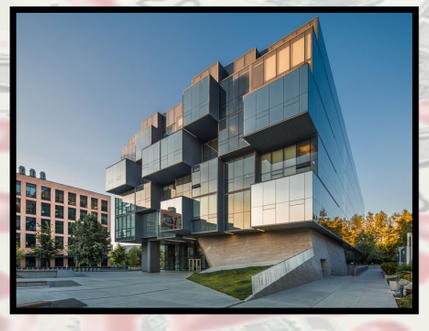
WHEN IT COMES TO EVIDENCE-BASED PRACTICE

James McCormack
BSc (Pharm), PharmD
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

TO GET A HANDOUT GO HERE
http://therapeuticseducation.org/handouts

peerevidence.ca
therapeuticseducation.org

Financial Conflicts of Interest

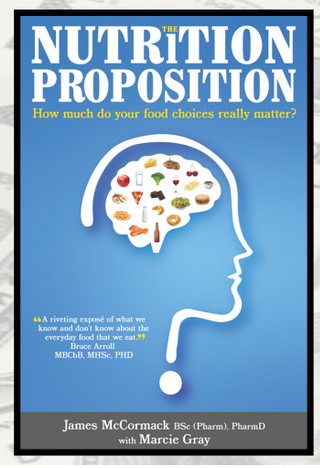


- ☑ Entire salary comes through the UBC Faculty of Pharmaceutical Sciences - also some legal/ educational work

- ☑ I have received no honorarium or research money from the drug industry in the last 30 or so years

- ☑ Premium podcast subscription Best Science (BS) Medicine podcast - therapeuticseducation.org

- ☑ I have a self-published book called “The Nutrition Proposition”



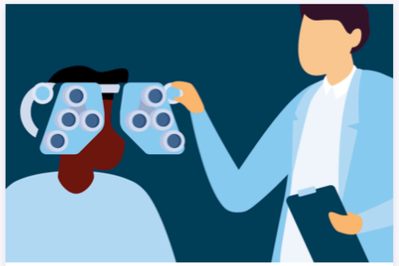
Tools For Practice

#352 Do-It-Yourself Hearing Aids

Read
0.25 Credits Available

#351 Flaked out? Topical treatment for seborrheic dermatitis

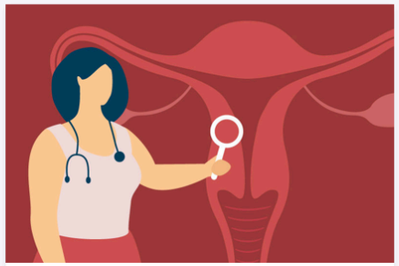
Read
0.25 Credits Available



#350 Not a Dry Eye in the House – Looking into Artificial Tears

Read
0.25 Credits Available

#349 An ASA a day when a baby's on the way?



#348 How to Slow the Flow III: Tranexamic acid for heavy menstrual bleeding

#347 Chlorthali-D'OH!: What is the best thiazide diuretic for hypertension?

Since 2009

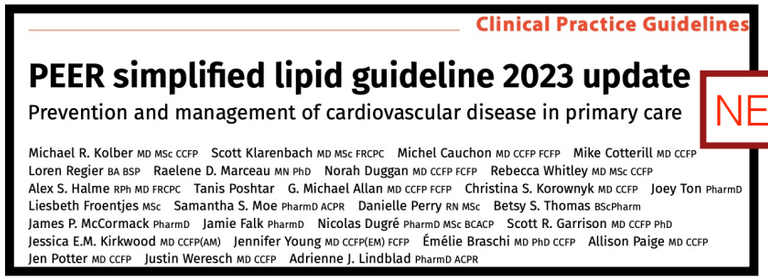
300 word primary-care synopses of the best available evidence

~350 to-date

https://cfpclearn.ca/tools-for-practice-library/

GUIDELINE PRINCIPLES

- No financial conflicts of interest
- Primarily written by primary care clinicians
- Thorough systematic review of the evidence by PEER using the GRADE framework
- Guideline Committee uses the review of evidence to create the guideline
- We focus on shared-decision making
- We have discussion thresholds, NOT treatment thresholds
- Always provide decision aids/calculators that give the benefit/harm numbers in absolute terms and always provide patient information sheets

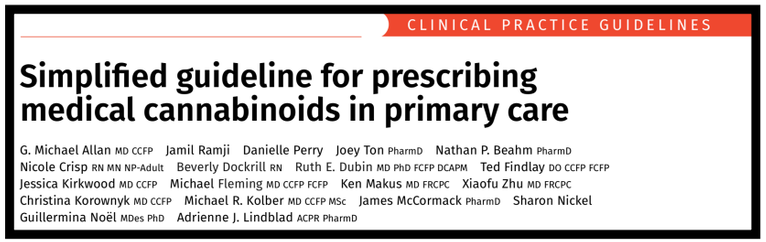

Clinical Practice Guidelines

PEER simplified lipid guideline 2023 update

Prevention and management of cardiovascular disease in primary care

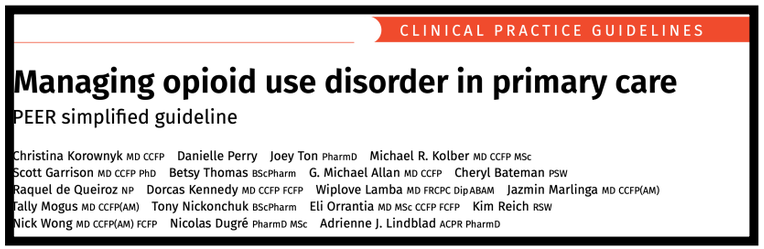
NEW

Michael R. Kolber MD MSc CCFP Scott Klarenbach MD MSc FRCPC Michel Cauchon MD CCFP FCFP Mike Cotterill MD CCFP
Loren Regier BA BSP Raelene D. Marceau MN PhD Norah Duggan MD CCFP FCFP Rebecca Whitley MD MSc CCFP
Alex S. Halme RPh MD FRCPC Tanis Poshtar G. Michael Allan MD CCFP FCFP Christina S. Korownyk MD CCFP Joey Ton PharmD
Liesbeth Froentjes MSc Samantha S. Moe PharmD ACPR Danielle Perry RN MSc Betsy S. Thomas BScPharm
James P. McCormack PharmD Jamie Falk PharmD Nicolas Dugré PharmD MSc BCACP Scott R. Garrison MD CCFP PhD
Jessica E.M. Kirkwood MD CCFP(AM) Jennifer Young MD CCFP(EM) FCFP Émélie Braschi MD PhD CCFP Allison Paige MD CCFP
Jen Potter MD CCFP Justin Weresch MD CCFP Adrienne J. Lindblad PharmD ACPR


CLINICAL PRACTICE GUIDELINES

Simplified guideline for prescribing medical cannabinoids in primary care

G. Michael Allan MD CCFP Jamil Ramji Danielle Perry Joey Ton PharmD Nathan P. Beahm PharmD
Nicole Crisp RN MN NP-Adult Beverly Dockrill RN Ruth E. Dubin MD PhD FCFP DCAPM Ted Findlay DO CCFP FCFP
Jessica Kirkwood MD CCFP Michael Fleming MD CCFP FCFP Ken Makus MD FRCPC Xiaofu Zhu MD FRCPC
Christina Korownyk MD CCFP Michael R. Kolber MD CCFP MSc James McCormack PharmD Sharon Nickel
Guillermina Noël MDes PhD Adrienne J. Lindblad ACPR PharmD


CLINICAL PRACTICE GUIDELINES

Managing opioid use disorder in primary care

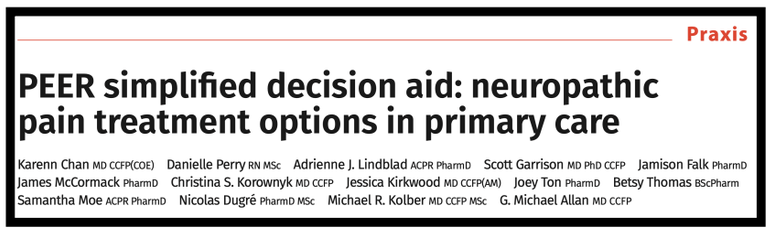
PEER simplified guideline

Christina Korownyk MD CCFP Danielle Perry Joey Ton PharmD Michael R. Kolber MD CCFP MSc
Scott Garrison MD CCFP PhD Betsy Thomas BScPharm G. Michael Allan MD CCFP Cheryl Bateman PSW
Raquel de Queiroz NP Dorcas Kennedy MD CCFP FCFP Wiplove Lamba MD FRCPC DipABAM Jazmin Marlinga MD CCFP(AM)
Tally Mogus MD CCFP(AM) Tony Nickonchuk BScPharm Eli Orrantia MD MSc CCFP FCFP Kim Reich RSW
Nick Wong MD CCFP(AM) FCFP Nicolas Dugré PharmD MSc Adrienne J. Lindblad ACPR PharmD


Praxis

PEER simplified decision aid: chronic back pain treatment options in primary care

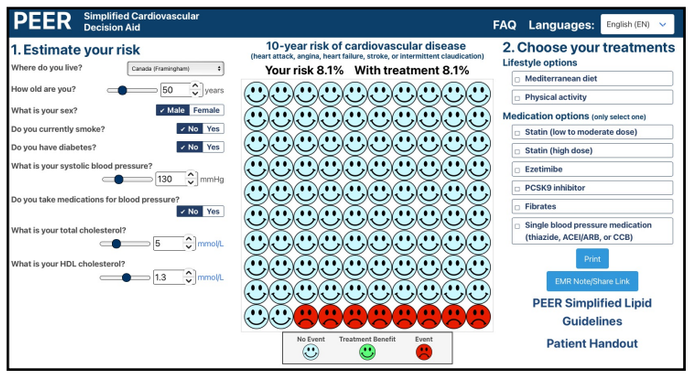
Jessica Kirkwood MD CCFP(AM) G. Michael Allan MD CCFP Christina S. Korownyk MD CCFP James McCormack PharmD
Scott Garrison MD PhD CCFP Betsy Thomas BScPharm Joey Ton PharmD Danielle Perry RN Michael R. Kolber MD CCFP MSc
Nicolas Dugré PharmD MSc Samantha Moe PharmD Adrienne J. Lindblad ACPR PharmD


Praxis

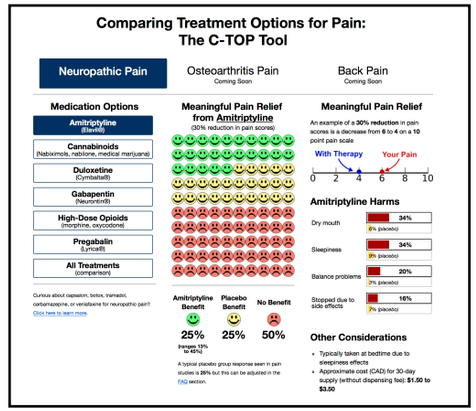
PEER simplified decision aid: neuropathic pain treatment options in primary care

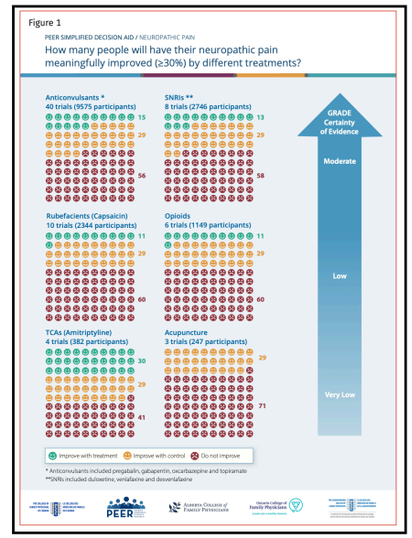
Karenn Chan MD CCFP(COE) Danielle Perry RN MSc Adrienne J. Lindblad ACPR PharmD Scott Garrison MD PhD CCFP Jamison Falk PharmD
James McCormack PharmD Christina S. Korownyk MD CCFP Jessica Kirkwood MD CCFP(AM) Joey Ton PharmD Betsy Thomas BScPharm
Samantha Moe ACPR PharmD Nicolas Dugré PharmD MSc Michael R. Kolber MD CCFP MSc G. Michael Allan MD CCFP

Published in Canadian Family Physician

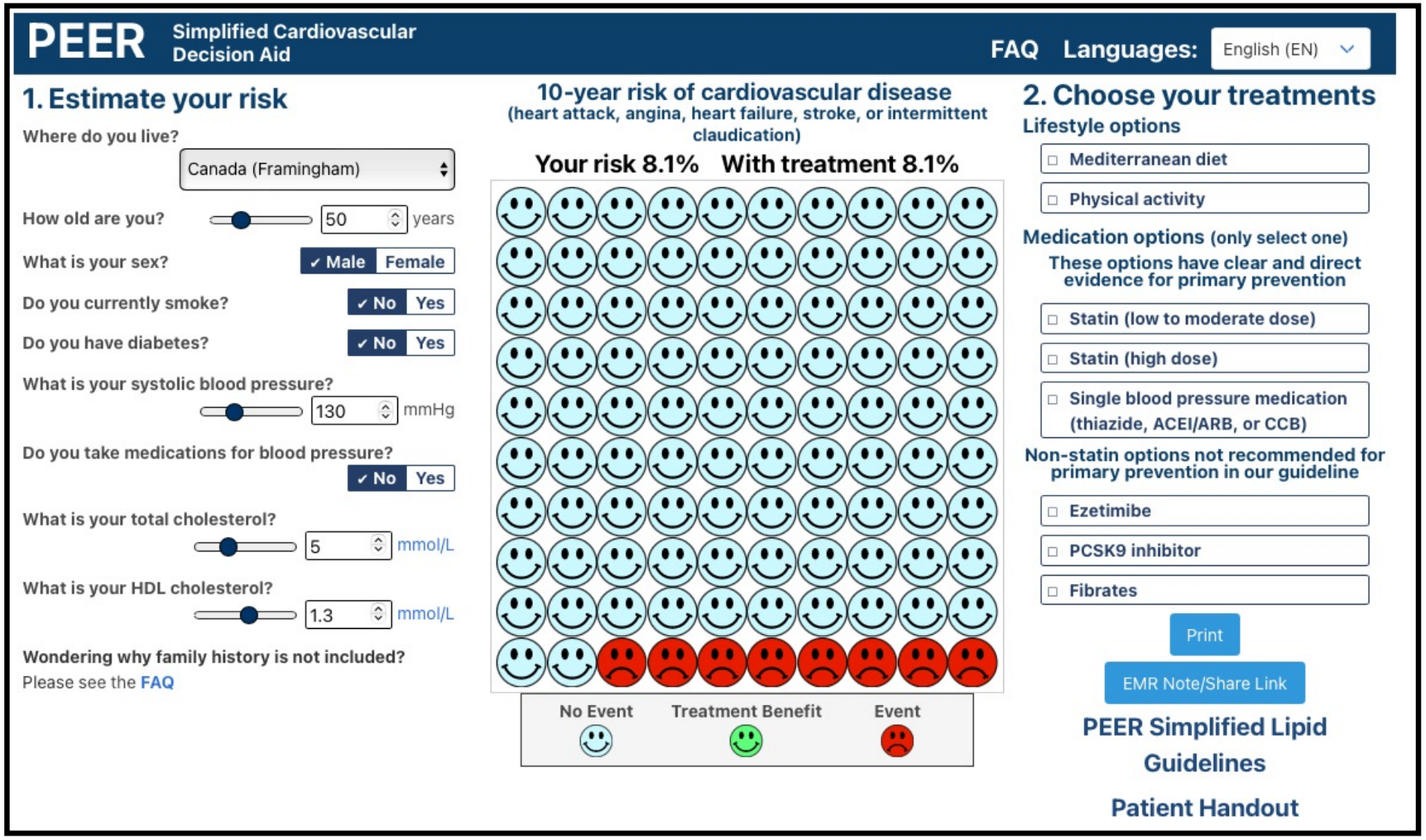


https://decisionaid.ca/cvd/



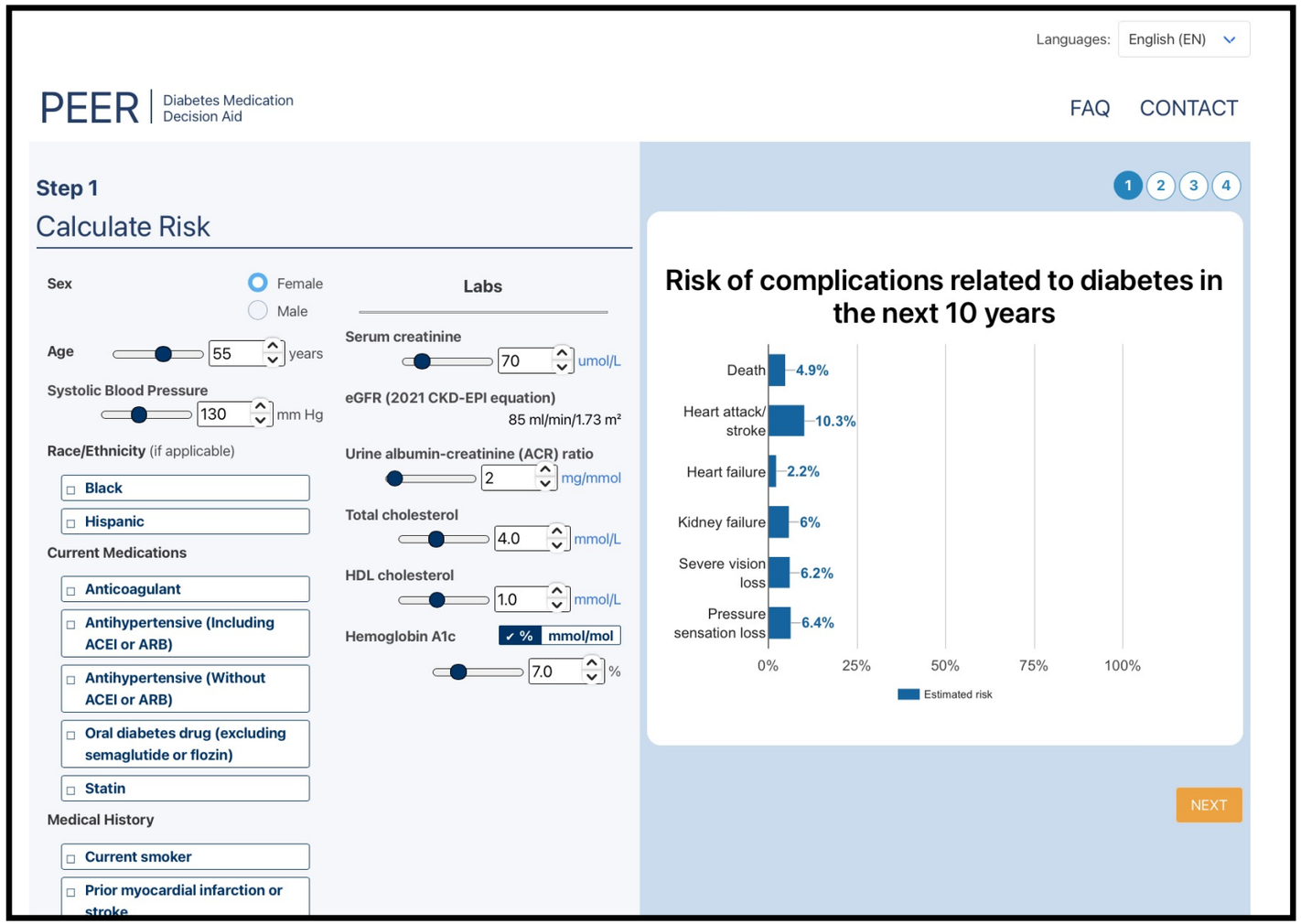


CVD decision aid



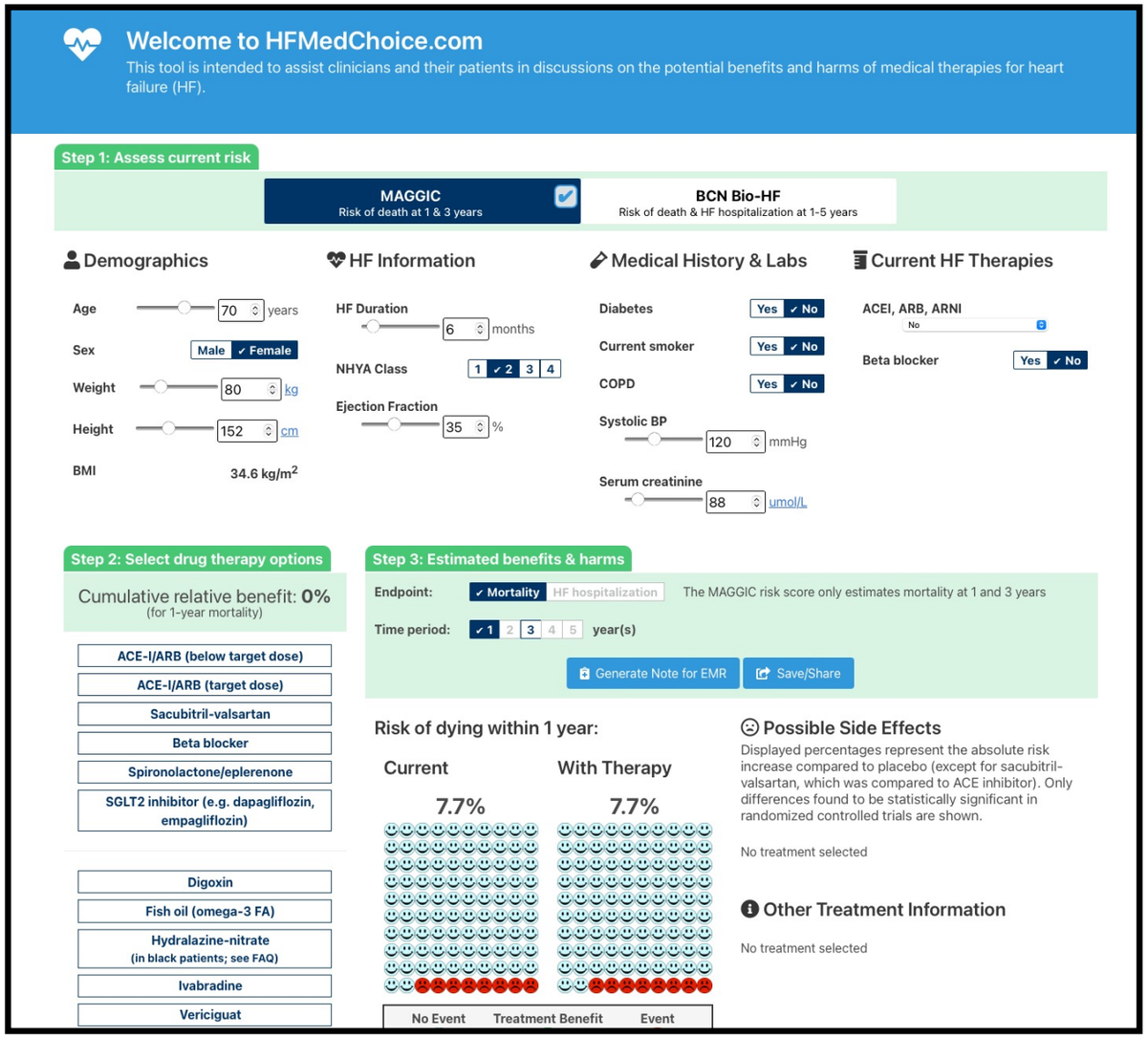
https://decisionaid.ca/cvd/

Diabetes



https://decisionaid.ca/diabetes/

Heart Failure



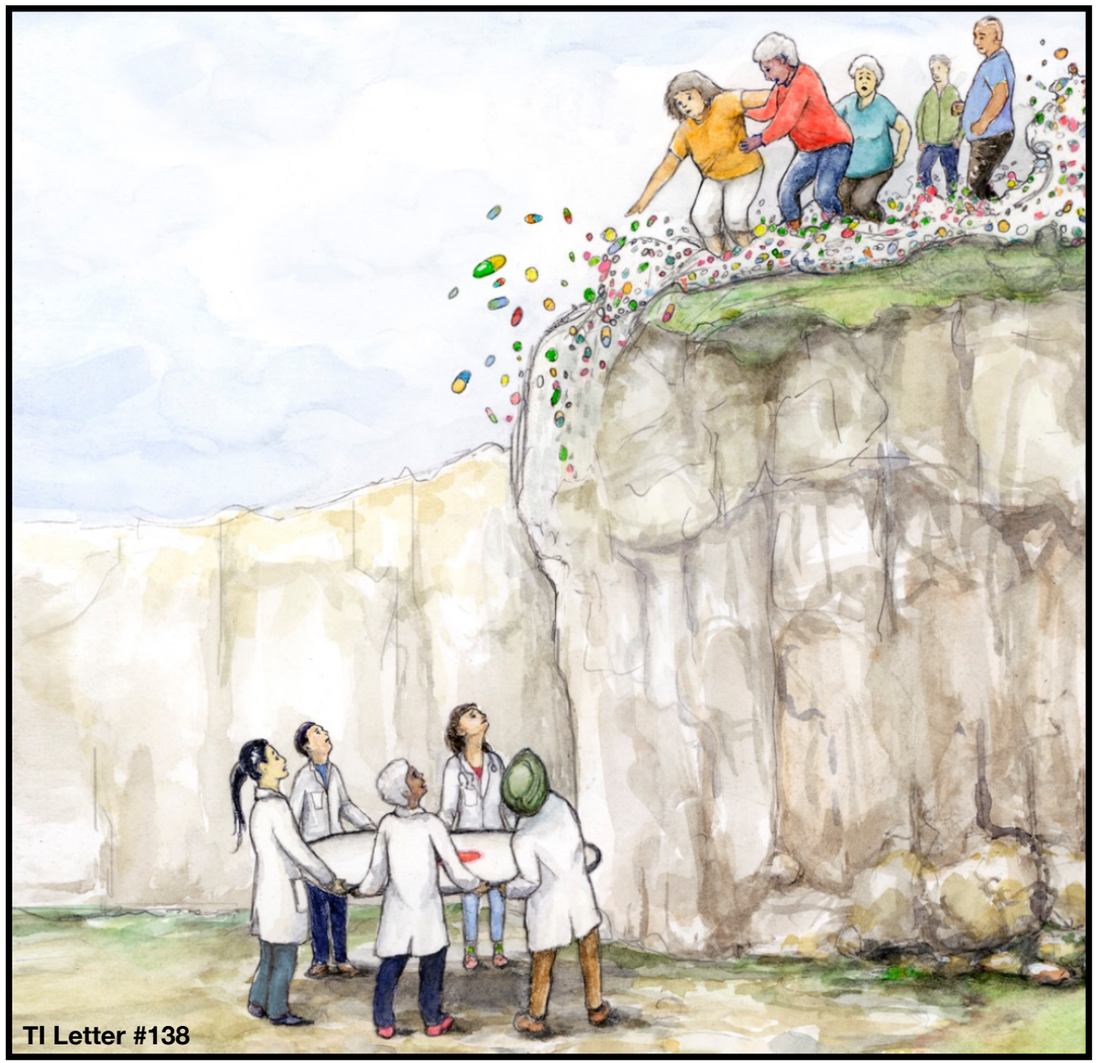
https://hfmedchoice.com

My Simple Philosophy on Treatments

These sorts of terms are uniformly uninformative - allopathic, conventional, mainstream, Western medicine, complementary, alternative, integrative, naturopathy, Chinese medicine, homeopathy, herbal

