 1

Standards of Medical Care in Diabetes—2015

Diabetes Care January 2015

113 PAGES

Risk estimation

no mention or discussion of the magnitude, in relative or absolute terms, of any adverse clinical endpoints associated with elevated glucose

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Diabetes Care January 2015

Impact of treatment

no mention of the magnitude with regards to retinopathy/ kidney disease/neuropathies

CVD - “16% reduction in events” and “reductions in MI” (15% sulfony/insulin, 33% met) and “in all-cause mortality (13% and 27%, respectively) from the UKPDS/ 10 year follow-up

“every HbA1c reduction of 1% may be associated with a 15% relative risk reduction in nonfatal myocardial infarction, but without benefits on stroke or all-cause mortality” and a 9% “reduction in major CVD outcomes”

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Diabetes Care January 2015

Potential Harms

12 classes of medications mentioned

~50 disadvantages/harms are listed in tables

nowhere in the tables, and only twice in the documents, are absolute numbers for side effects provided (SGLT2 inhibitors/mycotic infections and DPP-4/heart failure)

RICE - coined in 1978

"Coaches have used my "RICE" guideline for decades, but now it appears that both Ice and complete Rest may delay healing, instead of helping." – Gabe Mirkin, MD, March 2014

M - Move safely when you can as much as you can

C - Compress

E - Elevate

Questioning Ice/Cryotherapy

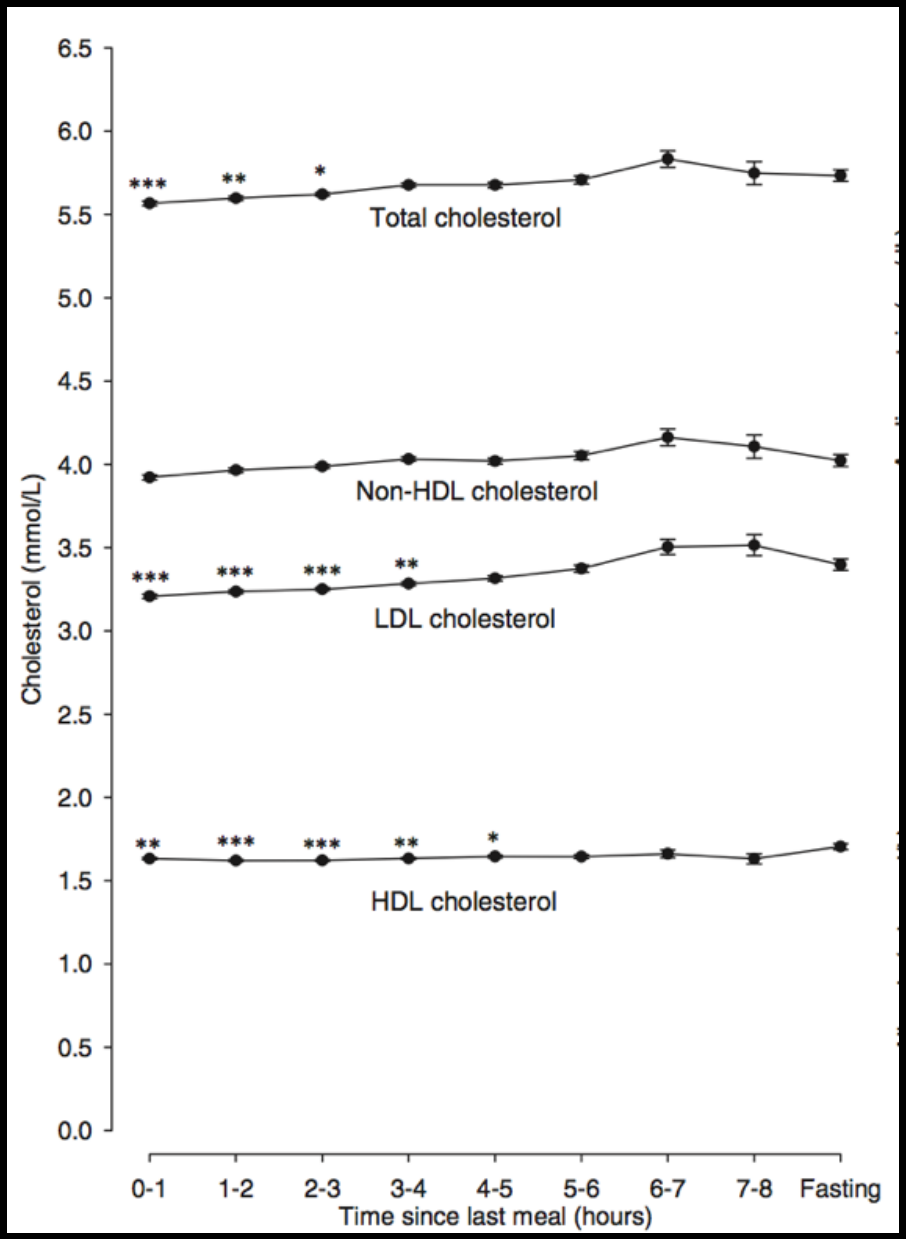
J Strength Con Res 2013;27:1354-61

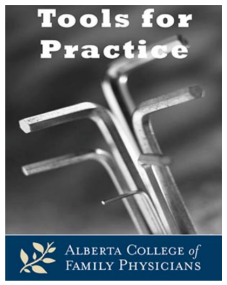
Am J Sport Med 2004;32:251-61

Sports Med 2012;42:69-87

J App Phys 2011;110:382-8

J Athl Train 2012;47:435-4





Can I get my cholesterol checked fast (without fasting)?