We all treat people with “things” - oral/IV/IM/topical, nutrition, surgery, talk, physical manipulations etc

I don’t care HOW treatments work, I care IF treatments work



The proportion of people over 65 taking prescription medications

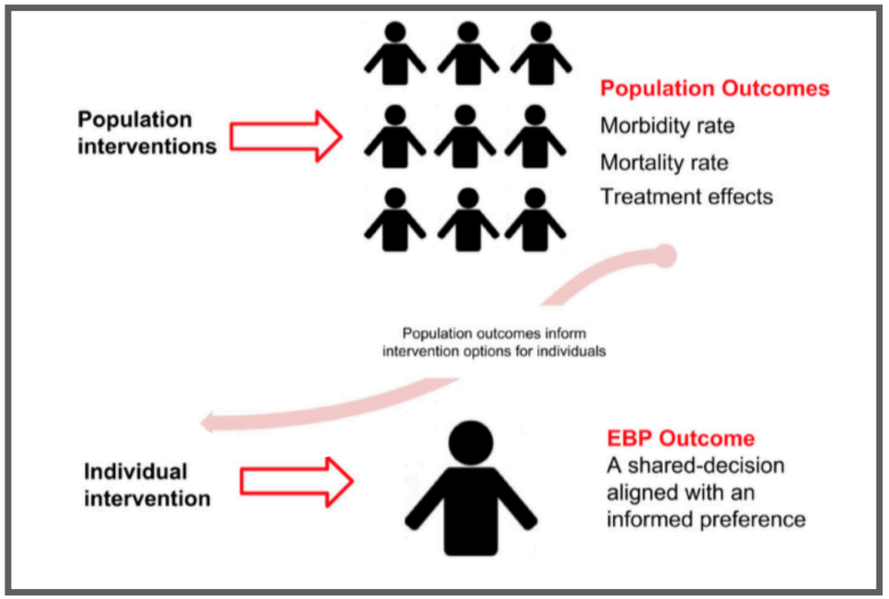
EBM analysis

OPEN ACCESS

Shared decision is the only outcome that matters when it comes to evaluating evidence-based practice

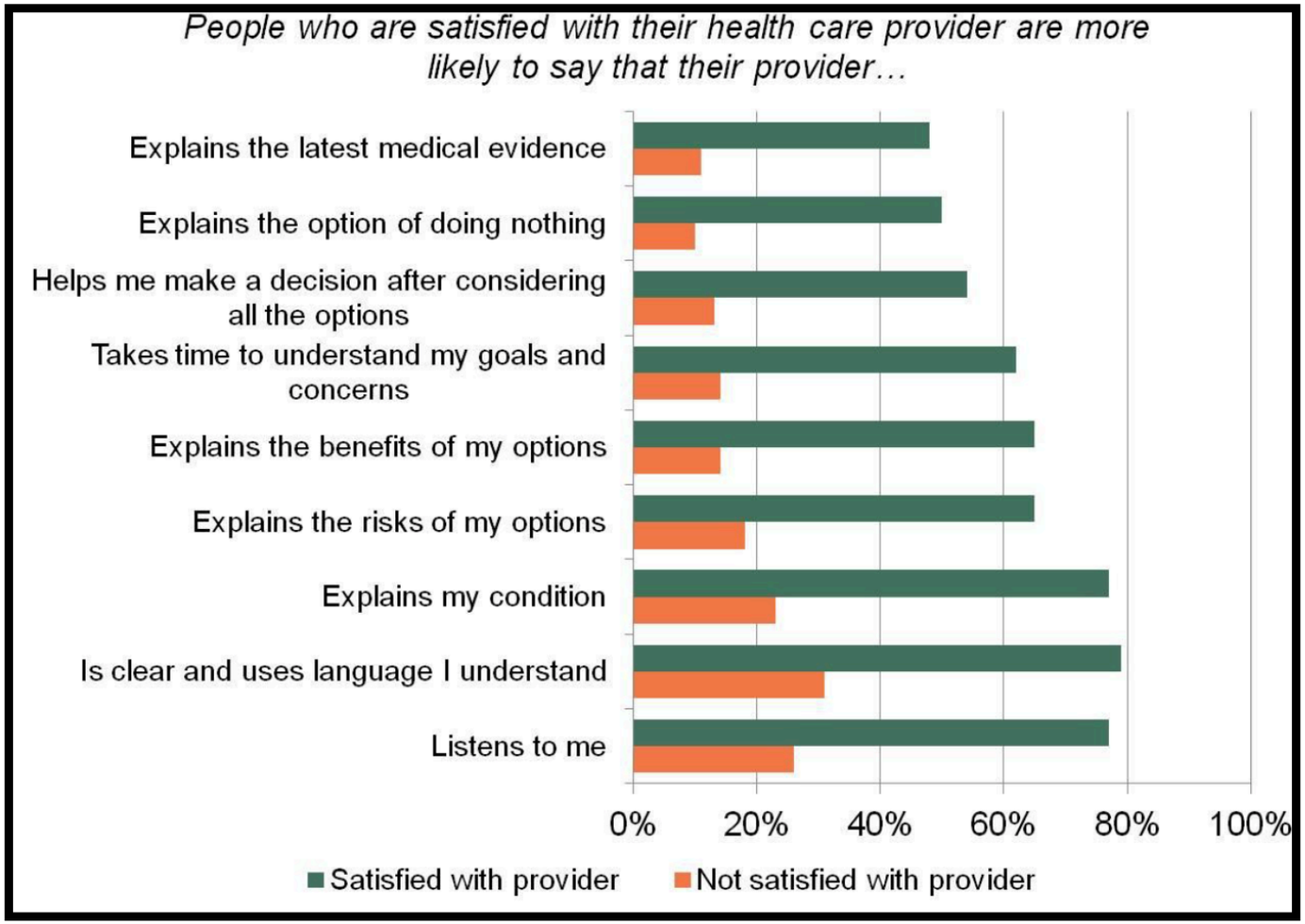
James McCormack,[1] Glyn Elwyn[2]

"in the vast majority of circumstances, the only outcome of relevance for EBP is to measure whether a shared decision was made"



doi:10.1136/ bmjebm-2018-110922

Satisfaction is linked to shared decisions



Communicating with patients on health care evidence.
Discussion Paper, Institute of Medicine, Washington, DC 2012

Where SDM may not work

EBM analysis

OPEN ACCESS

Shared decision is the only outcome that matters when it comes to evaluating evidence-based practice

James McCormack,[1] Glyn Elwyn[2] 2018

In most societies there are laws that prevent certain harm from occurring, where mental incapacity or strong personal beliefs may threaten the well-being of others

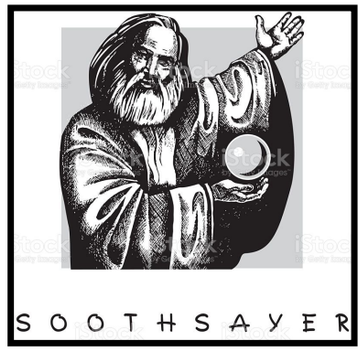
1. Jehovah Witness' refusal to transfuse blood to those in dire need

2. involuntary detention for psychiatrically unstable patients who risk harming themselves or others

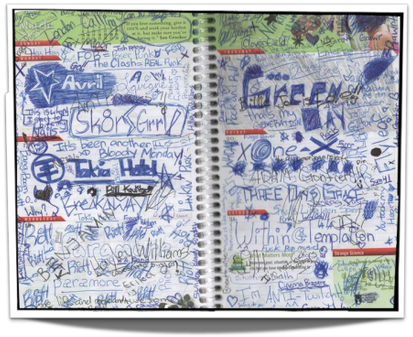
3. surrogates are asked to make decisions for those people truly unable to consent to treatment in immediate life-threatening situations

4. smoking bans that lead to important reductions in morbidity and mortality

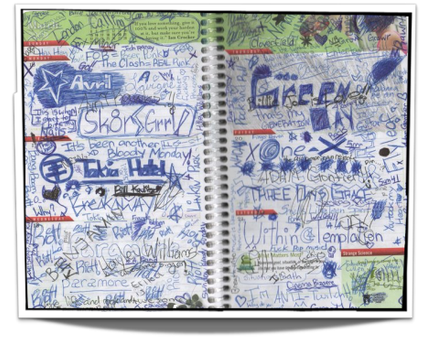
5. an intriguing example that some would consider an important exception is mandatory vaccination with the potential of herd immunity. In this case, a shared-decision not to be vaccinated for a transmissible disease could lead to inherent harm of others.



Its not that difficult



My Agenda



Much of what we do, even with the best of intentions, is not that effective

Most guidelines are a BIG problem

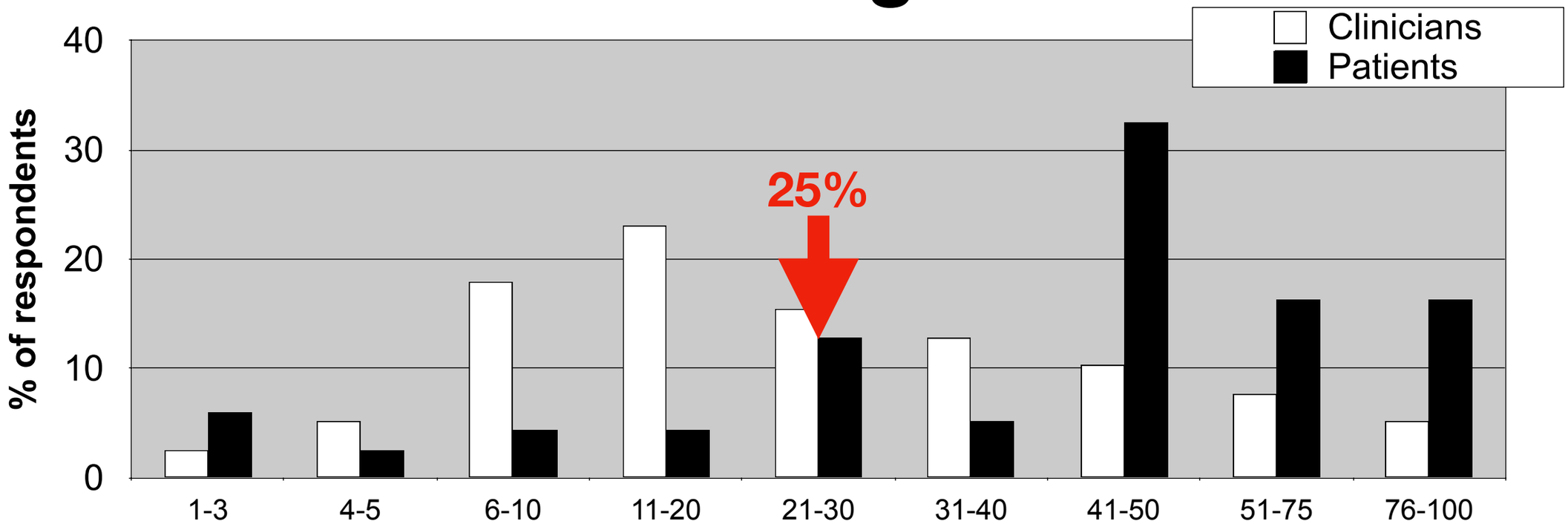
Some treatments (medications, nutrition, activity) can be effective and even life-saving BUT many aren't and they all have the potential for harm, inconvenience and cost

I believe the size of the effect for many of these treatments is much smaller than people think

Lab test variation makes many tests (especially repeat tests) of questionable use and are simply misleading

The recommended doses for most medications are too high

What is "High Risk"



Chance of a heart attack in the next 5 years (%)

A 60 y/o, male, smoker, diabetic,
SBP 180, total cholesterol 7.2 mmol/L

5-year risk of heart attack PLUS stroke is at most ~ 25%

The Magnitudinous Problem

More
Increased
Reduced
Improved
Decreased
Higher
Lower
High
Low
Significant
Less
Fewer
Worsened

Better
Worse
Greater
Uncommon
Superi
Ba
wer
Important

Co le
ant
Tiny
Inferior
Lesser
Small
Bigger
Major

Severe
Weak
Strong
Different
Faster
Shorter
Longer
Shortened
Lengthened
Extreme
Unlikely
Short
Many/Most

Convey a story but not really the evidence/ numbers

All these words likely mean something different to everyone

Examples that probably require quantification clarification

Your salary will be **INCREASED**

Turn left after a **MODERATE** number of kilometres

You will be getting a **SHORT** jail sentence

You have an **UNLIKELY** chance of getting an STD

You have a **SIGNIFICANT** chance of a heart attack

A **SMALL** tube will be placed a **CONSIDERABLE** distance into your rectum

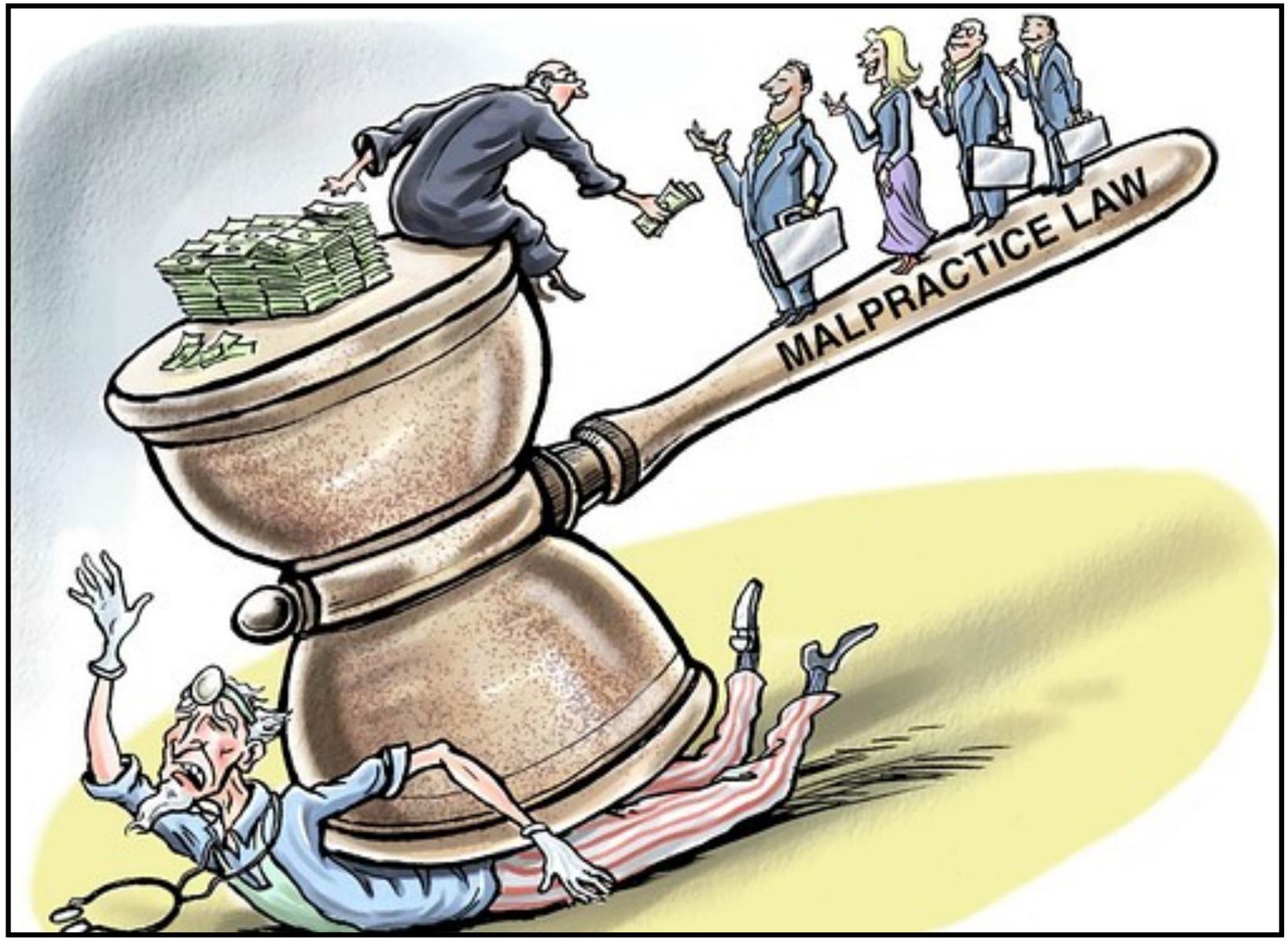
Beware of “qualitative quantification”

Qualitative descriptor	EU assigned frequency	Mean frequency estimated by participants (n=200)
Very common	>10%	65% (24·2)
Common	1–10%	45% (22·3)
Uncommon	0·1–1%	18% (13·3)
Rare	0·01–0·1%	8% (7·5)
Very rare	<0·01%	4% (6·7)

Values are mean (SD).

OFF BY
~350% to 18,000%

Lancet 2002;359:853–54


MALPRACTICE LAW

Medico-legal considerations

Most healthcare professionals feel considerable pressure to follow guidelines (and respond to other performance metrics) to the letter. This can hinder their ability to make genuinely appropriate decisions with an individual, for whom sticking exactly to the guideline may not be the best thing.

Using information on this website may open up the possibility of deviating from guidelines (or what might be defined as standard “best” practice by other sources).

In this section, we highlight key statements from authorities on this issue, to support your decision making.

The bottom line is that:

- It is acceptable (and indeed often good practice) to not directly adhere to a particular guideline recommendation for an individual.

However,

- Guidelines are an important reference point for practice, clinicians are expected to be aware of them and not simply ignore them.
- A deviation from a guideline recommendation should be undertaken for a justifiable clinical reason, or after a shared decision with a patient regarding their preferences.
  - Note: not all guideline recommendations are strong “must do” instructions anyway.
- Good documentation of these decisions is important.

What does NICE say?
more

General Medical Council Guidance on Decision Making and Consent
more

The Montgomery Judgement
more

Documentation standards
more

In conclusion

Individualised, person-centred care underpinned by good quality evidence, clinical judgement and shared decision-making has always been the aim of evidence-based practice.

Clinical guidelines are an important part of this, but were never intended to rigidly enforce treatments for individuals. “Guidelines, not tramlines” was a recurring message from the former Chair of NICE, Professor Sir David Haslam.

The threat of complaints, litigation or censure from external bodies can loom large in the minds of people working in healthcare. However, the fear of this is probably out of proportion to the likelihood of a successful case against them.

A clinician practising good quality shared-decision making, supported by the best evidence available to them, and who adequately documents this process, has the law on their side.

https://gpevidence.org/key-concepts/medico-legal-considerations/

“Standard of Care”
and follow
Clinical Practice Guidelines

Shared Decision Making
(SDM)

May or may not follow
Clinical Practice Guidelines

Medicolegal Sidebar: Clinical Practice Guidelines—Do They Reduce Professional Liability Risk?

Joseph P. McMenamin MD, JD, Wendy Teo BA(Cantab), BM BCh (Oxon), LLM, B. Sonny Bal MD, JD, MBA, PhD

"Clinical practice guidelines, however, are designed to improve care, not to define standard care. They can also limit physician autonomy, impose rules that are adopted mainly to avoid litigation risk, and may be developed by physicians with relevant financial conflicts. **In our view, courts should exclude clinical practice guidelines from evidence of the standard of care or of its breach."**

Clin Orthop Relat Res (2020) 478:23-25

Patient preferences for shared decisions: A systematic review

Betty Chewning [a,*], Carma L. Bylund [b], Bupendra Shah [c], Neeraj K. Arora [d], Jennifer A. Gueguen [e], Gregory Makoul [f]

"the number of patients who prefer participation has increased over the past three decades so that the majority of patients prefer to participate in decisions"

Patient Educ Couns (2011), doi:10.1016/j.pec.2011.02.004

Factors involved in deciding to start preventive treatment: qualitative study of clinicians' and lay people's attitudes

David K Lewis, Jude Robinson, Ewan Wilkinson **BMJ 2003;327:841**

"Many of the preferences expressed by the clinicians and lay people in this study are at odds with recommendations in guidelines"

Differing perceptions of intervention thresholds for fracture risk: a survey of patients and doctors **Osteoporos Int 2012;23:2135–40**

77% of doctors would recommend treatment

21% of our patient cohort would consider treatment justified

Durand *et al. BMC Health Services Research* (2015) 15:167
DOI 10.1186/s12913-015-0823-2

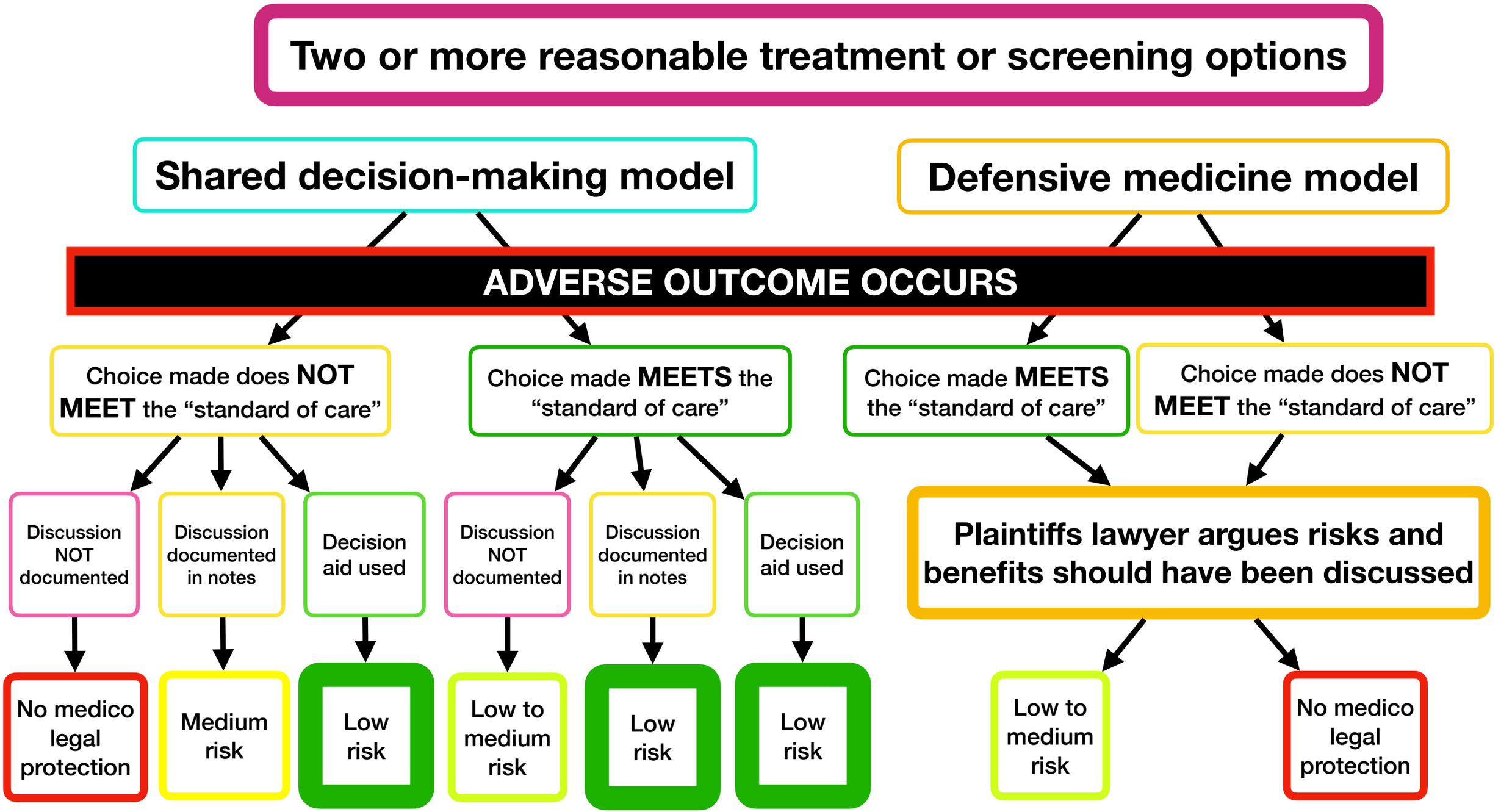
BMC
Health Services Research

RESEARCH ARTICLE Open Access

Can shared decision-making reduce medical malpractice litigation? A systematic review

Marie-Anne Durand[1,2*], Benjamin Moulton[3,4,5], Elizabeth Cockle[2], Mala Mann[6] and Glyn Elwyn[1,7]

"There is insufficient evidence to determine whether or not shared decision-making and the use of decision support interventions can reduce medical malpractice litigation. Further investigation is required."


Two or more reasonable treatment or screening options
Shared decision-making model
Defensive medicine model
ADVERSE OUTCOME OCCURS
Choice made does NOT MEET the "standard of care"
Choice made MEETS the "standard of care"
Choice made MEETS the "standard of care"
Choice made does NOT MEET the "standard of care"
Discussion NOT documented
Discussion documented in notes
Decision aid used
Discussion NOT documented
Discussion documented in notes
Decision aid used
Plaintiffs lawyer argues risks and benefits should have been discussed
No medico legal protection
Medium risk
Low risk
Low to medium risk
Low risk
Low risk
Low to medium risk
No medico legal protection

Reducing litigation risk

2 THINGS to DO

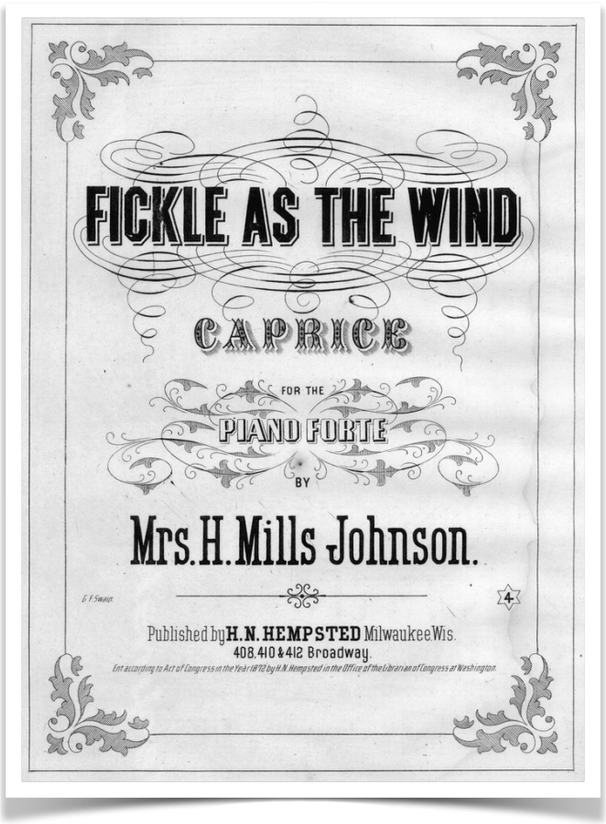
Shared decision-making model

1) Use a decision aid

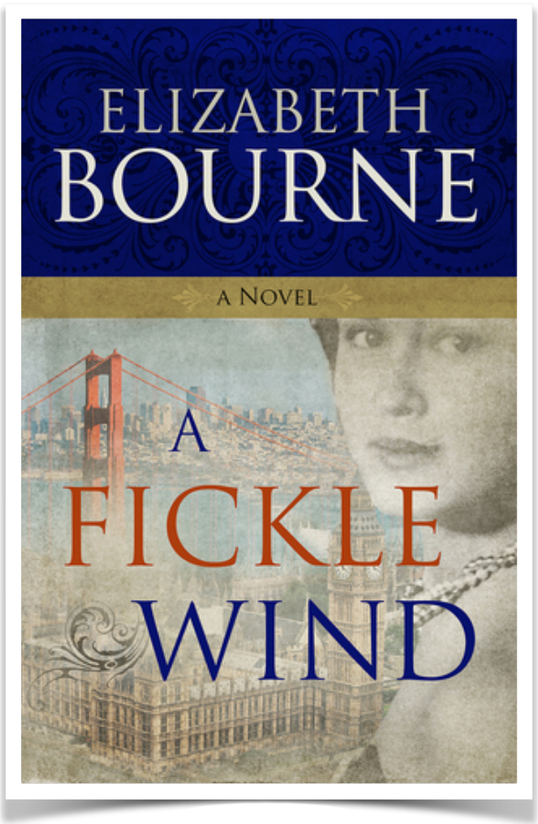
2) Document decision

“I would rather know evidence and try to apply it to each patient, than memorize guidelines and try to apply them to all patients”

Mark McConnell



The Fickle Nature of Guidelines



Guidelines would be awesome if they…

Were developed primarily by, and definitely for, the people that ultimately end up using them

Were a credible synopsis of the best available evidence presented in a way that clinicians could easily access and interpret

Allowed patient values and preferences to be taken into account

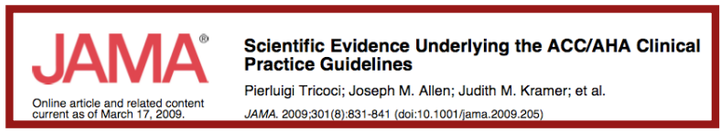
Wrong guidelines: why and how often they occur

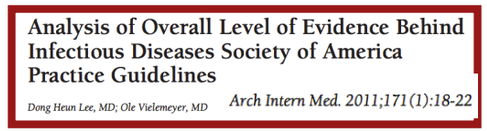
Primiano Iannone,[1] Nicola Montano,[2] Monica Minardi,[3] James Doyle,[3] Paolo Cavagnaro,[4] Antonino Cartabellotta[5]

"Unfortunately, depending on how their reliability is measured, up to 50% of guidelines can be considered untrustworthy. This carries serious consequences for patients' safety, resource use and health economics burden."

EBM 2017;22:1-3

Typically “evidence-based” guideline recommendations are not based on “solid” evidence





EVIDENCE LEVEL	Cardiology	Infectious disease	Endocrinology
1 or A based on RCTs	11%	14%	6%
3 or C based on opinion	48%	55%	35%

Factors Associated With High-Quality Guidelines for the Pharmacologic Management of Chronic Diseases in Primary Care

A Systematic Review

Caroline de Godoi Rezende Costa Molino, MS[1]; Nathalia Celini Leite-Santos, BS[1]; Franciele Cordeiro Gabriel, MS[1]; et al

» Author Affiliations

JAMA Intern Med. 2019;179(4):553-560. doi:10.1001/jamainternmed.2018.7529

Heart disease
Lung disease
Diabetes
Osteoporosis
Depression
Osteoarthritis
Dementia
GERD
BPH

421 CPGs (July 2011-August 2017) for the management of common non-communicable disease in primary care

24% were rated as high quality
lowest median domain scores
applicability (22%) and rigour of development (33%)

Systematic review of clinical practice guidelines recommendations about primary cardiovascular disease prevention for older adults

Jesse Jansen[1,2*], Shannon McKinn[1,2], Carissa Bonner[1,2], Les Irwig[1], Jenny Doust[1,3], Paul Glasziou[1,3], Brooke Nickel[1,2], Barbara van Munster[4,5] and Kirsten McCaffery[1,2]

47 guidelines	Discussed benefits	Discussed harms
CVD assessment and harms	19%	17%
Medications	32-33%	15-19%
Lifestyle	15%	0%

Deprescribing mentioned - 0%

BMC Family Practice (2015) 16:104 DOI 10.1186/s12875-015-0310-1

Guideline sponsorship

2009 - 2,300 guidelines in the National Guideline Clearinghouse

Guideline development

- 41% - medical speciality societies
- 22% - government agencies/nonprofit
- 17% - professional associations
- 9% - disease specific societies
- 4% - independent expert panels

at least 2/3 are being developed by groups with a clear potential for important biases

http://www.ncbi.nlm.nih.gov/books/NBK22928/

From 2008 to 2015

20 LARGE TRIALS IN A ROW SHOWED NO BENEFIT FROM CHANGING A SURROGATE MARKER

DIABETES
ACCORD, ADVANCE, VADT (aggressive A1c lowering)
ROADMAP (olmesartan)
ORIGIN (insulin)
SAVOR-TIMI 53 (saxagliptin)
EXAMINE (alogliptin)
ALECARDIO (aleglitazar)

GENERAL
ACTIVE (irbesartan/afib)
CRESCENDO (rimonabant)
VISTA-16 (varespladib)

5 cholesterol trials
8 diabetes/glucose trials
4 blood pressure trials
3 general risk reduction trials

LIPIDS
AIM-HIGH, HPS2-THRIVE (niacin)
ACCORD (fibrates)
dalOUTCOMES (dalcetrapib)
STABILITY (darapladib)

BLOOD PRESSURE
ALTITUDE (aliskiren)
VALISH, AASK, ACCORD (aggressive BP lowering)

FINALLY!!!!!2015

1) EMPA-REG OUTCOME (empagliflozin) - **1.6% ⬇** over 3 years
2) LEADER (liraglutide) - **1.8% ⬇** over 4 years
3) SPRINT (120mmHg vs 140mmHg) - **1.6% ⬇** (CVD) over 3 years but also **1.8% ⬆** (Kidney)
4) HOPE 3 - statins YES, BUT blood pressure no benefit
5) FOURIER - **1.6% ⬇** over 2 years BUT $15,000/year

BUT!!!!!

1) ACCELERATE (evacetrapib - increased HDL (130%), reduced LDL (40%) - **no CVD benefit**

LIPIDS
6 different guidelines

	2019 ESC/ EAS	**2022 USPSTF**	**2019 ACC/ AHA**	**2020 VA/DoD**	**2021 CCS**	**2016 Simplified Lipid**
Estimate CVD risk	**SCORE**	**ACC/AHA risk estimator**	**ACC/AHA risk estimator**	**FRS, ACC/AHA 10-year risk estimator**	**Framingham risk score or Cardiac Life Expectancy Model**	**Choose your risk calculator**
LDL targets	YES statins based on LDL (level varies depending on CVD risk)	NO statins based on risk threshold	YES statins based on LDL (level varies depending on CVD risk)	NO statins based on risk threshold	YES statins based on LDL (level varies depending on CVD risk)	NO statins based on shared decision-making

Treatment Threshold Wars

LODESTAR

JAMA | Original Investigation

Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease
A Randomized Clinical Trial

April 4, 2023
JAMA 2023;329:1078-1087

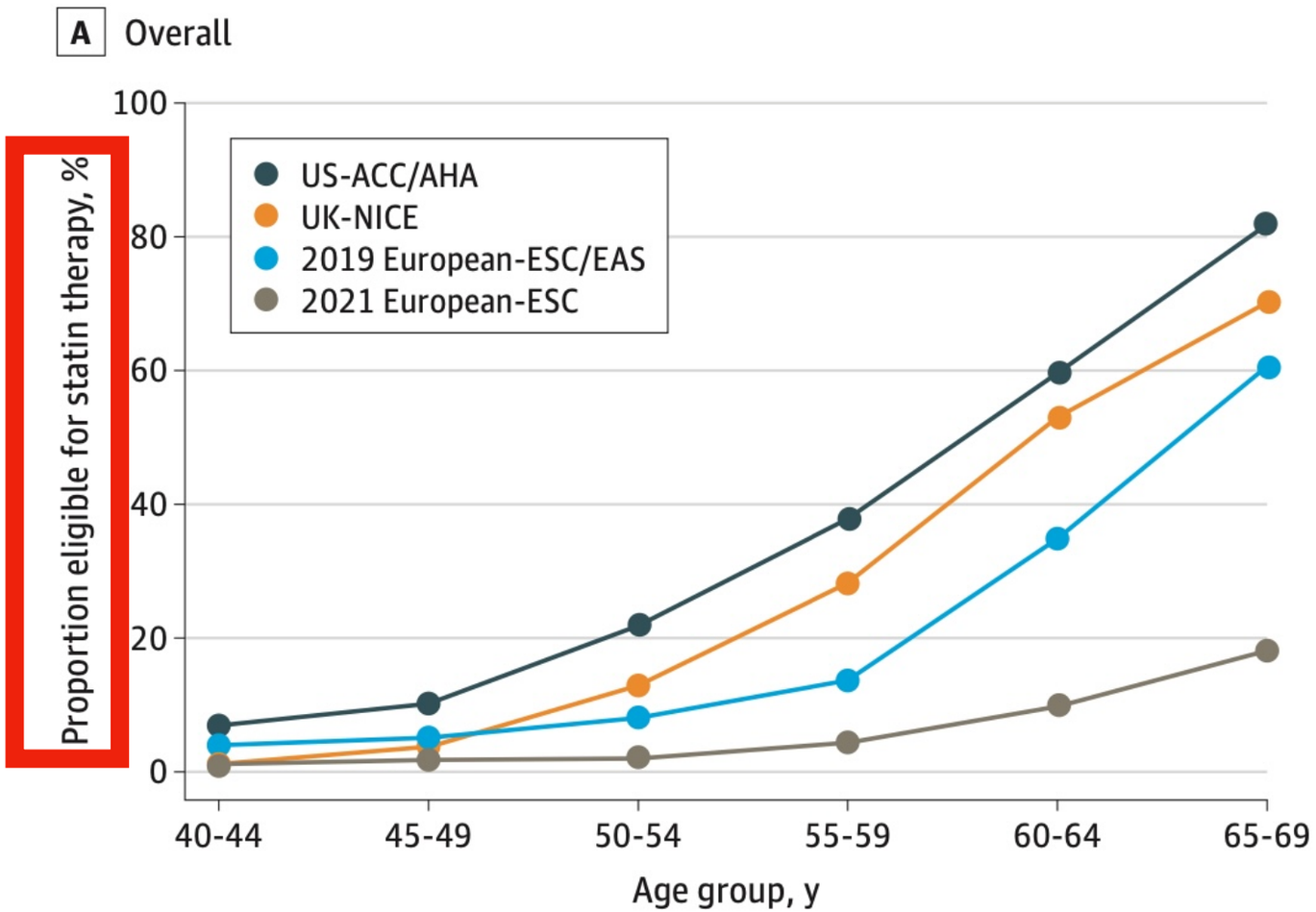
Treat-to-Target (~50%/40% on high/moderate intensity statin, 20% ezetimibe)
High-Intensity Statin (~90% on high intensity statin, 10% ezetimibe)

What the authors said

Conclusions

Among patients with CAD, a treat-to-target LDL-C strategy of 50 to 70 mg/dL as the goal was noninferior to a high-intensity statin therapy for the 3-year composite of death, MI, stroke, or coronary revascularization. These findings provide additional evidence supporting the suitability of a treat-to-target strategy that may allow a tailored approach with consideration for individual variability in drug response to statin therapy.

Figure 2. Statin Eligibility for Primary Prevention of Atherosclerotic Cardiovascular Disease (ASCVD) Stratified by Sex and 5-Year Age Groups According to Guideline-Defined Class I/Strong Recommendations in Individuals Aged 40 to 69 Years



So choose whatever guideline matches your beliefs

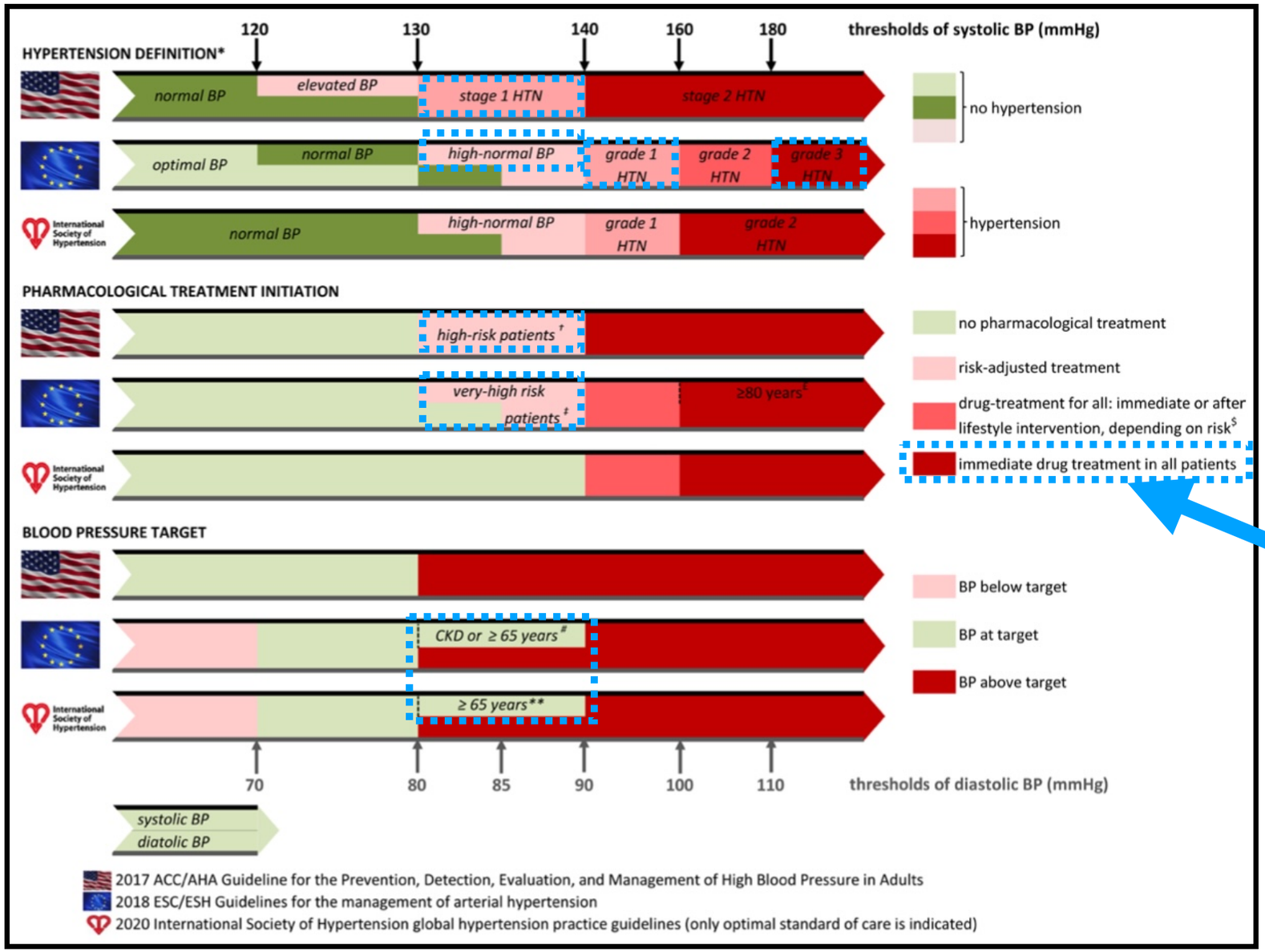
JAMA Cardiol. 2022;7(8):836-843. doi:10.1001/jamacardio.2022.1876

Three different hypertension guidelines

DEFINITION

TREATMENT

TARGET



NOTHING ABOUT VALUES AND PREFERENCES

Circulation 2022;146:805–807 DOI: 10.1161/CIRCULATIONAHA.121.055177

EFFECT OF PROPRANOLOL IN MILD HYPERTENSION

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MEDICAL REGISTRAR

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Lifetime CVD risk/benefit

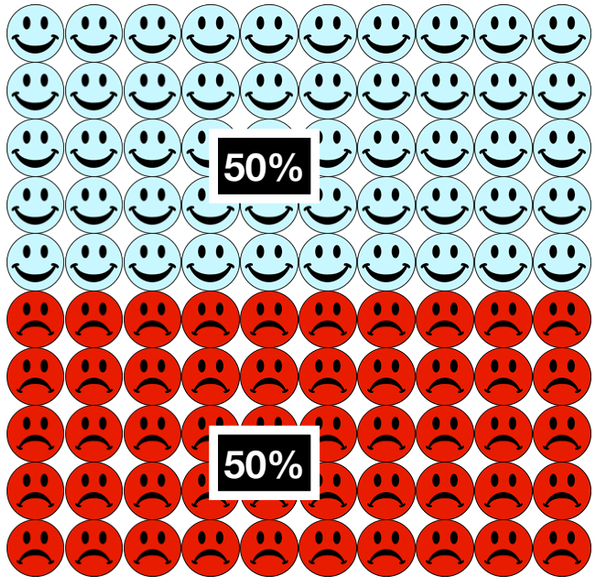
(most people don't benefit despite a lifetime of surrogate marker treatment)

Lifetime risk of CVD

Male with 2 CVD risk factors

(NEJM 2012;366:321-9)

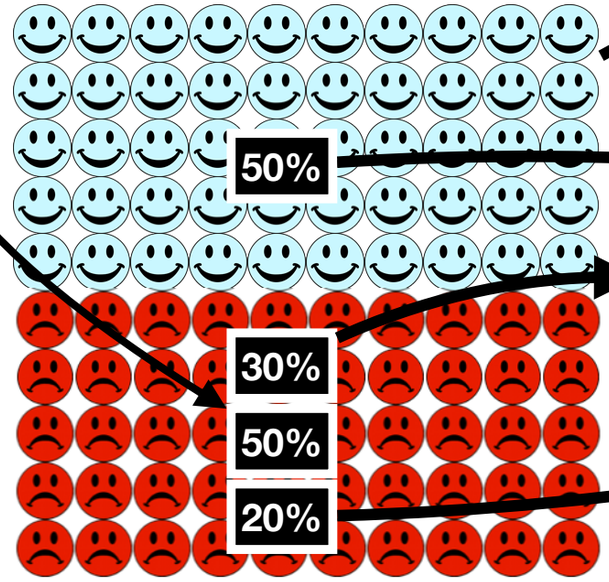
ROUGHLY 50%



Lifetime benefit

Assume with multiple risk factor modification we can reduce risk relatively by 60% (VERY optimistic)

50% ➡ 20%



100% get this "TREATMENT" or "INTERVENTION

30%
DO BENEFIT

70%
DO NOT BENEFIT
despite a
LIFETIME
of treatment

EDITORIAL ■

Challenging treatment thresholds

James McCormack PharmD, **Aseem Malhotra** MRCP and **David Newman** MD

National organisations such as NICE or American College of Cardiology (ACC)/American Heart Association (AHA) regularly release cardiovascular disease (CVD) guidelines that recommend lifestyle and medication interventions along with treatment thresholds based either on risk factors or calculated CVD risks.

The release of these recommendations predictably leads to intense debate from healthcare organisations, government, industry, and clinicians on whether or not the recommendations are reasonable. At one extreme the recommendations are typically pilloried as being sufficiently weak to cost lives, while others insist the guidelines have threatened public health through over-medication.

This overwrought debate is rooted, we believe, in the mysterious imperative to provide treatment thresholds, rather than offer a reasonable synopsis of best evidence and its limitations so that patients and clinicians can apply individual values. Such a best-evidence approach would support the increasing call – and need – for shared decision making in professional society guidelines.[1] Moreover, care guided by treatment thresholds largely removes individual preference from the exam room while care explicitly informed by best evidence allows tailoring to a patient's values and priorities.

When it comes to CVD risk factors, some population health advocates justify threshold-based guidelines by estimating how many heart attacks or strokes might be prevented across a population. This approach may be reasonable with vaccination for transmissible diseases, or public health regulations that demonstrate reliable and rapid near-total reductions in morbidity and mortality (eg public smoking bans). However, risk factor modification with lifestyle interventions may for some individuals be unacceptably inconvenient, burdensome, or costly. In addition it is neither feasible nor desirable to speculate on a population's values or preferences. Such questions are best left to individuals, as evidenced by one recent survey study demonstrating marked variation in negative values assigned to the act of taking daily pills: some respondents would refuse daily medications even if an inexpensive pill would cause no side-effects and add 10 years to their life.[2] What current guidelines therefore fail to address is the negative value assignments associated with commonly prescribed and recommended healthcare interventions.

Hopefully most clinicians and patients will agree with the principle that information is power. While not all patients will want to take the pills, undergo invasive procedures, or take on lifestyle changes commonly used for risk factor modification, all should have access to basic facts and evidence about the utility of these options.

Lifestyle interventions

Clinicians and patients should know that roughly 80 per cent of CVD can be attributed to modifiable lifestyle factors such as nutrition, physical activity and smoking. Patients should be counselled about the nature and value of a healthy diet – a Mediterranean diet in moderation, with as little processed food as possible, is a cardiovascular intervention tested in randomised trials and shown to reduce CVD events.[3] Patients should know that physical activities, particularly enjoyable ones, can lead to important, lasting health and quality of life benefits.[4] Finally, patients should be counselled and supported to quit smoking. While associated with some costs and inconvenience, those three interventions rarely include significant harm risk, can prolong life, and have the added advantage of substantial non-cardiovascular benefits. Still, the decision to capitalise will remain individual.

Blood pressure	ALTITUDE, VALISH, AASK, ACCORD
Lipid	AIM-HIGH, HPS2-THRIVE, ACCORD, dalOUTCOMES, STABILITY
Glucose	ACCORD, ADVANCE, VADT, ROADMAP, ORIGIN, SAVOR-TIMI 53, EXAMINE, ALECARDIO, TECOS

Table 1. CVD risk-factor modification studies that showed no overall CVD benefit

Theoretical benefits of risk-factor modification

Let us assume a person's lifetime risk of CVD is that of a male with two CVD risk factors, roughly 50 per cent.[5] Now let us assume that with multiple risk-factor modification we can reduce that risk relatively by 60 per cent, an optimistic assumption. This would shift a person's lifetime risk for CVD from 50 per cent to 20 per cent. In this best-case scenario approximately 30 per cent of individuals benefit, but 70 per cent do not, even despite a lifetime of treatment. This is critical for clinicians and patients to appreciate: not everyone benefits when they reduce CVD risk factors.

Indeed it may be equally important for patients and physicians to understand that over the last five or so years, a number of large, well-designed studies have shown either no benefit or harm from interventions (primarily medications) that successfully modified CVD risk factors (see Table 1). Thus not only do a limited percentage of patients benefit, but in the case of risk factor modification with medications the endeavor may not always lead to a change in important clinical outcomes.

A potential solution

Below is an example of using best evidence to construct a script for offering information patients can use. We offer statins as an example, as they have likely been studied more than any risk reduction medication.

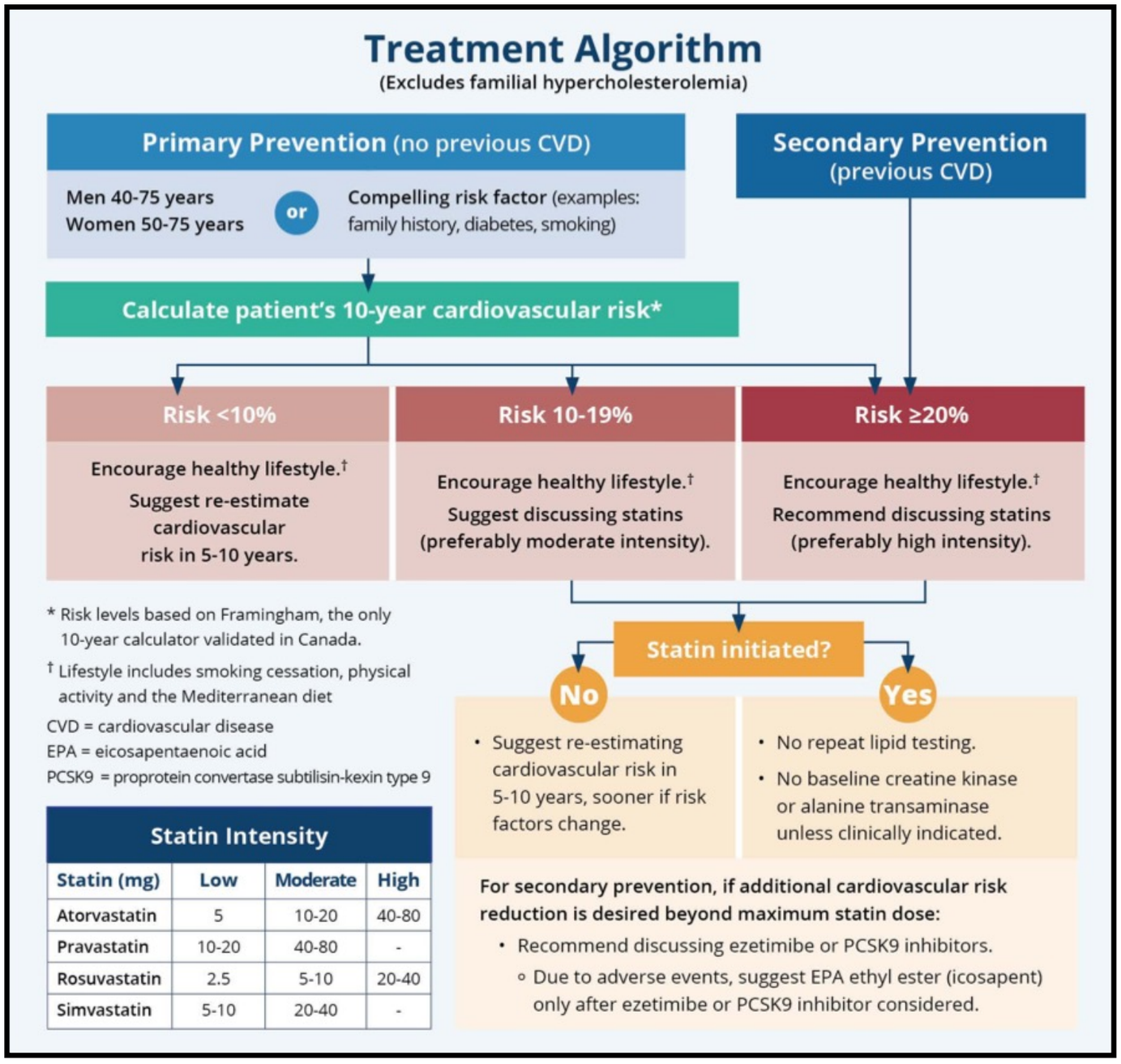
prescriber.co.uk

Prescriber 5 September 2015 ■ 5

Prescriber 2015;26:5-7

Hey, watch me pull a treatment threshold out of my butt!