Clinical Question: Can non-fasting lipid levels be used to predict future cardiovascular disease (CVD) risk?

Non-fasting and fasting HDL and non-HDL cholesterol similarly predicted CVD risk

Circ 2008;118:2047-56

Ignore Most
New Things?

New and improved

vs

Unsafe/withdrawn

The last decade (2000s)

Drugs considered to provide substantial improvements (PMPRB)

19

Drugs removed from the market (FDA etc)

Xigris - for severe sepsis

23

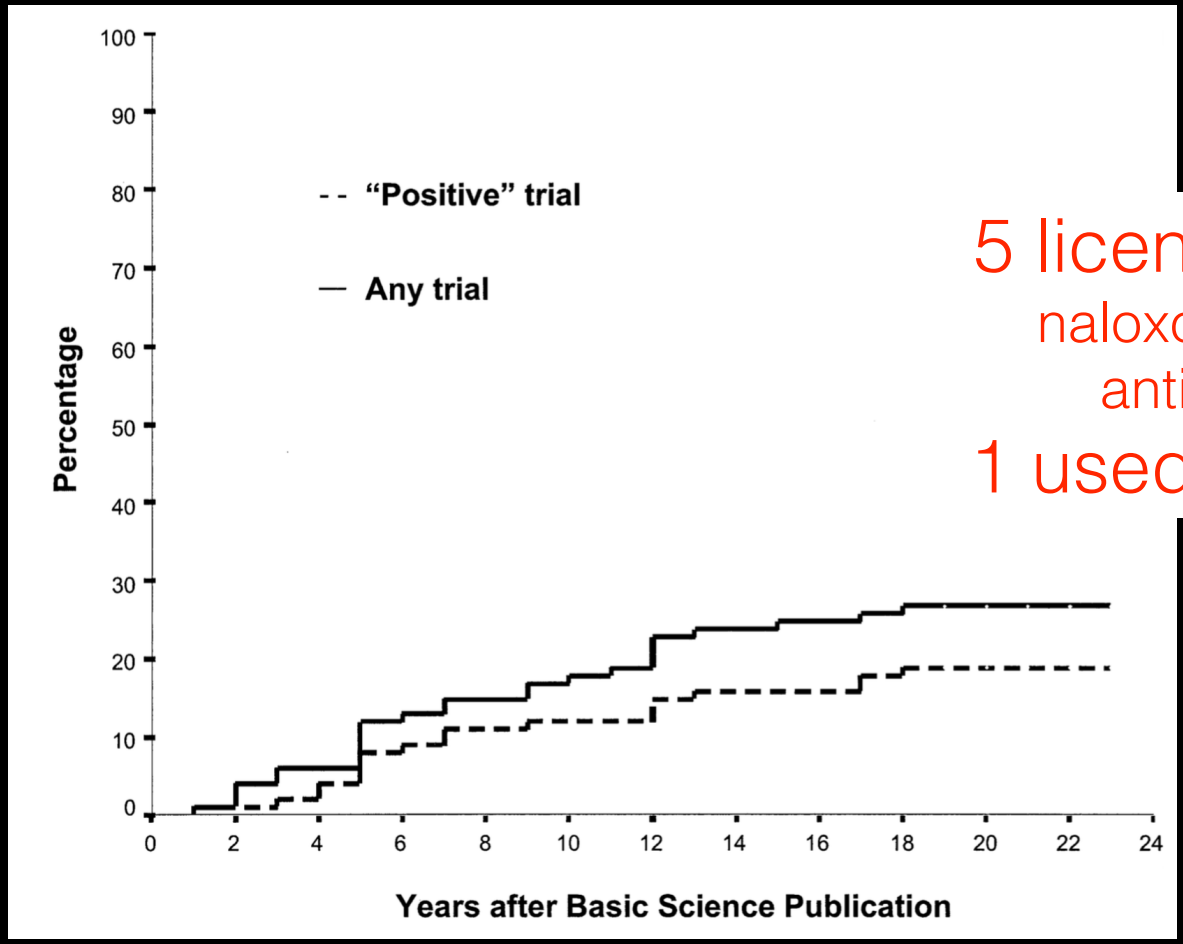
Became one of these

Golden Pill Award

PRESCRIRE AWARDS

	Major therapeutic advance	Clear advantage	Modest improvement
2011	0	0	0
2012	0	0	2 abiraterone (prostate CA) boceprevir (Hep C)
2013	0	0	1 meningococcal conjugate vaccine (infant immunization)
2014	1 cholic acid (hereditary bile acid deficiency)	3 imatinib (ALL) artesunate (malaria) sofosbuvir (HepC)	1 sodium phenylbutyrate coated granules (urea cycle disorders)

101 articles, published between 1979 and 1983 in six major basic science journals, which clearly stated that the technology studied had novel therapeutic or preventive promises



5 licensed for clinical use

naloxone, pergolide, alpha-1 antitrypsin, interleukin 2

1 used extensively - ACEI

Am J Med 2003; 114:477-84

We Are All Individuals

Every patient is an “n of 1” study
Every treatment is an experiment

Dealing with the guaranteed uncertainty

- remember it isn't you taking the medication
- approach each treatment with healthy skepticism
- ask if I do nothing what will happen and if I treat what will happen
- where possible, engage the patient in the decision making process
- an immediate response is rarely required but…
- start with either very low doses or pretty big doses
- rarely, if ever, use new therapies
- re-evaluate on regular basis