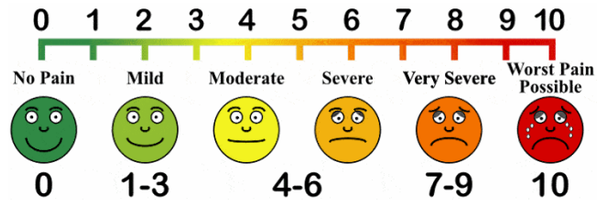
GUIDELINE WRITERS



Discussion Thresholds NOT Treatment thresholds

https://www.cfp.ca/content/69/10/675

Medications for Symptoms



% of people who benefit in the treatment arm - that will be what you see in practice over placebo

% of people who benefit in the placebo arm - subtract that from the treatment to see how many actually benefit from the medication

6-8 weeks	No longer depressed
Medication	50%
Placebo	40%
Medication benefit	50-40 = 10%
If person responds, the chance it is the medication	10/50 = 20%

The Placebo Group Effect

not the placebo effect and these are ballpark numbers

~0% - general anesthesia

~5% - psychosis

~10% - sildenafil, OCD

~20% - Alzheimer's meds, acetaminophen for headaches, side effects

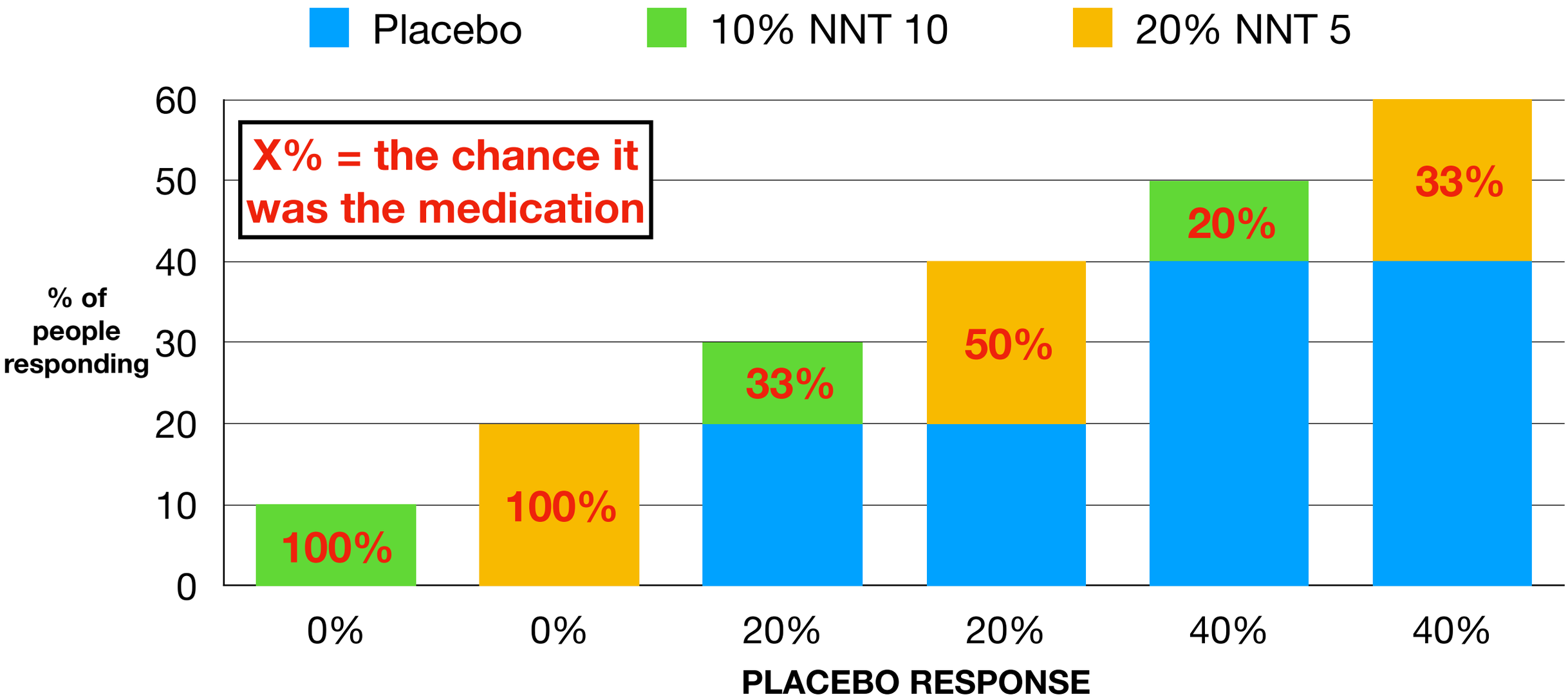
~25% - menopausal symptoms, migraine (frequency/severity), GAD

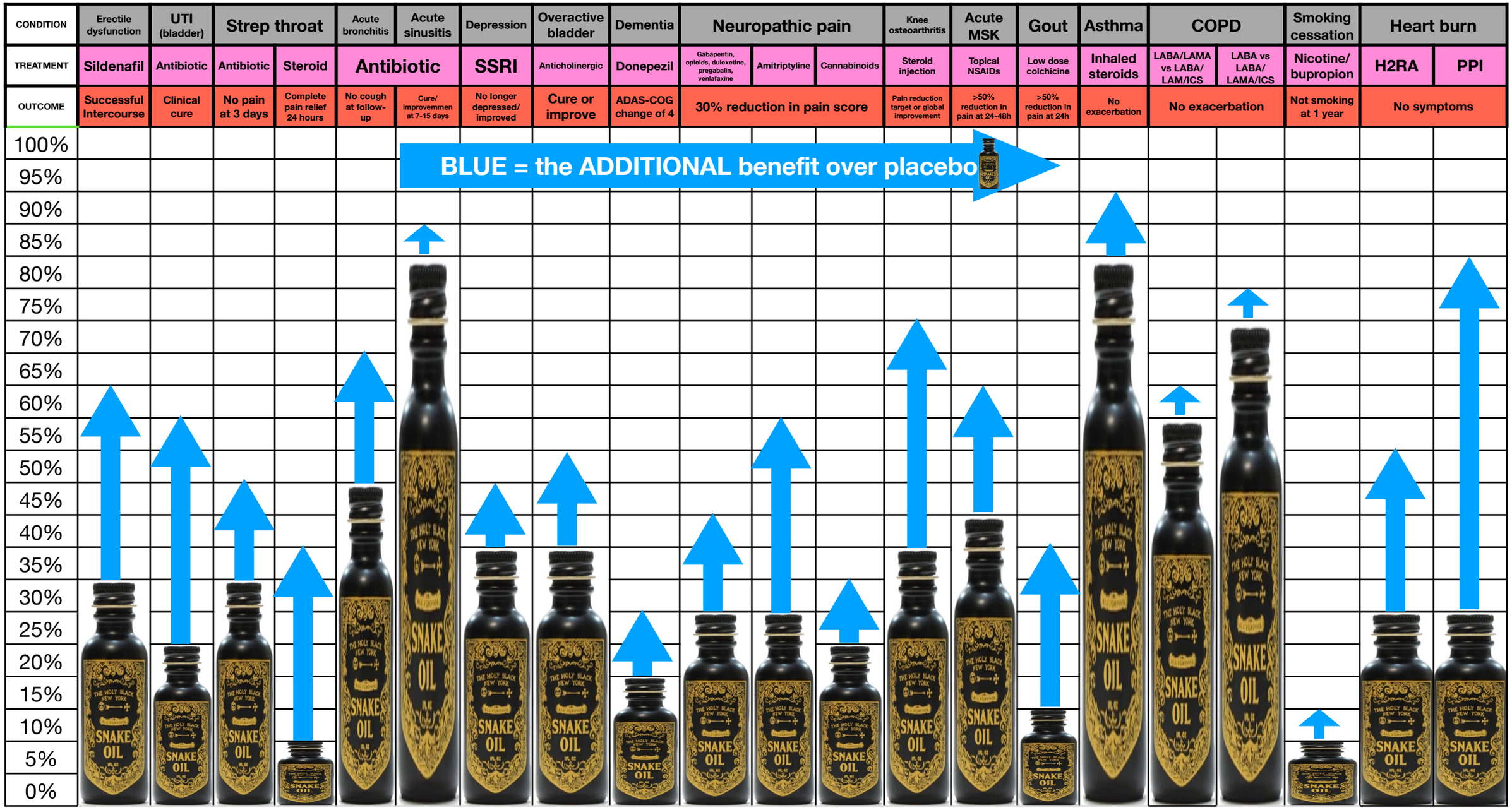
~30% - blood pressure goal, depression, PTSD, PPIs/H2RA, sore throat, NSAIDs for OA, inhalers for COPD

~40% - panic disorders

#s for psychiatric conditions from Psychological Medicine 2005;35:743–9

You need to know what goes on in the placebo group




CONDITION
Erectile dysfunction
UTI (bladder)
Strep throat
Acute bronchitis
Acute sinusitis
Depression
Overactive bladder
Dementia
Neuropathic pain
Knee osteoarthritis
Acute MSK
Gout
Asthma
COPD
Smoking cessation
Heart burn
TREATMENT
Sildenafil
Antibiotic
Antibiotic
Steroid
Antibiotic
SSRI
Anticholinergic
Donepezil
Gabapentin, opioids, duloxetine, pregabalin, venlafaxine
Amitriptyline
Cannabinoids
Steroid injection
Topical NSAIDs
Low dose colchicine
Inhaled steroids
LABA/LAMA vs LABA/ LAM/ICS
LABA vs LABA/ LAMA/ICS
Nicotine/ bupropion
H2RA
PPI
OUTCOME
Successful Intercourse
Clinical cure
No pain at 3 days
Complete pain relief 24 hours
No cough at follow-up
Cure/ improvemmen at 7-15 days
No longer depressed/ improved
Cure or improve
ADAS-COG change of 4
30% reduction in pain score
Pain reduction target or global improvement
>50% reduction in pain at 24-48h
>50% reduction in pain at 24h
No exacerbation
No exacerbation
Not smoking at 1 year
No symptoms
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
BLUE = the ADDITIONAL benefit over placebo
SNAKE OIL

1) Erectile dysfunction

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1570825833_tfp245pde5ifv.pdf

2) UTI

https://www.journalofinfection.com/article/S0163-4453(09)00002-4/fulltext

3) Strep throat antibiotic

Cochrane Library CD000023

4) Strep throat steroids

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1418054647_tfp127steroidssorethroatfv.pdf

5) Bronchitis

https://doi.org/10.1002/14651858.CD000245.pub4

6) Sinusitis

Cochrane Library CD000243

7) Depression

https://www.bmj.com/content/360/bmj.k1073

8) Overactive bladder

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1433184756_updatedtfp54overactivebladderandanticholinergicdrugs.pdf

9) Dementia

https://gomainpro.ca/wp-content/uploads/tools-for-practice/1397843505_20140218_085747.pdf

10) Neuropathic pain

https://peerevidence.ca/wp-content/uploads/2022/04/PEER-Decision-Aid-Neuropathic-Pain.pdf

https://www.cfpc.ca/CFPC/media/Resources/Addiction-Medicine/Cannabinoid_Guidelines_One-Pager.pdf

11) Knee osteo

https://www.cfp.ca/content/cfp/66/3/191.full.pdf

12) Acute MSK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163964/pdf/emss-57980.pdf

13) Gout Low dose colchicine

Arth Rheum 2010;62:1060-8

14) **Asthma exacerbations on inhaled steroids** – depends what numbers/evidence you use – the bottom line is the absolute benefit is ~10-15%

Lancet 2003; 361: 1071–76

Mild persistent asthma budesonide vs placebo (adults and children)

45% of patients on placebo (vs 31% on budesonide) received inhaled, oral, or systemic steroids during

Severe exacerbation 6% vs 3% over 2 years

Cochrane Library CD011032

Intermittent ICS, with treatment initiated at the time of early symptoms,

Exacerbations requiring oral corticosteroids

School age children 48% vs 35% over 44 weeks

Adults – 6 months 3.5% vs 0.3%

Cochrane Library CD003135

Fluticasone versus placebo for chronic asthma in adults and children

Withdrawal due to clinical asthma exacerbation 11% vs 2% in adults

Cochrane Library CD002738

Withdrawal due to asthma exacerbation – children and adults

15% vs 3%

Mild to Moderate asthma

15% vs 6%

Overall exacerbations of asthma

6% vs 6%

15) **COPD exacerbations**

Cochrane Library CD012620

16) **Nicotine/bupropion smoking cessation**

Cochrane Library CD000146, Cochrane Library CD000031

17) **Heartburn**

Cochrane Library CD003244

Two “sobering” but very empowering concepts

PREVENTION

If a patient is on a medication for risk reduction (BP, chol, glucose BMD) the benefit they are receiving is likely not large enough for them to make up for the cost, inconvenience and adverse effects.

SYMPTOMS

If a patient seems to be getting a benefit from a medication for symptoms they likely aren’t - for many treatments more people benefit in the placebo group than the additional effect from the treatment

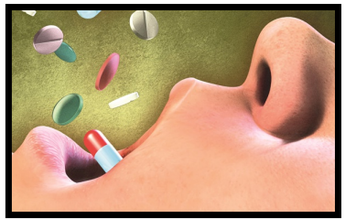
Inconvenience

Get the prescription

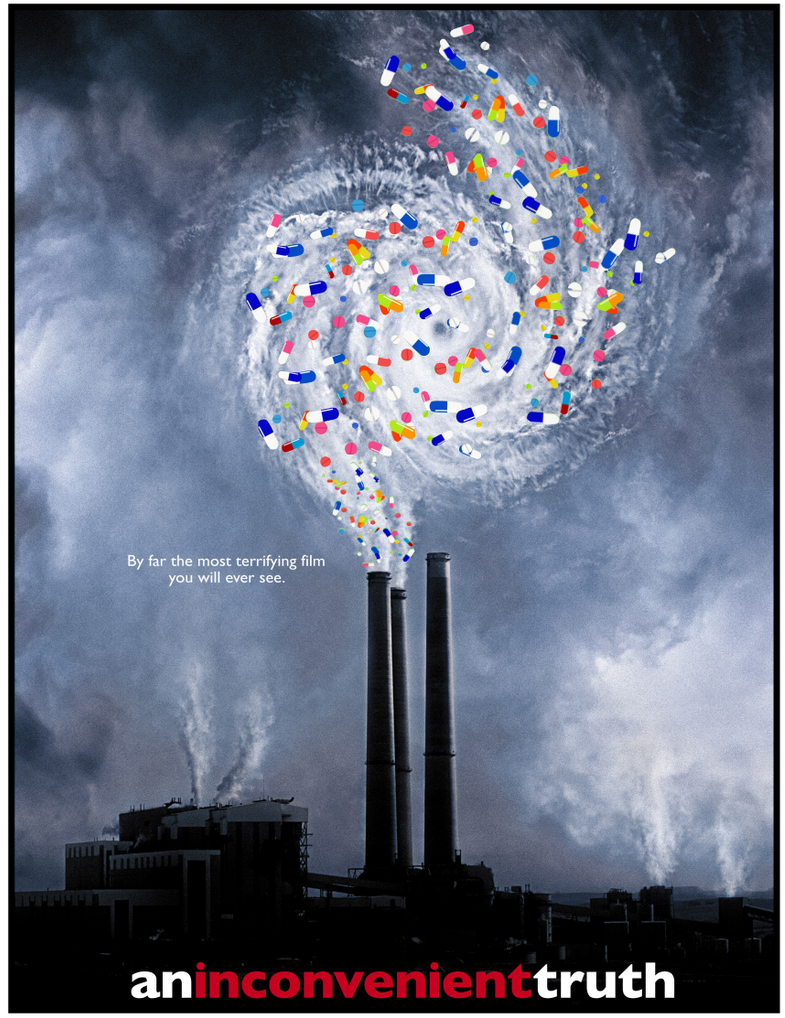
Fill the prescription

Pay for the prescription

Take the prescription



Labelling/worry

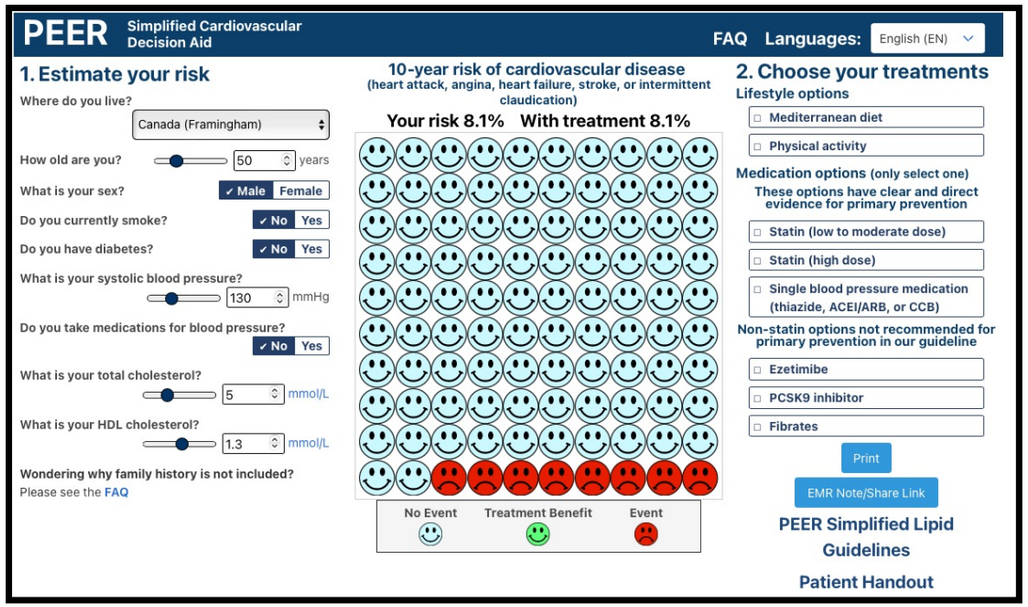


Medication examples

Prevention or Symptoms

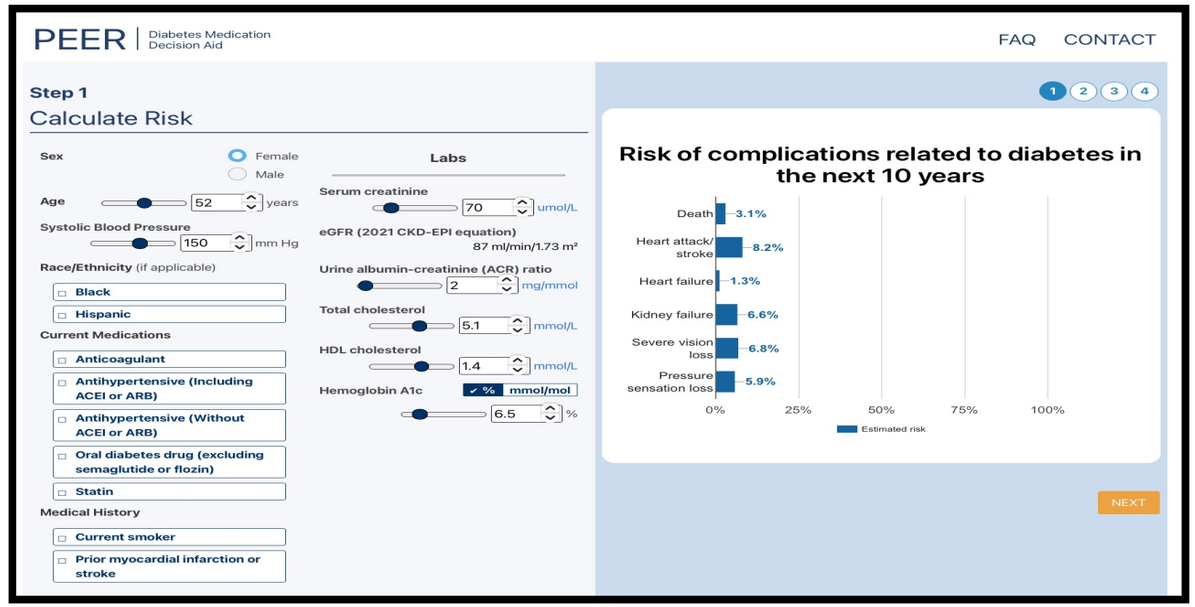
Case
Cardiovascular risk factors

Primary Prevention



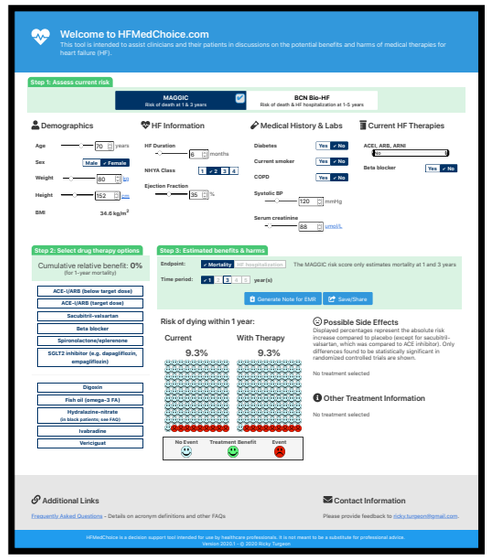
https://decisionaid.ca/cvd

Diabetes



https://decisionaid.ca/diabetes/

Heart Failure



https://www.hfmedchoice.com

Please consider these questions with the cases

What is important to the patient/caregiver?

What management options are available?

What is the evidence base for management options and where would you look if unsure?

How would you communicate evidence based principles to the patient and discuss the available options?

50 year-old person with “elevated risk factors”

BP = 150/100mHg

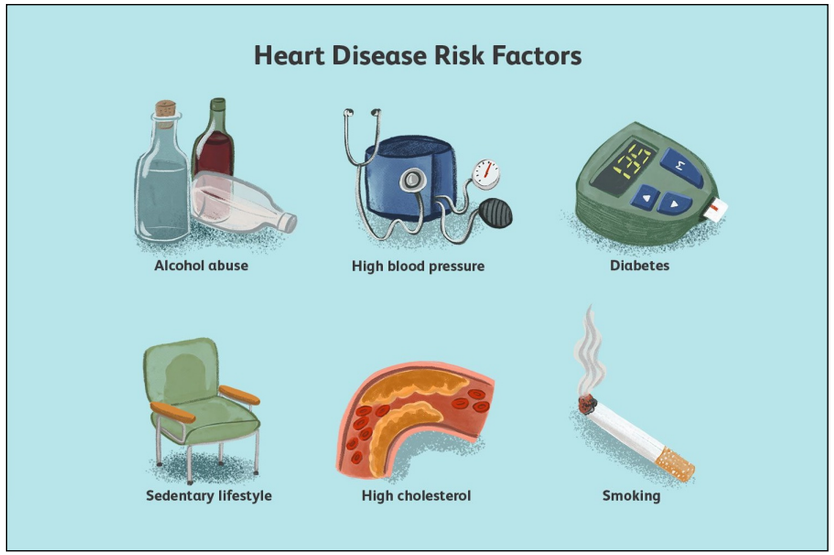
Total cholesterol = 5.1, LDL = 3.6, HDL = 1.1

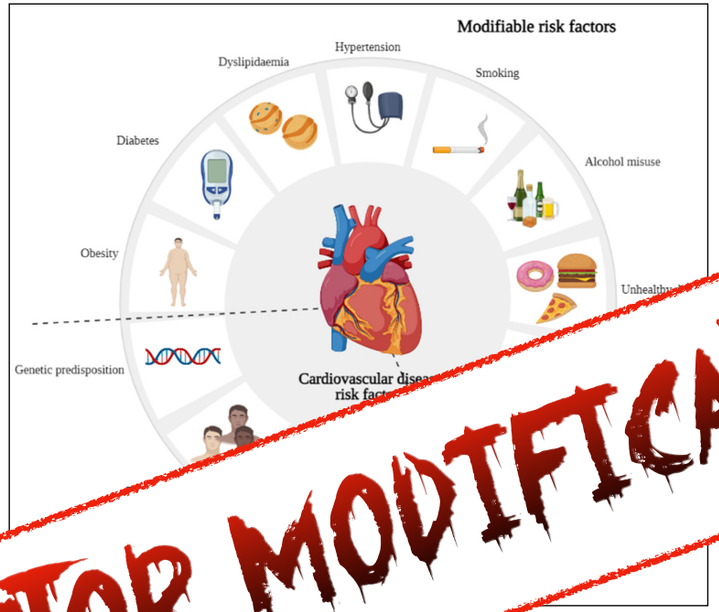
A1C = 6.5%

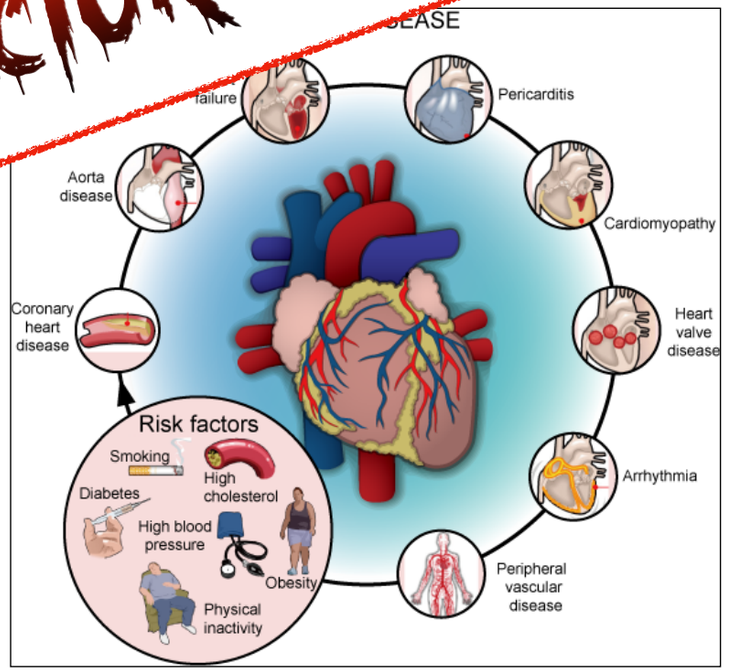
Non-smoker

Both parents alive but father had a heart attack at 80 and mother had one at age 75

RISK FACTOR MODIFICATION







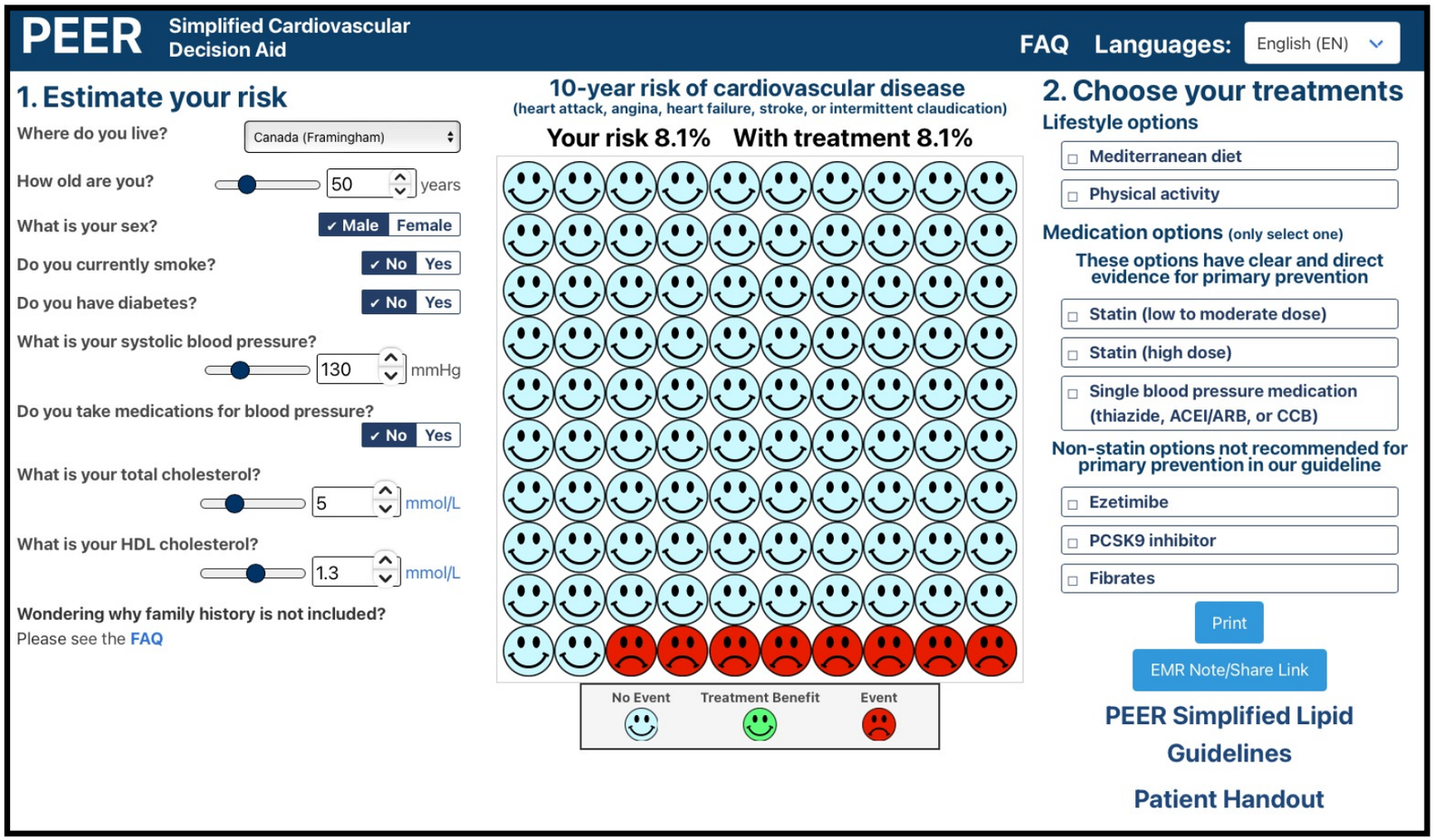
It’s all about figuring out

The *Ballpark* Chance
WITH NO TREATMENT

VS

The *Ballpark* Chance
WITH TREATMENT

CVD decision aid

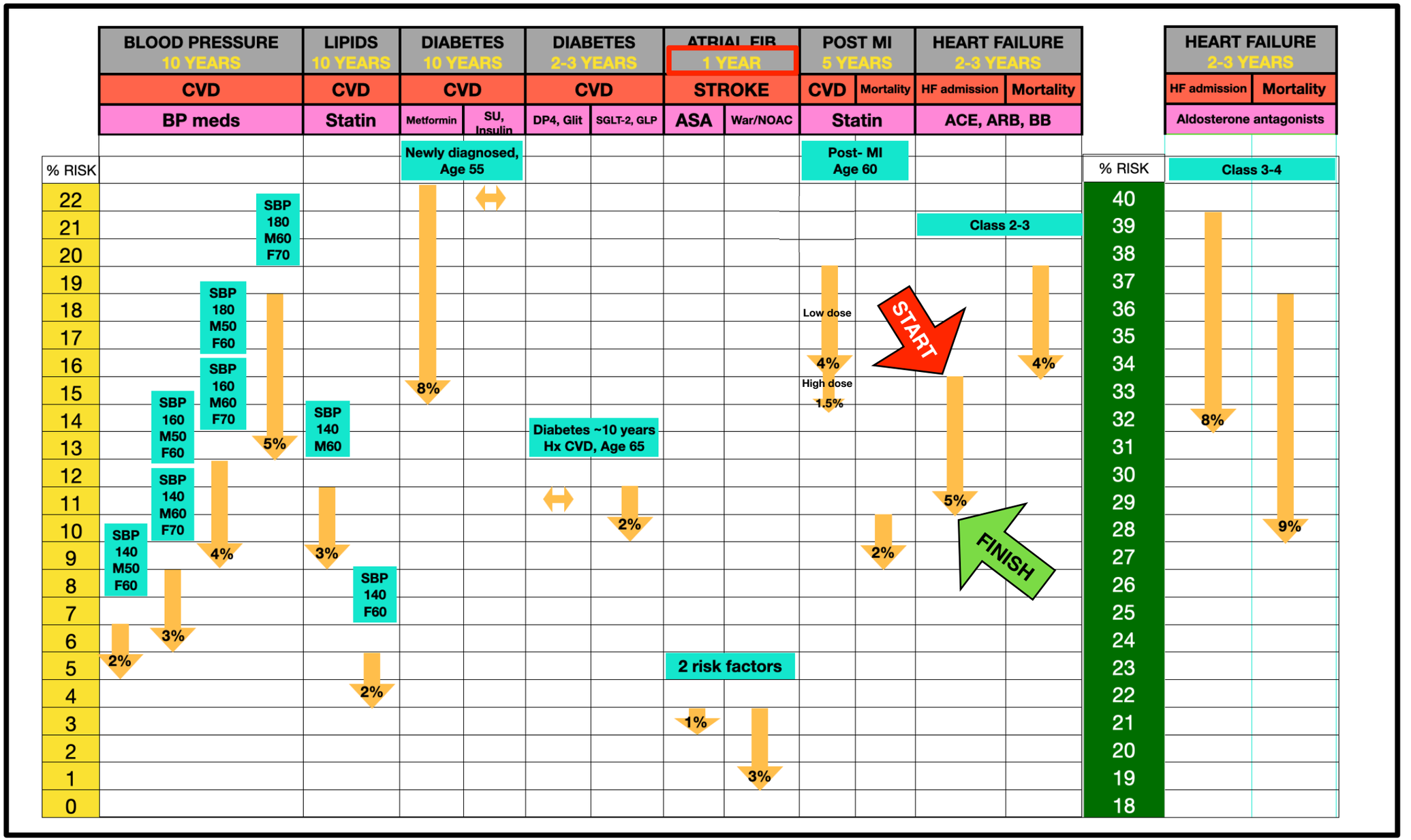


https://decisionaid.ca/cvd/

BALLPARK RELATIVE % BENEFITS FOR CARDIOVASCULAR PREVENTATIVE TREATMENTS

RRR%	
75	
70	
65	Warfarin/NOACS for A fib
60	
55	
50	Blood pressure diabetes
45	
40	
35	Metformin?, statins high dose, aspirin for A fib
30	Mediterranean diet, blood pressure
25	Physical activity plus QOL, statins low dose, ACEI/BB/aldo antag for heart failure
20	
15	PCSK9, SGLT2, GLP
10	
5	Ezetimibe
0	Fibrate, niacin , DPP4, SU, insulin, glitazones

BALLPARK ABSOLUTE % BENEFITS FOR PREVENTATIVE TREATMENTS



Not a single benefit is >10% and most are 5% or less

The large placebo controlled RCTs evaluating the impact of medications on CVD outcomes in T2DM

YEAR	NAME		MEDICATION	RESULT	OUTCOME CHANGED	ABSOLUTE DIFFERENCE/TIME
1970	UGDP	SU	tolbutamide (Orinase)	NEGATIVE	CVD mortality	↑8%/5 years
1971		BG	phenformin (DBI)	NEGATIVE	Mortality	↑ 6%/5-8 years
1976		SU	tolbutamide (Orinase)	NEGATIVE	Fatal MI	↑ 5%/5 years
1982		IN	insulin	NEUTRAL		
1998	UKPDS 33/34	IN,SU	insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL		
1998		IN,SU,BG	metformin, insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL except POSITIVE for metformin	Mortality MI	↓7%/11 years ↓ 6%/11 years
2003	STOP-NIDDM	OTH	acarbose (Precose)	POSITIVE	MI	↓ 1.5%/3 years
2005	PROACTIVE	GLIT	pioglitazone (Actos)	POSITIVE	MI	↓ 1.5%/3 years
2007	RECORD	GLIT	rosiglitazone (Avandia)	NEGATIVE	Heart failure	↑ 1%/4 years
2012	ORIGIN	IN	insulin	NEUTRAL		
2013	EXAMINE	DPP4	alogliptin (Nesina)	NEUTRAL		
2014	SAVOR-TIMI 53	DPP4	saxagliptin (Onglyza)	NEGATIVE	Heart failure	↑ 1%/2 years
2014	ALECARDIO	OTH	aleglitizar	NEUTRAL		
2015	ELIXA	GLP	lixisenatide (Adlyxin)	NEUTRAL		
2015	TECOS	DPP4	sitagliptin (Januvia)	NEUTRAL		
			2015			
2015	EMPA-REG	SGLT-2	empagliflozin (Jardiance)	POSITIVE	Mortality Heart failure	↓ 2.5%/3 years ↓ 1.5%/3 years
2016	SUSTAIN 6	GLP-1	semaglutide (Ozempic)	POSITIVE	Combined outcome	↓ 2%/2 years
2016	LEADER	GLP-1	liraglutide (Victoza)	POSITIVE	Mortality Combined outcome	↓ 1%/4 years ↓ 2.5%/4 years
2017	CANVAS	SGLT-2	canagliflozin (Invokana)	POSITIVE	Combined outcome Heart failure Amputations	↓ 2%/3.5years ↓ 1%/3.5 years ↑ 1%/3.5 years
2017	EXSCEL	GLP	exenatide (Byetta)	NEUTRAL		
2017	ACE	OTH	acarbose (Procose)	NEUTRAL		
2017	Omarigliptin	DPP4	omarigliptin	NEUTRAL		
2018	HARMONY	GLP	albiglutide (Tanzeum)	POSITIVE	Combined outcome	↓ 2%/2 years
2018	CARMELINA	DPP4	linagliptin (Tradjenta)	NEUTRAL		
2018	DECLARE-TIMI 58	SGLT-2	dapagliflozin (Farxiga)	POSITIVE	Combined outcome (primarily heart failure)	↓ 1%/4 years
2019	REWIND	GLP-1	dulaglutide (Trulicity)	POSITIVE	Combined outcome Renal outcomes	↓ 1.5%/5.4 years ↓ 2.5%/5.4 years
2019	PIONEER 6	GLP -1 (oral)	semaglutide (Ozempic)	POSITIVE	CVD mortality Mortality	↓ 1%/1.5 years ↓ 1.5%/1.5 years
2019	CREDENCE	SGLT-2	canagliflozin (Invokana)	POSITIVE	Combined CVD outcome Combined renal outcome outcomes	↓ 2.5%/2.6 years ↓ 3%/2.6 years
2020	VERTIS-CV	SGLT-2	ertugliflozin (Steglatro)	NEUTRAL		
2020	SCORED	SGLT-2	sotagliflozin (Inpefa)	POSITIVE	Combined CVD outcomes	↓ 1.9%/1.5 years
2021	AMPLITUDE	GLP-1	efpeglenatide	POSITIVE	Combined outcome	↓ 2.2%/2 years

Typically 1-3% absolute ↓ over 2-5 years

	Negative	Neutral	Positive
TOTAL	5	14	14
SU	2	1	0
BG	1	0	1
IN	0	4	0
Glit	1	0	1
DPP4	1	4	0
GLP-1	0	2	6
SGLT-2	0	1	5
Other	0	2	1

Average % change in LDL
VERSUS
The % measurement variation for lipids in individual patients

LDL Changes

Average % change in LDL with 10-20 mg of a STATIN

40%

+10%

Additional % change in LDL by INCREASING DOSE to 40-80 mg

Additional % change in LDL by adding EZETIMIBE

+15%

Average change per year in cholesterol

Cholesterol Measurement Variation

Analytic plus biological variation of TC/LDL/HDL

~10%-20%

Size of the change to be sure a change in LDL has occurred

~20-30%

If a change in LDL seen (with 2 measurements) is less than this we can't be confident that a change has occurred

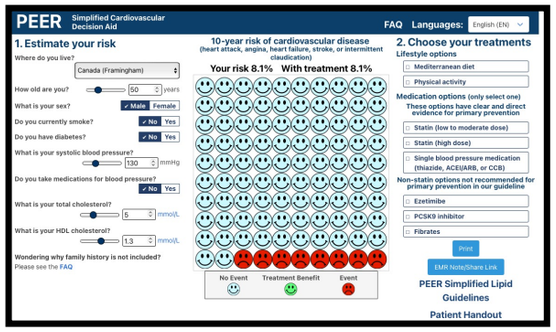
Yearly ⬆ in cholesterol

~1%/year

Preventive Medicine 2000;30:138–45
Ann Intern Med 2008;148:656-61

"Intermediate" Risk Person

50 y/o MALE DIABETIC
Non-smoker
Systolic BP 130 mmHg
Total cholesterol 4.4 mmol/L (170 mg/dL)
HDL 1 (40)



RISK FACTOR CHANGES	Estimated 10-year risk	Estimated absolute benefit Statin ~25%⬇
Baseline	15%	3.8%
⬆10 years in age	25%	6.3%
⬆ 10 years in age + 2%/yr ⬆TC/HDL	26% 30 if just TC⬆	6.5% 7.5
⬆10 years in age + 1mmHg/yr⬆	28%	7%

Case
UTI

“Warning signs” of Pyelonephritis

Fever

Systemic symptoms

Flank pain or tenderness in a patient with symptoms of cystitis

Pyuria

Is it something else?

Vaginal discharge

Painful intercourse

What % of patients with uncomplicated cystitis go on to develop pyelonephritis?

Meta-analysis of 2 RCTs - N=962

No significant difference in risk of pyelonephritis among patients with treated or untreated uncomplicated cystitis (OR 0.33, 95% CI 0.04-2.70)

Treated cystitis: 0-0.15% of patients developed pyelonephritis

Untreated cystitis: 0.4-2.6% of patients developed pyelonephritis

Rx Files Mar 2017

What helps in diagnosing symptomatic uncomplicated urinary tract infections in adult women?

BOTTOM LINE **TFP October 2022**

Individual symptoms and leukocytes on urinalysis generally add little to diagnosis. Presence of nitrites increases the probability of UTI, but their absence means little. About 60% of women presenting to primary care with possible UTI have a UTI (before any history, physical or testing). A single urine culture likely misses cases, meaning prevalence is even higher.

MINI BOTTOM LINE

No testing required

Do we need to use antibiotics to treat uncomplicated symptomatic urinary tract infections?

TFP November 2022

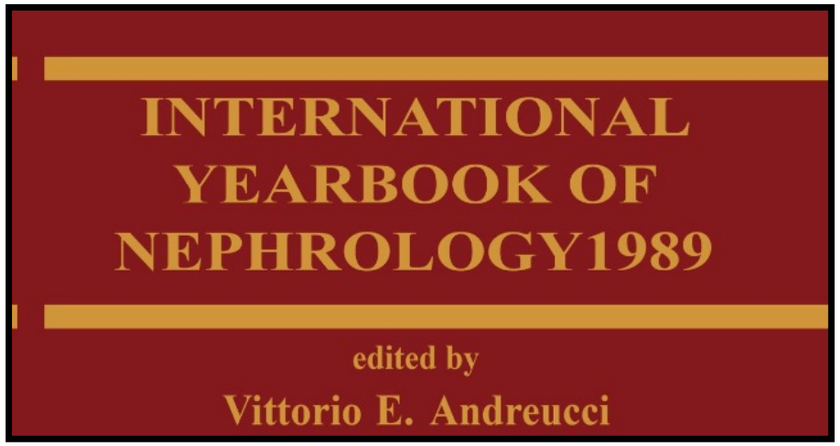
About two-thirds of non-pregnant adult women with uncomplicated symptomatic UTI will have persistent symptoms without treatment. At 3-4 days, 46% of women treated symptomatically with NSAIDs alone will be symptom-free versus 67% given antibiotics. By one month, fever and/or pyelonephritis developed in 1.2% given NSAIDs alone versus 0.2% given antibiotics. Women with uncomplicated symptomatic UTI should be offered antibiotics.

MINI BOTTOM LINE

25-30% get better on placebo

45% with NSAIDs

60-70% on antibiotics



Dosing of antibiotics is somewhat/a lot magical

As recently as the early 1960's urinary infections were often treated with antibiotics for six months or more - perhaps changing the antibiotic every month. This was due to the belief that such infections often progressed to chronic pyelonephritis, a view discredited by the studies of Kimmelstiel (1).

There are quite a few old (70s-80s) trials of single doses of amoxicillin, TMP/SMX, trimethoprim, nitrofurantoin, ciprofloxacin showing effectiveness

Case
Depression

32 year old woman with depression

32 year old woman presents with an 8 month history of persistent low mood, fatigue, anhedonia and poor motivation.

She denies any suicidal ideation. She lives with her partner, who is supportive.

She thinks that she would benefit from taking an antidepressant but is worried about becoming "addicted" to medication

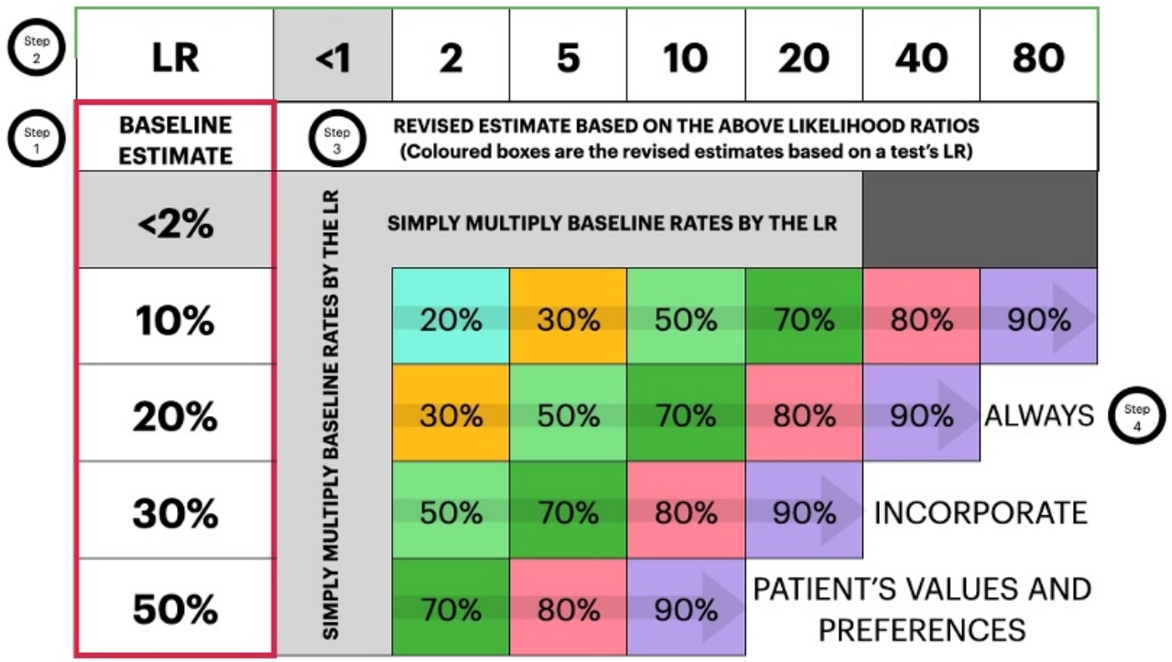
Depression “Screening”

In the last month do you feel depressed?
In the last month have you been bothered by little interest or pleasure in doing things?
Both questions Yes or Both No

LR= 5/0.05

BMJ, doi:10.1136/bmj.38607.464537.7C

10% - pre-test
post test if pos ~30%
post test if neg <1%
20% - pretest
post test if pos ~50%
post test if neg ~1%



Medications for Depression

% of people who benefit in the treatment arm - that will be what you see in practice over placebo

% of people who benefit in the placebo arm - subtract that from the treatment to see how many actually benefit from the medication

6-8 weeks	No longer depressed
Medication	50%
Placebo	40%
Medication benefit	50-40 = 10%
If person responds, the chance it is the medication	10/50 = 20%

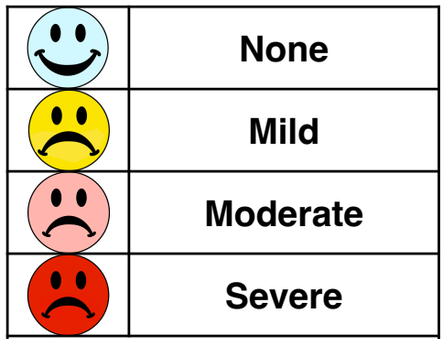
A SUGGESTION FOR HOW TO TAPER SSRIs

Reduce dose by 25% every week
(i.e. week 1-75%, week 2-50%, week 3-25%) and this can be extended or decreased (10% dose reductions) if needed.

If intolerable withdrawal symptoms occur (usually 1-3 days after a dose change), go back to the previously tolerated dose until symptoms resolve and plan for a more gradual taper.

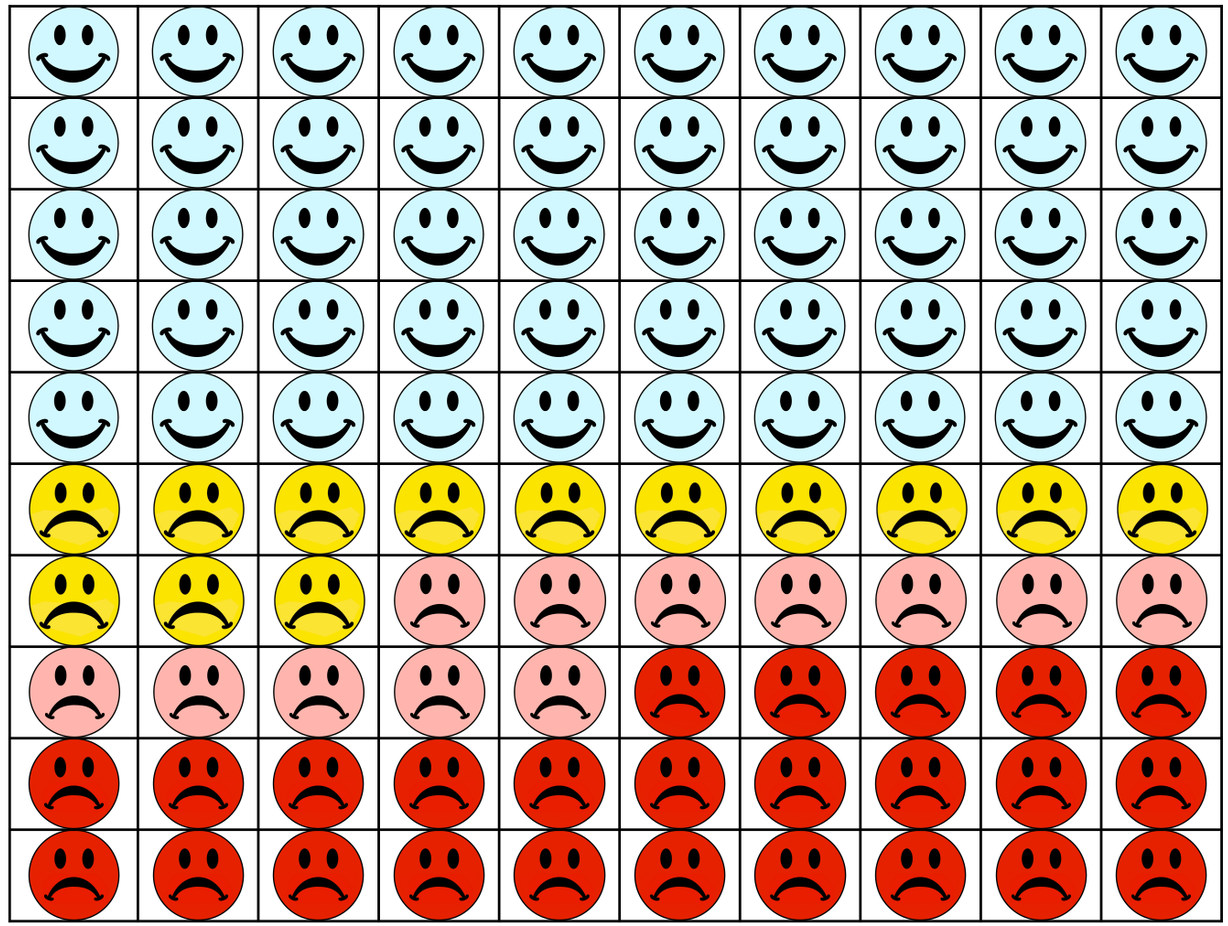
Dose reduction may need to slow down as one gets to smaller doses.

Overall, the rate of discontinuation needs to be controlled by the person taking the medication.



WITHDRAWAL SYMPTOMS
nausea, diarrhea, abdominal pain, sweating, headache, dizziness, cold and flu-like symptoms, anxiety, agitation, distress, irritability, trouble sleeping (often with vivid or disturbing nightmares), unusual sensory experiences (e.g. electric shock-like and other unusual sensations feelings, visual after images), sound and light sensitivity, muscle aches and pains, chills, confusion, pounding heart (palpitations), restlessness and akathisia, unusual movements, mood changes, agitation, distress, rarely suicidal ideation

Severity of withdrawal symptoms in 100 people who try to get off SSRIs



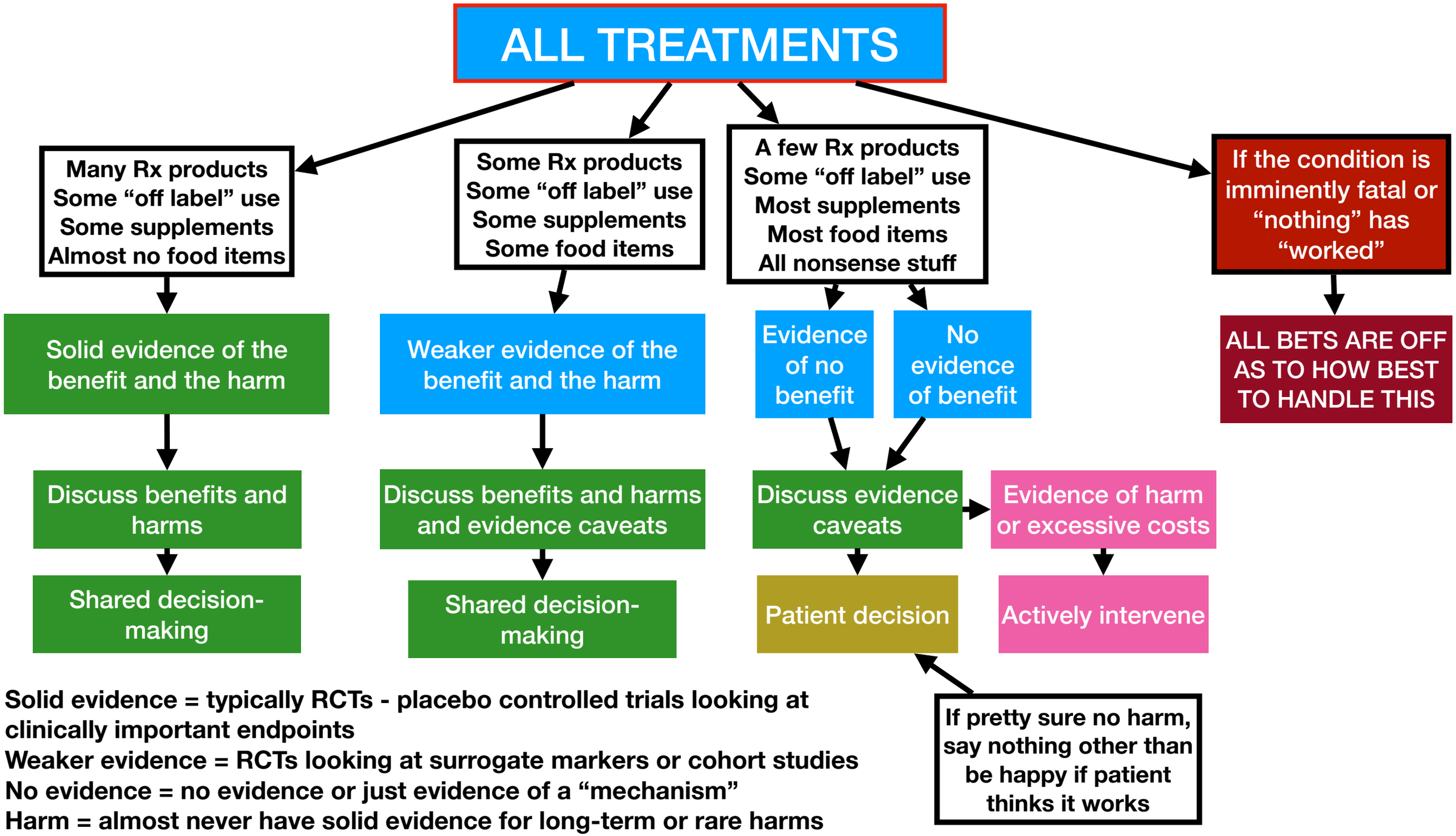
The average duration of symptoms is unclear but seems to be ~ 5-10 days. However, there are many reports suggesting for some patients, (magnitude unclear) symptoms can last weeks to months

Addict Behav. 2018 Sep 4. pii: S0306-4603(18)30834-7. doi: 10.1016/j.addbeh.2018.08.027

Costs

HYPOGLYCEMIC AGENTS						
Biguanides						
Metformin	Glucophage	500 mg	2 BID	**$25**	BC / EIA - Covered	
Metformin SR	Glumetza SR	1000 mg	2 QD	**$225**	BC - NC / EIA - SA	
Dipeptidylpeptidase-4 Inhibitors (DPP-4)						
Linagliptin	**Trajenta**	5 mg	QD	**$280**	BC - SA / EIA - Covered	
Saxagliptin	Onglyza	5 mg	QD	**$305**	BC - SA / EIA - Covered	
Sitagliptin	**Januvia**	100 mg	QD	**$335**	BC / EIA - SA	
Glucagon-like Peptide 1 Agonist (GLP-1)						
Lixisenatide	**Adlyxine**	0.02 mg SQ	QD	**$390**	BC - SA / EIA - Covered	
Semaglutide	**Ozempic**	0.5 mg SQ	Once weekly	**$675**	BC - SA / EIA - Covered	
Glucagon-like Peptide 1 Agonist (GLP-1)-1.2 mg SQ						
Liraglutide	**Victoza**	1.2 mg SQ	QD	**$670**	BC / EIA - NC	
Glucagon-like Peptide 1 Agonist (GLP-1)-1.8 mg SQ						
Liraglutide	**Victoza**	1.8 mg SQ	QD	**$1000**	BC / EIA - NC	
Insulin						
Regular insulin	**Novolin Toronto/Humulin R**	100 U/ml	As dir	**$65**	BC / EIA - Covered	Prices may vary between pharmacies, relative differences likely consistent.Max allowable price for 1500 Units of penfill insulin.
Long-acting insulin	**Novolin NPH/Humulin N**	100 U/ml	As dir	**$65**	BC / EIA - Covered	Prices may vary between pharmacies, relative differences likely consistent.Max allowable price for 1500 Units of penfill insulin.
Rapid-acting insulin	**Apidra**	100 U/ml	As dir	**$75**	BC / EIA - Covered	Prices may vary between pharmacies, relative differences likely consistent.Max allowable price for 1500 Units of penfill insulin.
Rapid-acting insulin	**Novorapid/Humalog**	100 U/ml	As dir	**$85**	BC / EIA - Covered	Prices may vary between pharmacies, relative differences likely consistent.Max allowable price for 1500 Units of penfill insulin.

https://pricingdoc.acfp.ca/pricing/

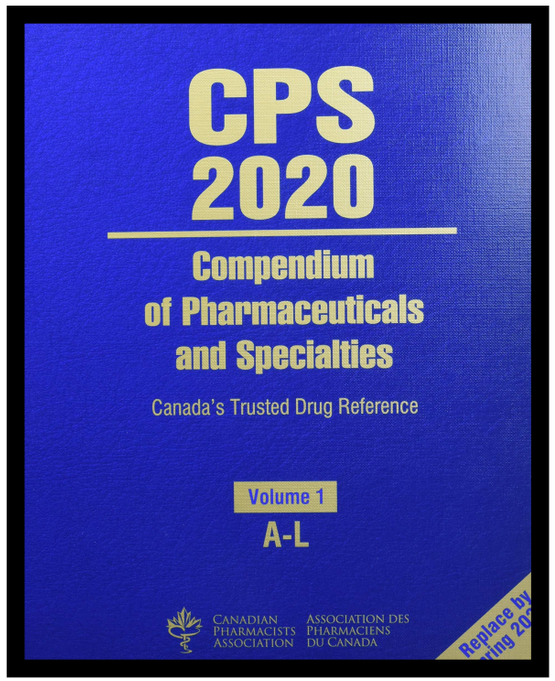


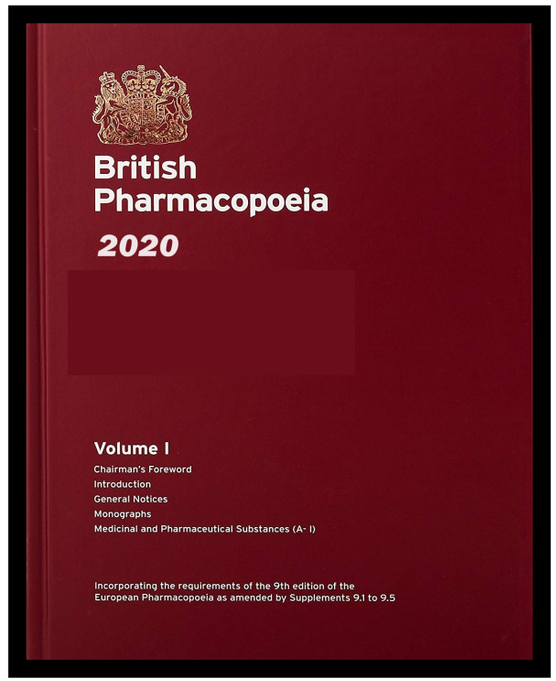
Solid evidence = typically RCTs - placebo controlled trials looking at clinically important endpoints
Weaker evidence = RCTs looking at surrogate markers or cohort studies
No evidence = no evidence or just evidence of a "mechanism"
Harm = almost never have solid evidence for long-term or rare harms

This simple concept can eliminate most medication problems

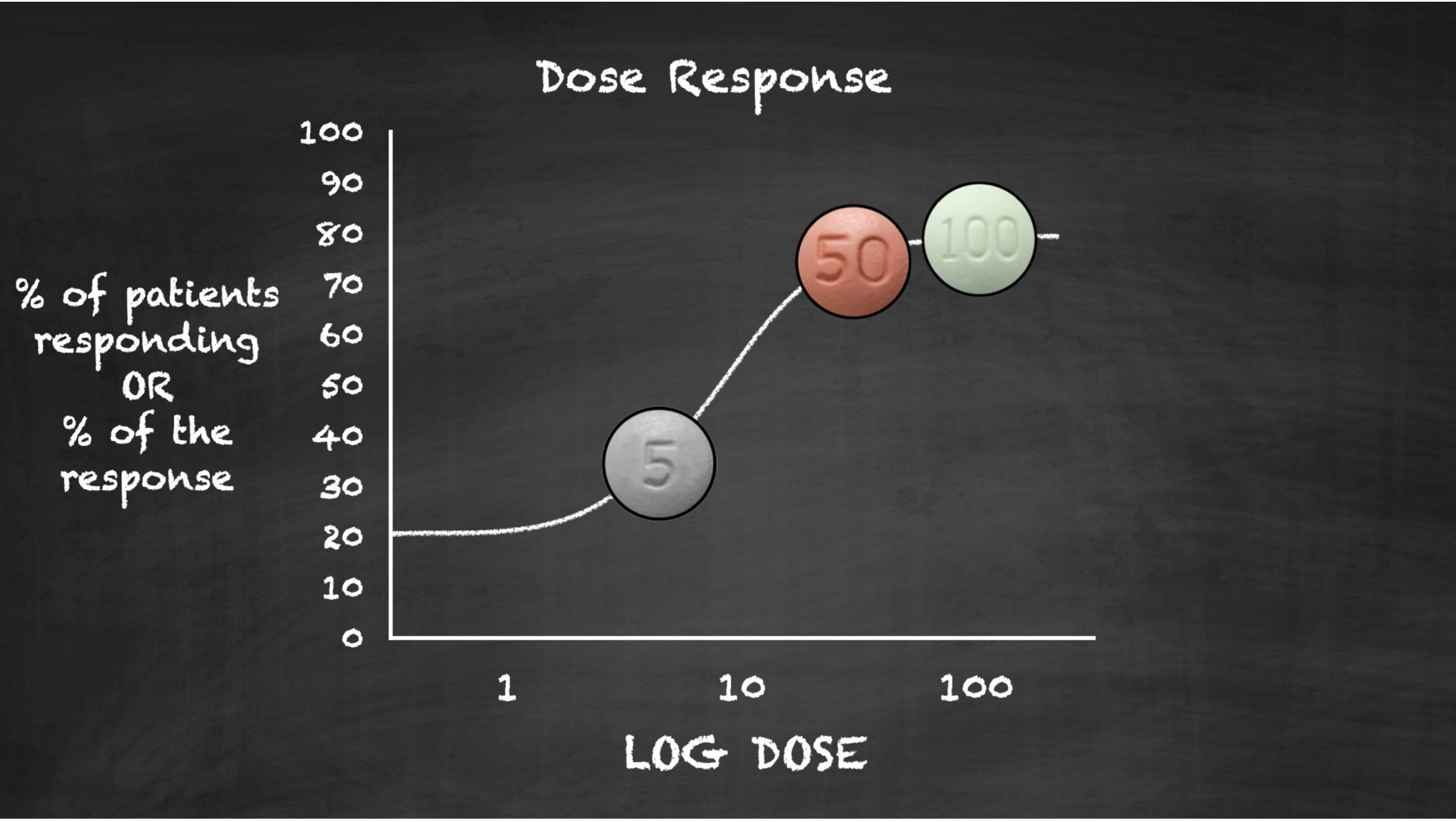
USE VERY LOW DOSES

The doses in these books





are all "WRONG" for individual patients


Dose Response
100
90
80
70
60
50
40
30
20
10
0
% of patients responding OR % of the response
5
50
100
1
10
100
LOG DOSE

”Unless the condition is severe or life-threatening, drug treatment can be started at a very low dose (half or one-quarter the recommended starting dose)”

CMAJ 2011. DOI:10.1503 /cmaj.091481

Most of the effect of a medication comes from the “low” starting doses AND doubling a dose never doubles the effect - in fact it sometimes has no additional effect

Doxepin (Sinequan)

Depression - start 25-50 mg - optimal 75mg -150mg up to 300mg

Doxepin in the Treatment of Primary Insomnia:
A Placebo-Controlled, Double-Blind,
Polysomnographic Study

J Clin Psychiatry
2001;62:453-63

"The results support the effectiveness of low doses (25-50 mg) of doxepin to improve sleep"

INSOMNIA Sleep 2007; 30: 1555–61

Efficacy and Safety of Three Different Doses of Doxepin in Adults with Primary Insomnia

All three doses worked better than placebo
AND
NO side effects over placebo

A recommended low dose was still 25-50 times TOO HIGH

A Dose of Reality

When a new drug comes on the market almost never have more than 2 doses been studied

To get a drug on the market you have to show it works therefore one has to choose a dose that is high enough that if it is going to work it will work in almost everyone

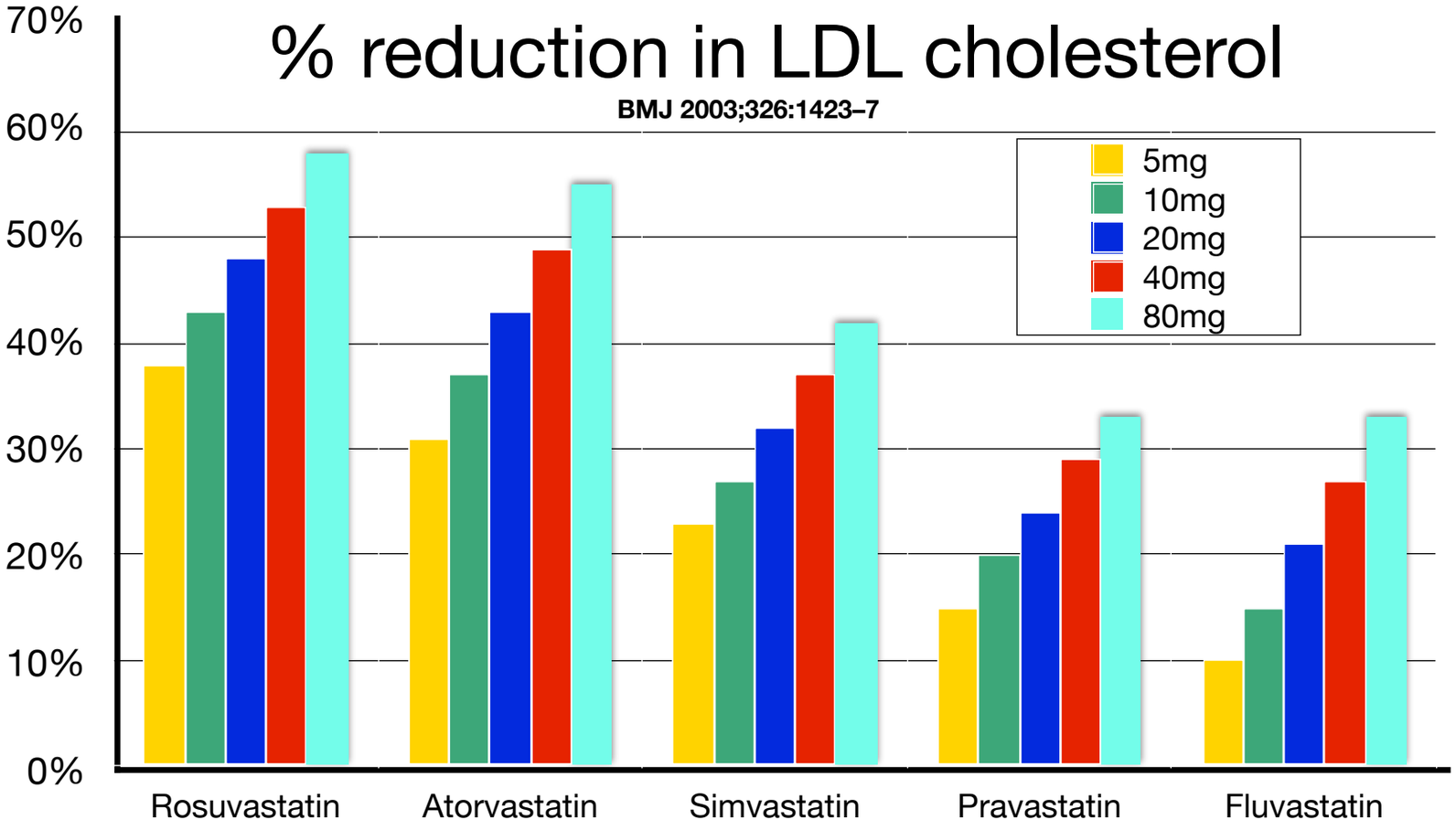
Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999†

dosage changes occurred in 21%
of all new molecular entities

80% were dose decreases

"this pattern may represent a systematic flaw in pre-marketing dosage evaluation; it has been common practice in the pharmaceutical industry to undertake phase III trials evaluating drug effectiveness at or near maximum-tolerated doses."

Pharmacoepidemiology and Drug Safety 2002;11:439–446

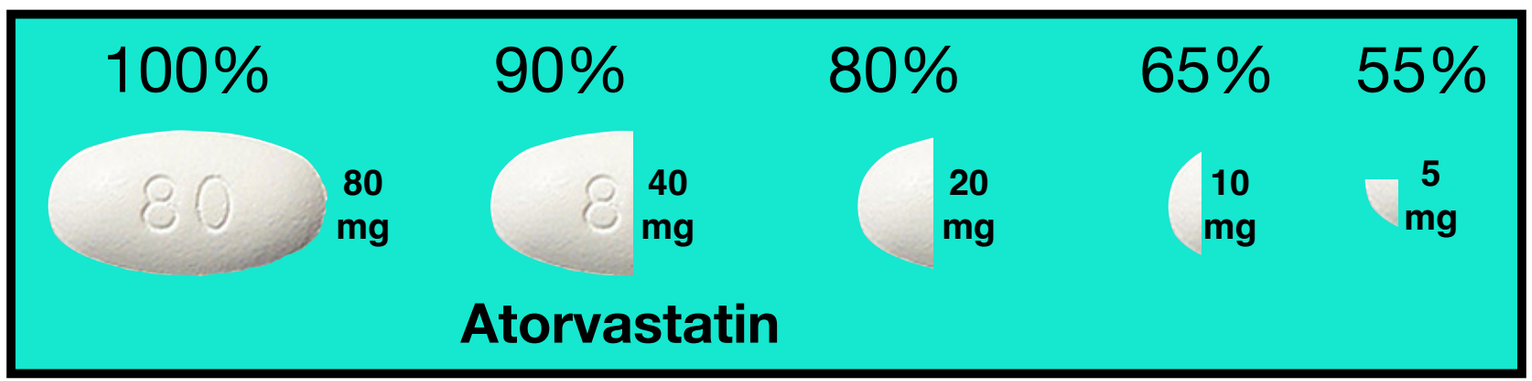


20 mg dose
~ 30% ⬇ in LDL

⬆ 40-80 mg dose
get an extra ~ 10% ⬇ in LDL

20 mg dose of either rosuvastatin or atorvastatin
~ 85-90% of people get at least a 30% or more reduction in LDL

Increasing to 40 or 80 mg
only gets another 5% of people past that 30%



European Heart Journal – Cardiovascular Pharmacotherapy (2016) 2, 212–217 doi:10.1093/ehjcvp/pvw006

A Sample of Low-Dose RCT Evidence

12.5 mg hydrochlorothiazide	first marketed at 50 to 200 mg daily
5 mg daily fluoxetine (Prozac)	similar effects to those seen at 20 mg and 40 mg daily
150 mg daily bupropion (Zyban)	produces the same rate of smoking cessation at one year as 300 mg daily
0.5 mg BID varenicline (Champix)	produces the same rate of smoking cessation at one year as 1.0 mg BID
25 mg ranitidine (Zantac)	as effective as 75 mg and 125 mg for heartburn relief
25 mg sumatriptan (Imitrex)	works as well as100 mg
0.25 mg ezetimibe (Ezetrol)	1/40th of the recommended initial starting dose provides 50% of the LDL lowering effect
1, 3 and 6 mg doxepin (Sinequan)	all doses equally effective for sleep - originally used 25-50 mg
25 mg sildenafil (Viagra)	effective as 50, 100 mg for erectile dysfunction
200 mg ibuprofen (Motrin)	as effective as 400 mg for migraine headache
1.8 mg colchicine	as effective as 4.8mg for acute gout with less adverse events
15 mg elemental iron daily	as effective for anemia in elderly as 50 mg and 150 mg with a lower incidence of side effects
6.25 mg captopril (Capoten)	25 mg PO TID is still a commonly recommended initial starting dose for hypertension

CMAJ 2011. DOI:10.1503 /cmaj.091481

Advantages of starting with “very” low doses

1. Get the potential “placebo group effect” without deception
2. Patients are engaged in the process of finding the best dose for them
3. Cost savings can be considerable and most adverse events can be minimized
4. Most clinically relevant drug interactions can be avoided

Approaches differ depending on outcome

Every patient is an experiment - dose and effect

SYMPTOMS - we can usually figure out if it is working - but it is tricky

PREVENTION - one will never know if it worked

Expectations

We need to do these LESS

follow guidelines LESS

treat to preventative thresholds LESS

worry about surrogate markers LESS

label LESS - pre-everything

stress about what we eat LESS

WAY LESS MECHANISM OF ACTION - just the best available evidence

nuanced/personalized nutrition - low carbs, low fat, high fat, high carbs, polyphenols, lectins, flavanols, antioxidants

lab testing and measurements LESS

screening LESS - next year’s talk :)

We need to do these MORE

MORE shared-decision making

MORE discussion around preventative thresholds

MORE focus on evidence that looks at important clinical outcomes

MORE explaining the best available evidence

MORE explaining the huge uncertainty we have in healthcare

MORE lower doses

encourage eating the Mediterranean Diet in Moderation - best weight you can achieve being healthy and enjoying life

encourage the enjoyment of eating

encourage doing physical activity people enjoy

When do we have debate about health issues?

1. the answer may be impossible to know
2. the best available evidence is tenuous
3. the potential difference in outcome is “small”
4. there is a belief about “a mechanism”
5. the stakes are high - pharmaceutical and nutrition beliefs are very “marketable”

FOOD, especially with individual nutrients, HAS ALL OF THESE

2015 DGAC: MEETING 7 December 15, 2014

Science Base Chapter:

Food and Nutrient Intakes, and Health: Current Status and Trends

Subcommittee 1

health.gov

HOWEVER, THE FINAL REPORT RELEASED IN JANUARY 2016 STATED "individuals should eat as little cholesterol as possible"

- Chol… …it of concern for

…Intakes, and Health: Current Status and Trends

THE NUTRITION PROPOSITION

HOME ABOUT WHY READ THIS BOOK? THE MENU SAMPLES REVIEWS FAQs CONTACT

RELEASED APRIL 2022

updated regularly

What does the evidence really say about your food choices?

Read The Introduction

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The Nutrition Proposition
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Paperback or Kindle Edition

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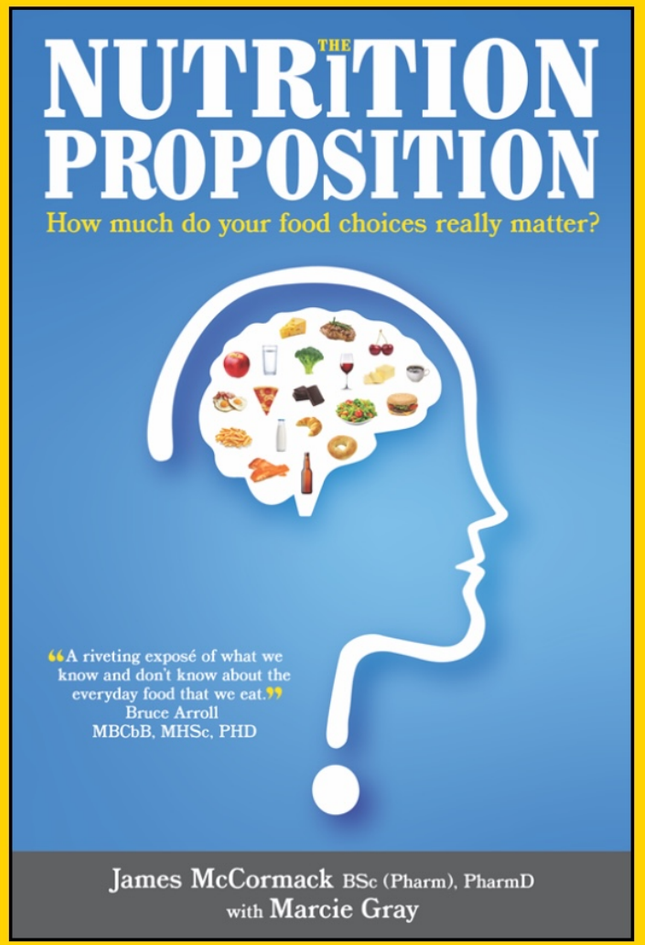


"The Nutrition Proposition is a mammoth contribution to the world's understanding of the science behind nutritional hype. James McCormack helps strip the science of nutrition down to its bare essentials."

Alan Cassels
Author of Selling Sickness and Seeking Sickness

"A riveting expose of what we know and don't know about the everyday food that we eat."

Bruce Arroll, MBChB, MHSc, PhD
Head of the Department of General Practice
and Primary Health Care University of Auckland

"I would recommend this book for anyone who communicates with the public about health - who might not be well prepared to explain the nuance that exists with almost any health-related study, and certainly studies on nutrition topics. The authors' depth of experience, appreciation for history, case examples, and humour make this a meaningful addition to a syllabus or a personal library."

Gary Schwitzer
Publisher, HealthNewsReview.org

The Only Nutrition Book That Won't Tell You What To Eat!!

But It Will Tell You What We Know And Don't Know About Food

nutritionproposition.com

It’s really easy to simply state these things are good or bad for your health

Drinking 2, 4, 6 or 8 glasses of water a day

Drinking 0, 1, 2 or 3 alcoholic beverages a day

Eating 2, 3, 4, 5, 6 or 7 servings of fruits and vegetables a day

Eating 0, 1, 2 or 3 eggs a day

Adding salt to food

Restricting or increasing the amount of carbs, fat and protein

Adding sugar to 1, 2, 3, 4 or 5 cups of coffee or tea a day

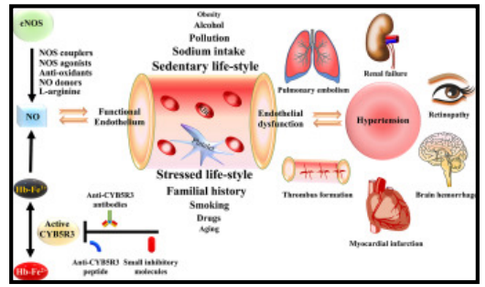
Being a meat eater, a vegetarian, or a vegan

Eating a doughnut, cheesecake, ice cream, or chocolate

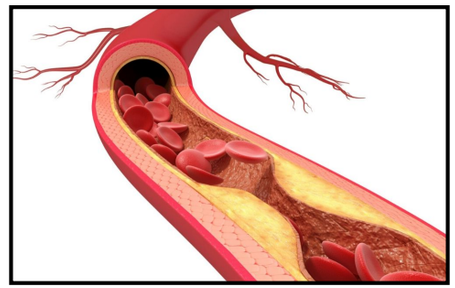
Drinking a glass of milk or a soft drink a day

Eating an apple a day

Everything is “linked”

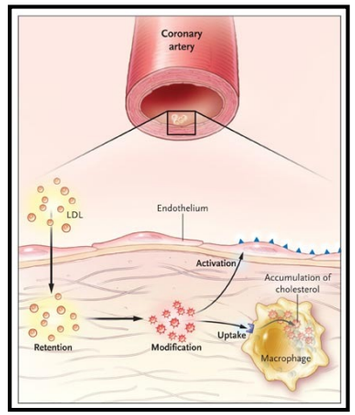


“Clogged” arteries



“Smart” words

Images with “arrows”



“Medical” References

The impact of nutrition on **SURROGATE markers (lipids, blood pressure etc)** and the impact that has on **ESTIMATED heart attack/stroke risk**

EXAMPLE
50 y/o female
Non-smoker
No diabetes
Total cholesterol - 5.2 mmol/L (200 mg/dl)
HDL - 1.3 mmol/L (50 mg/dL)
Systolic blood pressure - 130 mmHg

→

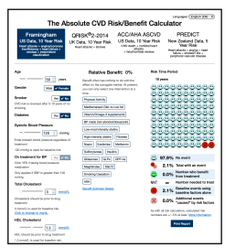
10 year heart attack/stroke risk
5%
8% IF MALE

→

Surrogate change from being vegetarian vs omnivore
Total cholesterol ⬇11%
HDL ⬇6%
Systolic blood pressure ⬇5mmHg

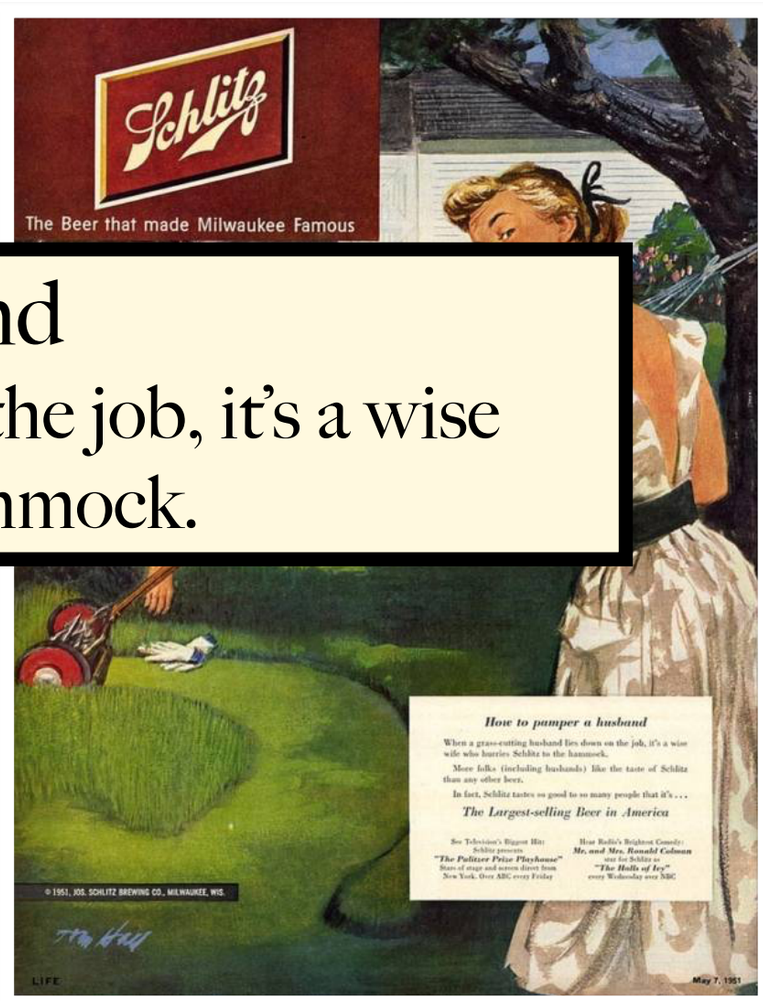
REASONABLE ESTIMATE OF THE IMPACT ON RISK
~1% absolute decrease over 10 years
~2% absolute decrease over 20 years

The Absolute CVD Risk/Benefit Calculator
cvdcalculator.com



Studies of the Mediterranean diet show it produces minimal if any changes on surrogate markers

The Golden? Days of Alcohol



How to pamper a husband

When a grass-cutting husband lies down on the job, it's a wise wife who hurries Schlitz to the hammock.

Alcohol ingestion can absolutely be harmful

CONTEXT MATTERS

The psychosocial impacts of alcohol ABUSE are devastating to individuals, families and the general public - cirrhosis, violence, accidents

Drinking and driving is 1000% wrong - SELFISH!!

Binge drinking can lead to very poor judgments

Anything more than 3 drinks a day is likely a health issue
BUT what about 1, 2, or 3

A History Lesson

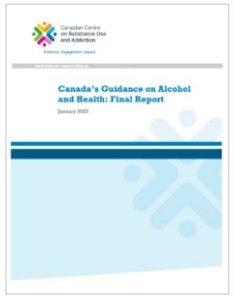
REPORT

Alcohol and Health in Canada: A Summary of Evidence and Guidelines for Low-Risk Drinking

Alcohol | Health Effects

2011

Publication date: 2011
Author: Canadian Centre on Substance Use and Addiction



REPORT

Canada's Guidance on Alcohol and Health: Final Report

Alcohol

2023

Publication date: 2023
Author: Canadian Centre on Substance Use and Addiction

"no more than
10 drinks a week for females
and **15 drinks for males**"

Do not drink and drive

Do not drink when pregnant

"A continuum of health risk starting with consumption as low as

3 standard drinks per week"

"We now know that even a small amount of alcohol can be damaging to health"

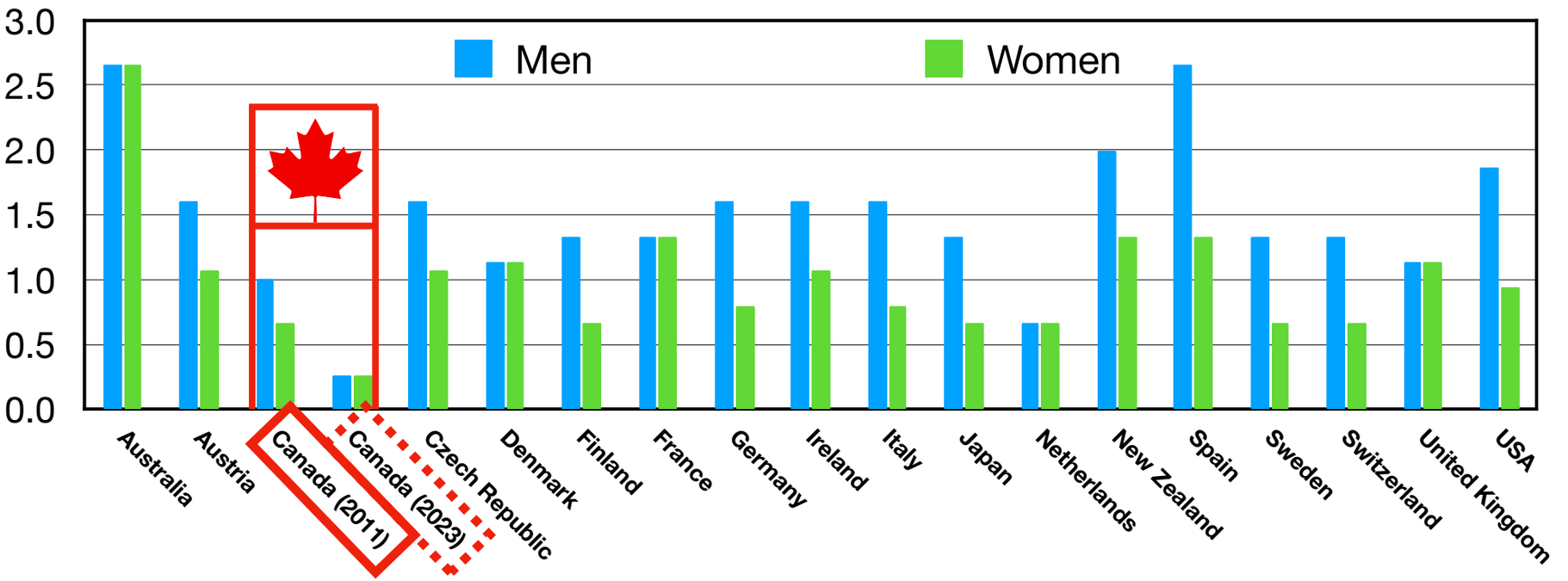
"Drinking alcohol, even a small amount, is damaging to everyone"

Canadian Centre on Substance Use and Addiction
Evidence. Engagement. Impact.

Across The 🌍

Recommended maximum intake of alcoholic beverages

Drinks/day



Release dates of these recommendations are variable

IARD
INTERNATIONAL ALLIANCE FOR RESPONSIBLE DRINKING

How Much Do We drink?

	Zero	If you do drink - typical drinking day		
		1-2/day	3-4/day	5+ a day
Women	23%	74%	17%	9%
Men	18%	54%	23%	23%

2005 (over the past year) - https://www.ccsa.ca/sites/default/files/2019-05/ccsa-004028-2005.pdf

Alcohol

Lancet 2018

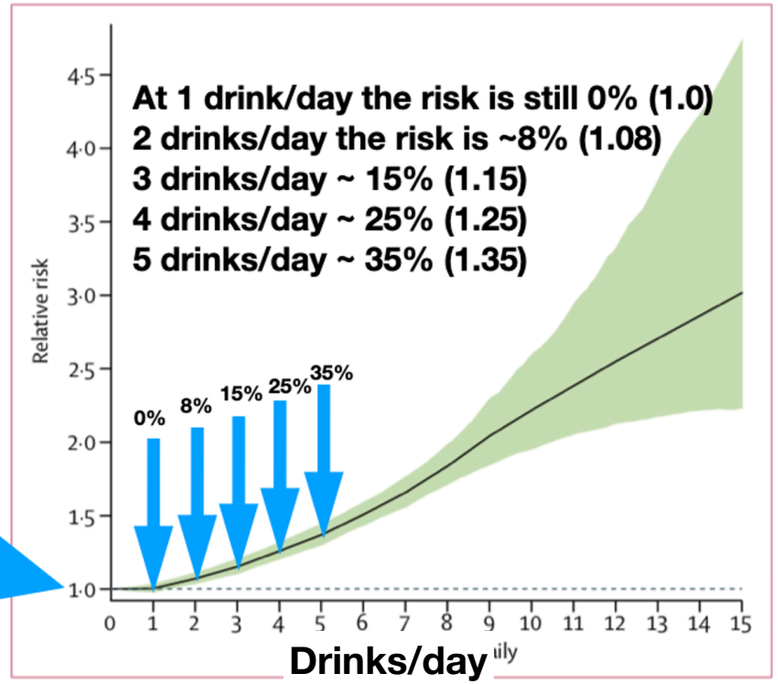
Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

*GBD 2016 Alcohol Collaborators**

"We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption and

the level of consumption that minimises health loss is zero"

1.0 means no increased risk of mortality attributable to alcohol



ABSOLUTE NUMBERS - the number who would experience an alcohol related problem

OVER ONE YEAR	Additional people out of 100,000	Extrapolated Increase over 30 years
1 drink a day	4	0.1%
2 drinks a day	63	1.5%
5 drinks a day	338	10%

TOP 3 HARMS - tuberculosis, road injuries, self harm

HEALTH

Proposed update to Canada's alcohol guidelines suggests as few as 3 drinks per week

By **Cassandra Szklarski** · **The Canadian Press**
Posted August 30, 2022 1:23 pm · Updated August 30, 2022 6:42 pm

HEALTH | News

Proposed alcohol guidelines recommend no more than 2 drinks per week

A new measure of unhealthy drinking

PUBLISHED SEPTEMBER 1, 2022

If you have three or more alcoholic drinks in a week, you're putting your health at risk. That's according to a new report from the Canadian Centre on Substance Abuse and Addiction (CCSA). The government of Canada's current recommendations are more than a

CALGARY | News

Calgarians react to new guidelines for alcohol intake

Having three to six drinks per week increased the risk to moderate, while having more than six was found to contribute to increased risks of cancer, stroke, heart disease and situations of violence.

HOME > LOCAL NEWS

1 drink a day means higher risk of heart disease, stroke, cancer: Report

A recent report highlights the many health risks associated with consuming just one alcoholic drink a day

Michael Ranger
Sep 5, 2022 3:00 PM

Living

Are Canadians drinking too much alcohol?

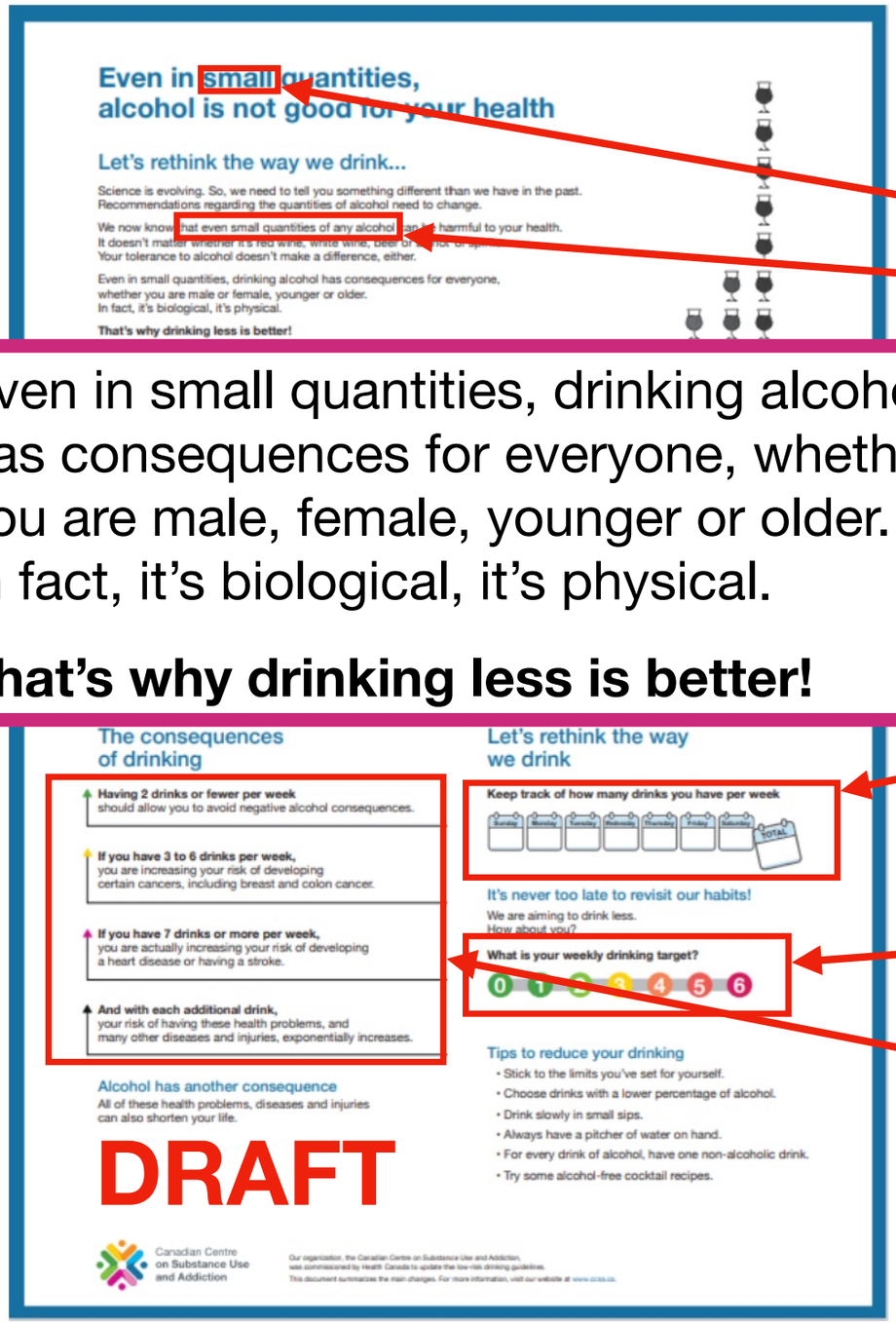
By **NetNewsLedger** - September 7, 2022 182

Are Canadians Drinking too much?

THIS IS THE PUBLIC SUMMARY (August 2022)

created by the Canadian Center on Substance Use and Addiction

and they asked for public consultation



Even in small quantities, drinking alcohol has consequences for everyone, whether you are male, female, younger or older.
In fact, it's biological, it's physical.

That's why drinking less is better!

The terms small, low, moderate, increasingly high risk are too subjective and in no way inform people as to the actual size of the risks

Not sure the weekly amount is all that useful - likely better to think about drinks per day given that when people "drink", they drink "daily"

Not sure of the point of having a weekly target of drinks - kind of sounds like a challenge to achieve either high or low

There are no numbers here and it implies each category has only the risks listed - there is no mention of liver cirrhosis which may numerically be the largest risk

Why Did They Choose Not To Include Numbers?

Public Consultation: Summary of Key Actions Taken

The responses received from the open consultation were analyzed and categorized. The table below presents the main categories of comments as well as the actions taken by the LRDG-Scientific Expert Panel (LRDG-SEP) to address comments which fell within the scope of this project's mandate.

There were several suggestions made for knowledge mobilization activities, including knowledge synthesis, dissemination, transfer and exchange. These suggestions have been recorded but are not listed here as they could not be considered for action (i.e., could not lead to edits and revisions of the final report).

Consultation comment or suggestion	Action taken
Public Summary	
Provide more information about specific cancers.	There are already many consequences of different types

The objective of the document is to communicate information without statistics that would need contextual information and more explanations to be easily understood. No statistics were added.

USE WITH CAUTION - the numbers below are my attempt at trying to get useful numbers (I spent 1/2 a day extracting data) from the August 2022 publication "Update of Canada's Low-Risk Alcohol Drinking Guidelines: Final Report for Public Consultation". I've listed where I got the numbers and more than happy to correct if there are errors or misinterpretation

TO HELP YOU MAKE AN INFORMED DECISION
HERE ARE THE LIFETIME RISKS OF 1 TO 3 ALCOHOL DRINKS DAILY

THIS IS CONSIDERED A DRINK

"From Fig 1/Fig 2 - Lifetime Risk of Alcohol-Attributable Death and Disability paper"

LIFETIME RISK (absolute%)

DRINKS/ per day	1	2	3
			
	PREMATURE (before age 75) ALCOHOL ATTRIBUTABLE DEATH		
Females	0.5%	1.5%	2.5%
Males	0.5%	2%	3%
	ALCOHOL ATTRIBUTABLE DEATH		
Females	1.5%	4%	7%
Males	1.5%	4%	7%

All the numbers are ballpark estimates based on the best available evidence

"From Appendix 2 - Table 1 and 2"

CAUSES OF DEATH

Cancer
25%-33%*

Liver cirrhosis
20-25% in women
45-60% in men

Cardiovascular
10-25% in women
5-10% in men

Road injuries/or intentional injuries
20% in women
40% in men

Should reduce this risk somewhat

DON'T DRINK AND DRIVE

DON'T DRINK IF YOU ARE PREGNANT

*colorectal/breast/liver/oesophagus/mouth/pharnyx/larynx

The Top 5 Harms

CONTEXT MATTERS

4 were the same for men and women

intentional injuries

unintentional injuries

liver cirrhosis

colorectal cancer

DON'T DRINK IF YOU DO STUPID THINGS

DON'T DRINK AND DRIVE

and then breast cancer (women) and road injuries (men)

Lifetime cancer risk

Breast cancer

lifetime risk of dying would increase from 3% to roughly 3.5%

Colorectal cancer

lifetime risk of dying would increase from 3.0% to roughly 3.3%

Cirrhosis

CCSA reports that 1-2 to two drinks a day increases the risk of liver cirrhosis in both men and women
the single paper they use to support these claims states quite clearly that, “although consumption of 1–2 drinks was associated with a substantially elevated risk for liver cirrhosis in women, this was not the case in men”

based on the CCSA numbers

Alcohol Risk Visualizer

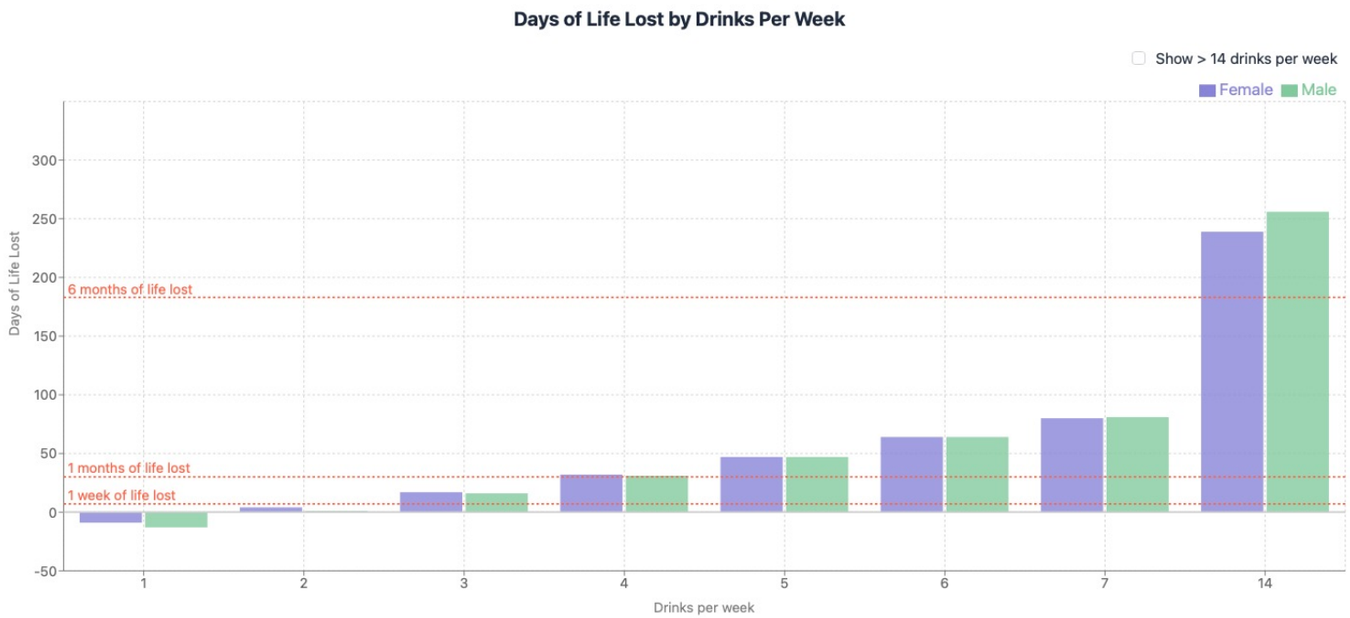
Based on the latest CCSA report on the lifetime risk of alcohol-attributable death and disability.

This chart shows how many days of life, on average, an individual could lose based on the amount of drinks they have per week.

myalcoholrisk.com

The CCSA considers one drink as:

- 341 ml (12 oz) of beer 5% alcohol or cooler 🍺
- 142 ml (5 oz) of wine 12% alcohol 🍷
- 43 ml (1.5 oz) of spirits (whiskey, vodka, gin, etc) 40% alcohol 🥃

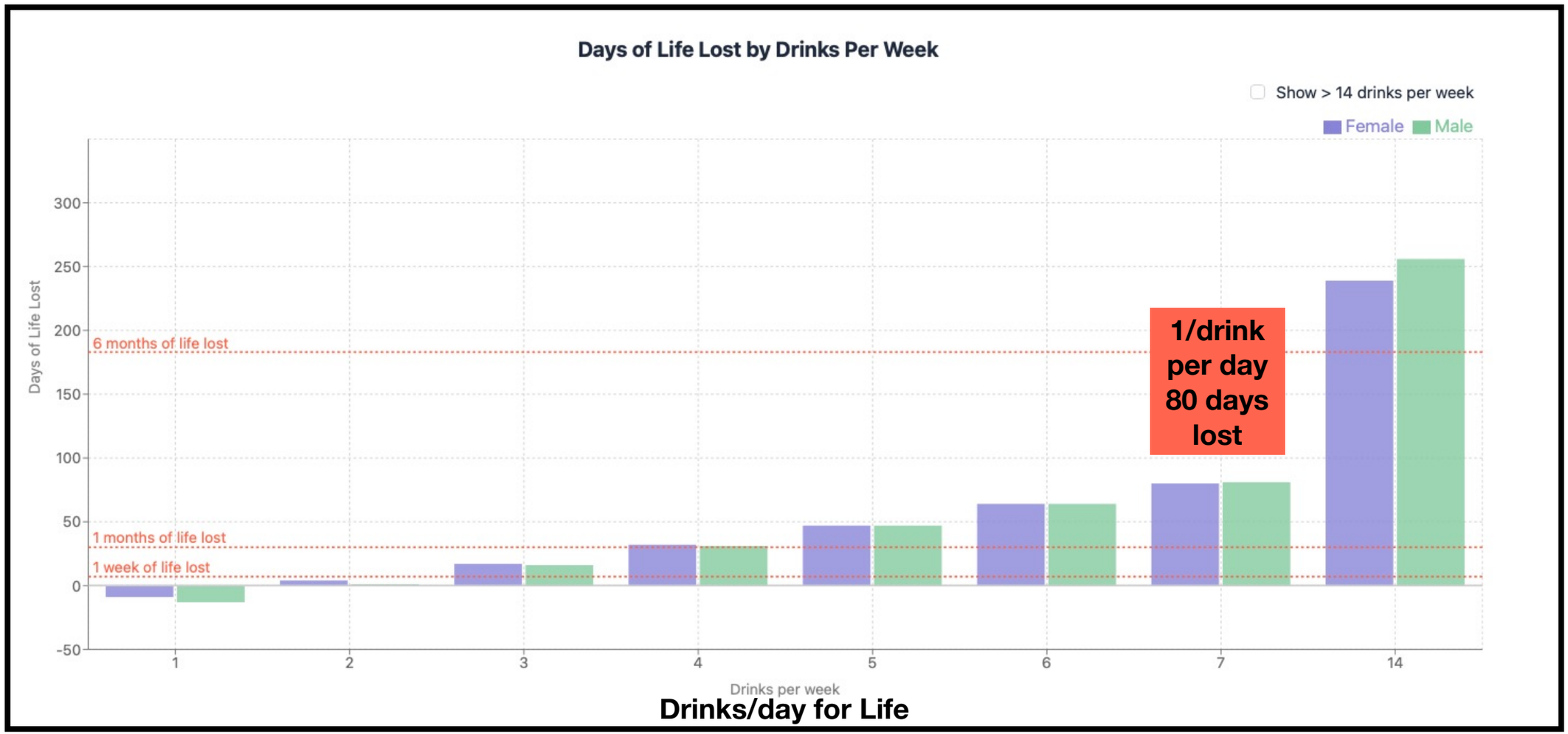


Combined Risk from 21 Different Health Outcomes

Disease selectors allow you to select the diseases you're interested in. For example, consider removing physical injuries if you don't drink and drive and you are not reckless when you drink.

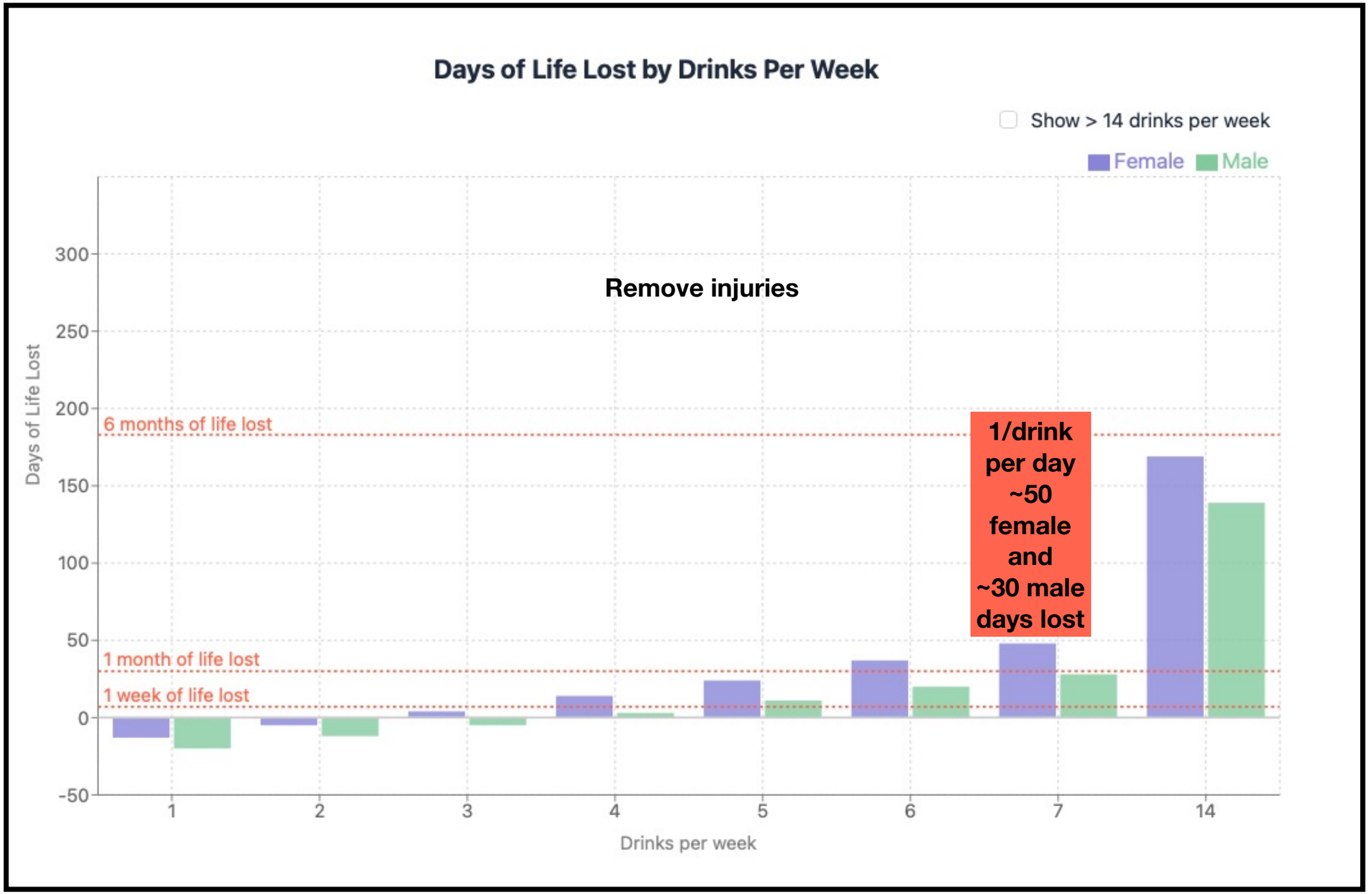
- **Cancer**
  - Oral cavity and pharynx cancer
  - Oesophagus cancer
  - Colorectal cancer
  - Liver Cancer
  - Breast cancer
  - Larynx Cancer
- **Cardiovascular Diseases**
  - Diabetes
  - Atrial fibriliation and flutter
  - Hypertension
  - Ischemic heart disease
  - Ischemic stroke
  - Intracerebral hemorrhage
  - Subarachnoid haemorrhage
- **Liver Damage**
  - Liver cirrhosis
- **Physical Injuries**
  - Road injuries
  - Other unintentioal injuries
  - Intentional injuries
- **Other**
  - Tuberculosis
  - Lower respiratory infections
  - Pancreatitis
  - Epilepsy

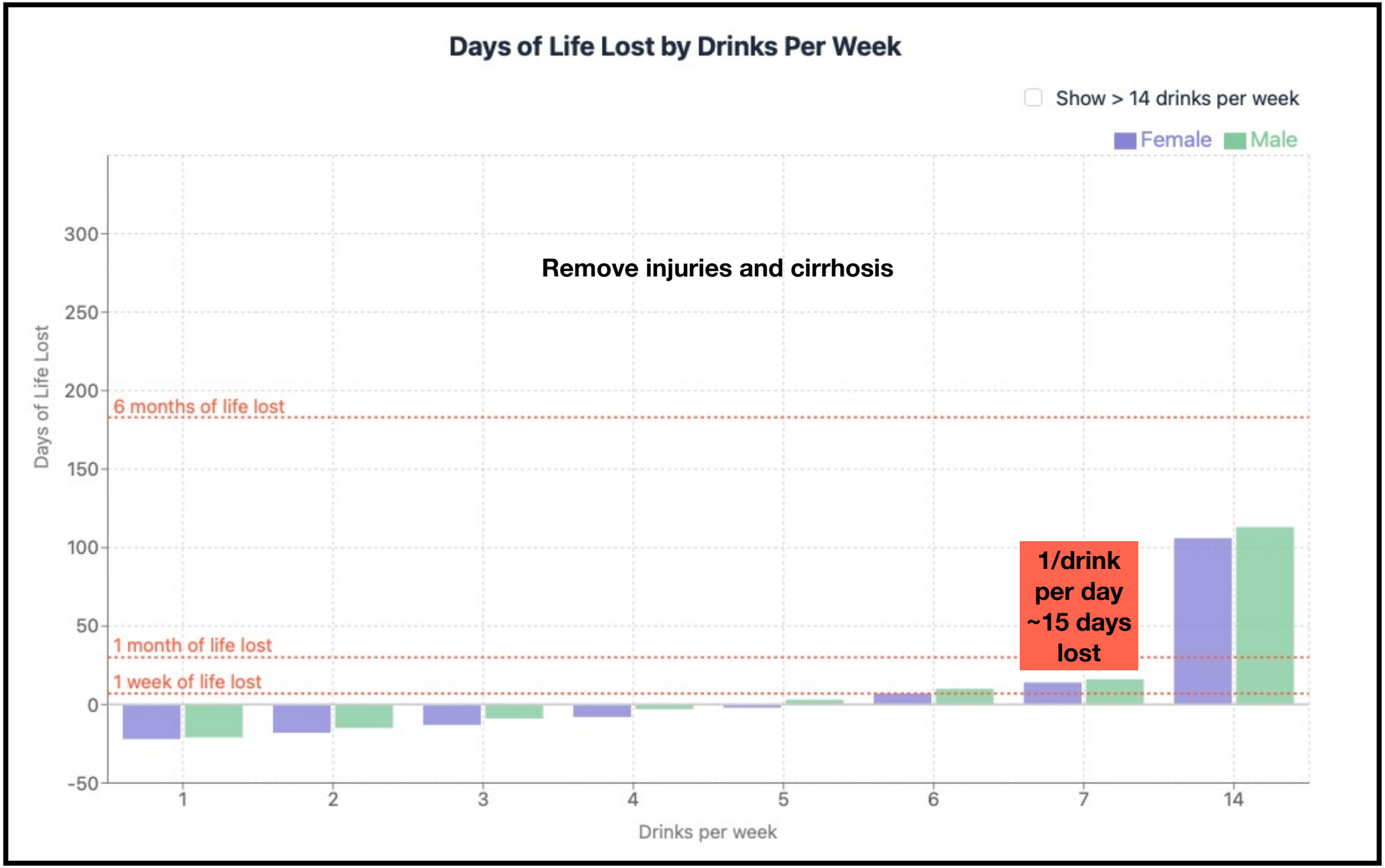
Days of Life Lost

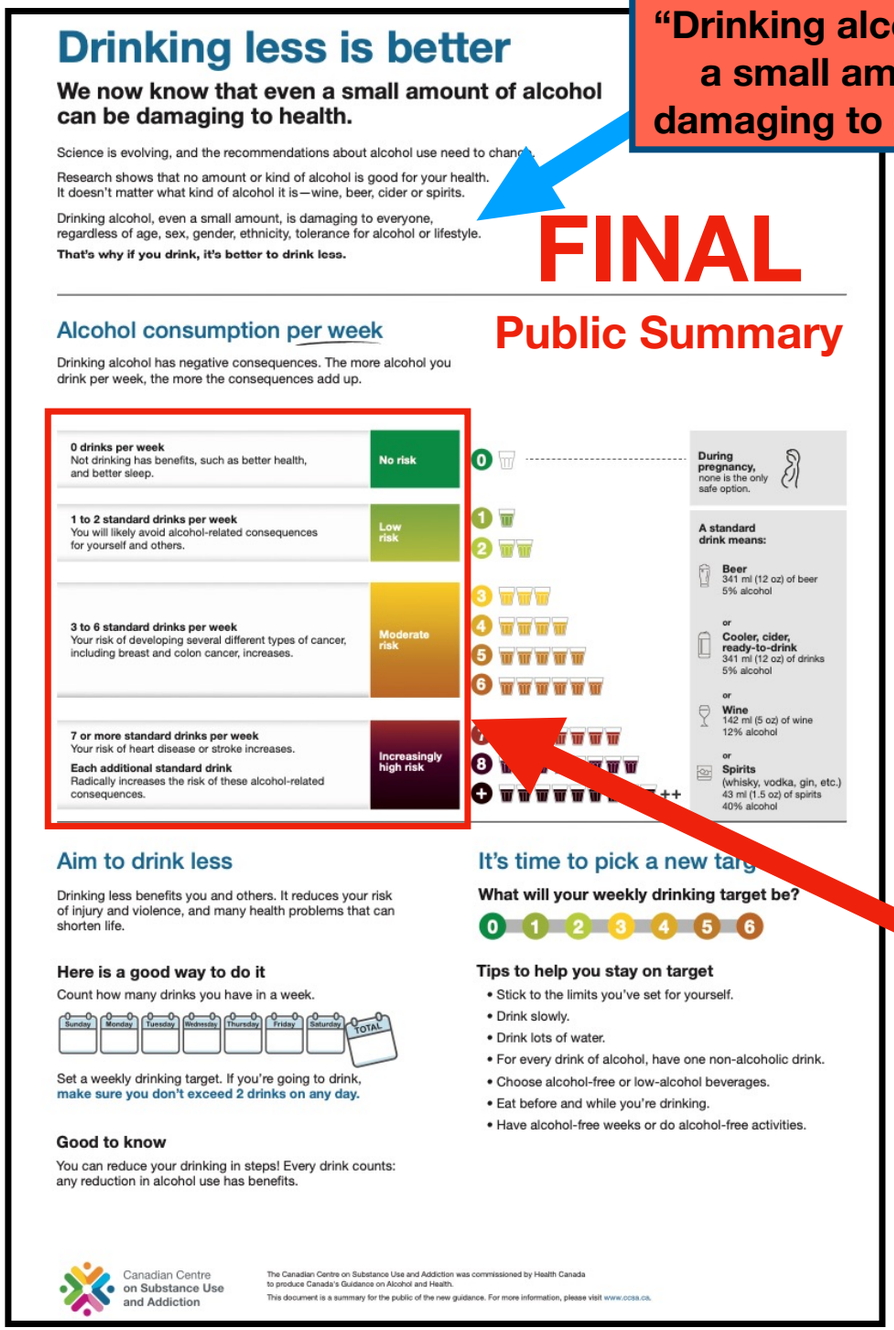


Drinks/day for Life

https://myalcoholrisk.com


Days of Life Lost by Drinks Per Week
Show > 14 drinks per week
Female
Male
Remove injuries
1/drink per day ~50 female and ~30 male days lost
6 months of life lost
1 month of life lost
1 week of life lost
Days of Life Lost
300
250
200
150
100
50
0
-50
1
2
3
4
5
6
7
14
Drinks per week


Days of Life Lost by Drinks Per Week
Show > 14 drinks per week
Female
Male
Remove injuries and cirrhosis
Days of Life Lost
300
250
200
150
100
50
0
-50
6 months of life lost
1 month of life lost
1 week of life lost
1/drink per day ~15 days lost
1
2
3
4
5
6
7
14
Drinks per week



Drinking less is better

We now know that even a small amount of alcohol can be damaging to health.

Science is evolving, and the recommendations about alcohol use need to change.

Research shows that no amount or kind of alcohol is good for your health. It doesn't matter what kind of alcohol it is—wine, beer, cider or spirits.

Drinking alcohol, even a small amount, is damaging to everyone, regardless of age, sex, gender, ethnicity, tolerance for alcohol or lifestyle.

That's why if you drink, it's better to drink less.

Alcohol consumption per week

Drinking alcohol has negative consequences. The more alcohol you drink per week, the more the consequences add up.

0 drinks per week — No risk
Not drinking has benefits, such as better health, and better sleep.

1 to 2 standard drinks per week — Low risk
You will likely avoid alcohol-related consequences for yourself and others.

3 to 6 standard drinks per week — Moderate risk
Your risk of developing several different types of cancer, including breast and colon cancer, increases.

7 or more standard drinks per week — Increasingly high risk
Your risk of heart disease or stroke increases.
Each additional standard drink
Radically increases the risk of these alcohol-related consequences.

During pregnancy, none is the only safe option.

A standard drink means:

- **Beer** 341 ml (12 oz) of beer 5% alcohol
- or **Cooler, cider, ready-to-drink** 341 ml (12 oz) of drinks 5% alcohol
- or **Wine** 142 ml (5 oz) of wine 12% alcohol
- or **Spirits** (whisky, vodka, gin, etc.) 43 ml (1.5 oz) of spirits 40% alcohol

Aim to drink less

Drinking less benefits you and others. It reduces your risk of injury and violence, and many health problems that can shorten life.

Here is a good way to do it

Count how many drinks you have in a week.

Sunday Monday Tuesday Wednesday Thursday Friday Saturday TOTAL

Set a weekly drinking target. If you're going to drink, **make sure you don't exceed 2 drinks on any day.**

Good to know

You can reduce your drinking in steps! Every drink counts: any reduction in alcohol use has benefits.

It's time to pick a new targ

What will your weekly drinking target be?

0 1 2 3 4 5 6

Tips to help you stay on target

- Stick to the limits you've set for yourself.
- Drink slowly.
- Drink lots of water.
- For every drink of alcohol, have one non-alcoholic drink.
- Choose alcohol-free or low-alcohol beverages.
- Eat before and while you're drinking.
- Have alcohol-free weeks or do alcohol-free activities.

Canadian Centre on Substance Use and Addiction

The Canadian Centre on Substance Use and Addiction was commissioned by Health Canada to produce Canada's Guidance on Alcohol and Health.
This document is a summary for the public of the new guidance. For more information, please visit www.ccsa.ca.

"Drinking alcohol, even a small amount, is damaging to everyone"

FINAL

Public Summary

My Opinion

The 2023 CCSA Alcohol Guidelines:

1. Are misleading
2. Don't provide appropriate "context"
3. Create unnecessary fear and confusion
4. In no way inform the public as to the absolute risks/benefits
5. Very likely have nothing to do with your values and preferences
6. Ignore the research (although it's not great) around the functional social benefits - they state it was "out of the scope for this summary" yet their research question clearly states "What are the risks and **benefits** (physical and mental health, and social impact)"

A number of their harm comments are not supported by their own data and their data show a CVD benefit at 1 drink a day that is greater than the cancer risks and this is not mentioned

Functional Benefits of (Modest) Alcohol Consumption

R. I. M. Dunbar[1] · Jacques Launay[1] · Rafael Wlodarski[1] ·
Cole Robertson[1] · Eiluned Pearce[1] ·
James Carney[1] · Pádraig MacCarron[1]

"Despite considerable research on the misuse of alcohol, no one has ever asked why it might have become universally adopted, although the conventional view assumes that its only benefit is hedonic"

"social drinkers have more friends on whom they can depend for emotional and other support, and feel more engaged with, and trusting of, their local community"

Adaptive Human Behavior and Physiology (2017) 3:118–133

Is a Glass of Wine Harmless? Wrong Question.

The latest alcohol advice ignores the value of pleasure.

By Emily Oster

The Atlantic
JULY 14, 2023

“A pleasure-agnostic approach to health advice is now in vogue … and is filtering down to the general public with sometimes absurd results.”

“Are there any data on health benefits to orgasms? The point of orgasms is that they are fun. We do not need to prove health benefits to want to have them.”

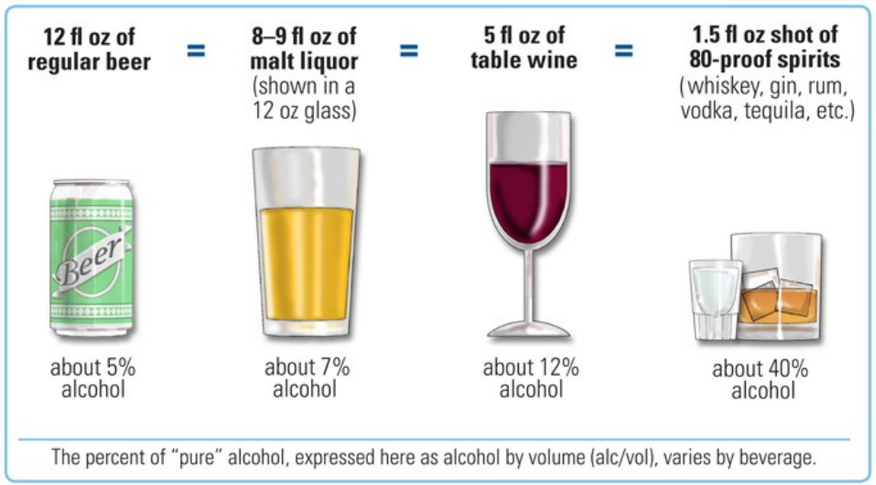
“Alcohol is probably not the key to longevity. But it’s not arsenic, either. In the immortal words of Cookie Monster, it’s a sometime food.”

The Bottom Line

If you have a history of an alcohol problem or are pregnant - DON'T DRINK

If you drink and drive, become aggressive when you drink, or have a history of doing stupid things when you drink - DON'T DRINK TO EXCESS

1-2 drinks a day doesn't seem to produce an INDIVIDUAL health risk OR benefit



Do I/You have an Alcohol Problem?

Just ask

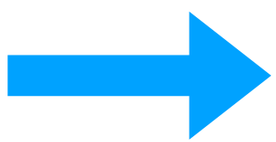
One Question

The NIAAA Single Alcohol Screening Question (SASQ)

“How many times in the past year have you had (4 for women/5 for men) or more drinks in a day?

Sens~80%, Spec ~87%, ~LR 6/0.25 - for UNHEALTHY DRINKING

Pre-test probability of unhealthy drinking?
5%
10%
20%
30%



Post-test probability based on answer	
None	1 or more times
1%	24%
3%	40%
5%	60%
10%	70%

JAMA. 2018;320(18):1910-1928. doi:10.1001/jama.2018.12086
https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol/screen-and-assess-use-quick-effective-methods#pub-toc4

A Simplified Approach

If there was a "1 or more" answer

ASK - On a **typical** day when you drink, how many drinks do you have?

LIKELY NO ISSUE* IF THEY SAY

1-2 drinks MOST DAYS

3-4 drinks 2-3 TIMES A WEEK

5-6 drinks 1-2 TIMES A MONTH

MORE THAN THIS - PROBLEM?

*** assuming not pregnant, not drinking and driving, not a previous alcoholic**

Fat - it's about what you report

Meta-analyses of RCTs of replacing saturated fat or reducing fat

IMPORTANT OUTCOMES

1) heart attacks
2) heart attacks plus strokes
3) mortality

TYPICALLY REPORTED ONLY

FAT IS BAD
3 articles since 2010

20-30%
lower relative risk

FAT IS **NOT** BAD
5 articles since 2013

No difference

THE EVIDENCE

Author	Year	RCTs	Coronary heart disease events	Coronary heart disease mortality	Cardiovascular disease events	Cardiovascular disease mortality	Total mortality
Mozaffarian	2010	8	~20%⬇	Not reported	Not reported	Not reported	Not reported
Ramsden	2013	15	Not reported	No difference	Not reported	No difference	Not reported
Schwingshackl	2014	15	Not reported	Not reported	No difference	No difference	No difference
			Not reported	Not reported	No difference	No difference	No difference
Ramsden	2016	5	Not reported	No difference	Not reported	Not reported	No difference
Harcombe	2016	10	Not reported	No difference	Not reported	Not reported	No difference
Hamley	2017	11	~20%⬇	No difference	Not reported	Not reported	No difference
		5	No difference	No difference	Not reported	Not reported	No difference
Sacks	2017	4	~30%⬇	Not reported	Not reported	Not reported	Not reported
Hooper	2020	15	No difference	No difference	~15%⬇	No difference	No difference

Meat

The New York Times

TheUpshot

THE NEW HEALTH CARE

Meat's Bad for You! No, It's Not! How Experts See Different Things in the Data

As the latest controversy over new research illustrates, nutrition science can be open to interpretation.

Oct 2019

By Aaron E. Carroll

Oct. 1, 2019

247

NutriRECS
Nutritional Recommendations and accessible Evidence summaries Composed of Systematic reviews

THI
True Health Initiative
A global coalition of world-renowned experts, fighting fake facts and combating false doubts to create a world free of preventable diseases

→ *Somewhere between zero and three servings per week is a good recommendation*

Oct 2019

Annals of Internal Medicine®

REVIEWS | 1 OCTOBER 2019
Red and Processed Meat Consumption and Risk for All-Cause Mortality and Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Cohort Studies FREE

REVIEWS | 1 OCTOBER 2019
Reduction of Red and Processed Meat Intake and Cancer Mortality and Incidence: A Systematic Review and Meta-analysis of Cohort Studies FREE

REVIEWS | 1 OCTOBER 2019
Health-Related Values and Preferences Regarding Meat Consumption: A Mixed-Methods Systematic Review FREE

Norrina Allen
stated the NutriRECs study contradicted previous research and also their new findings were "comparable with those reported in the literature" and then referenced

A riddle, wrapped in a mystery, inside an enigma

NutriRECS
"THI response was completely predictable and hysterical"

Adults can continue eating the same amount of red meat — whether unprocessed or processed — as is being done in typical omnivore diets

THI
"NutriRECs articles are information terrorism"
Called for Annals to retract publication

Feb 2020

JAMA Internal Medicine | Original Investigation

Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality

Victor W. Zhong, PhD; Linda Van Horn, PhD; Philip Greenland, MD; Mercedes R. Carnethon, PhD; Hongyan Ning, MD, MS; John T. Wilkins, MD, MS; Donald M. Lloyd-Jones, MD, Sch; Norrina B. Allen, PhD

"Small increased risk of heart disease and mortality"

THI
Praised the results and said findings were "consistent with virtually all prior research on the topic

See 'The Nutrition Proposition"

Meat - it's about your "values"

					Mortality		Overall cardiovascular	
Message	The two different meta-analyses of cohort studies	# of cohorts	What was examined	Time	Unprocesssed meat	Processed meat	Unprocessed meat	Processed meat
Continue to eat meat group	**Zeraatkar October 2019**	55	A 3 serving/ week REDUCTION*	11yr	*1.08 **Absolute ~1%**	*1.09 **Absolute ~1%**	*1.05 **Absolute <0.5%**	*1.03 **Absolute <0.5%**
Eat less meat group supported	**Zhong February 2020**	6	Each additional 2 serving/week INCREASE	19 yr	1.03 **Absolute ~1%**	1.03 **Absolute ~1%**	1.03 **Absolute ~0.5%**	**1.07 **Absolute ~2%**

*Because the Zeraatkar meta-analysis examined a REDUCTION in meat intake and the Zhong meta-analysis examined an INCREASE in meat intake numbers the Zeraatkar numbers have been inverted so they can be directly compared to the Zhong numbers
** for this number 2 versus zero servings a week, not 2 servings/week increase

So Why the Different Response?

NutriRECS

Focused exclusively on health outcomes associated with meat and did not consider animal welfare and environmental issues.
Also felt a 1% risk in 11 years was small

THI

Appear to think of this as more of a public health issue and that 1% risk means millions (1% of 300 million) could be affected and also considered the environmental perspective

From the upcoming book - The Nutrition Proposition

Fruits and Vegetable Servings

EXPRESS Home of the Daily and Sunday Express

Forget the five-a-day servings of fruit and veg... now you need seven to be healthy

7+ a day
March 2014

BBC NEWS HEALTH

Seven-a-day fruit and veg 'saves lives'

theguardian

News | Sport | Comment | Culture | Business | Money | Life & style

News › Society › Health

Five a day will do, larger study of fruit and veg intake suggests

Chinese and American researchers settle on lower number than seven-a-day recommendation of English study

5 a day
June 2014

The Telegraph

Home News World Sport Finance Comment Culture Travel Life Women Fashion

Women | Men | Motoring | Health | Property | Gardening | Food | History | Relationships

Health News | Health Advice | Diet and Fitness | Wellbeing | Expat Health | Pets Health

HOME » HEALTH » HEALTH NEWS

A five a day diet of fruit and vegetables is best – more is pointless study finds

Five five portions of fruit and vegetables per day and no more cuts your risk of dying early, a study has found, contradicting recent findings suggesting optimum number may be seven servings.

Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data

7 per day

J Epidemiol Community Health - March 2014

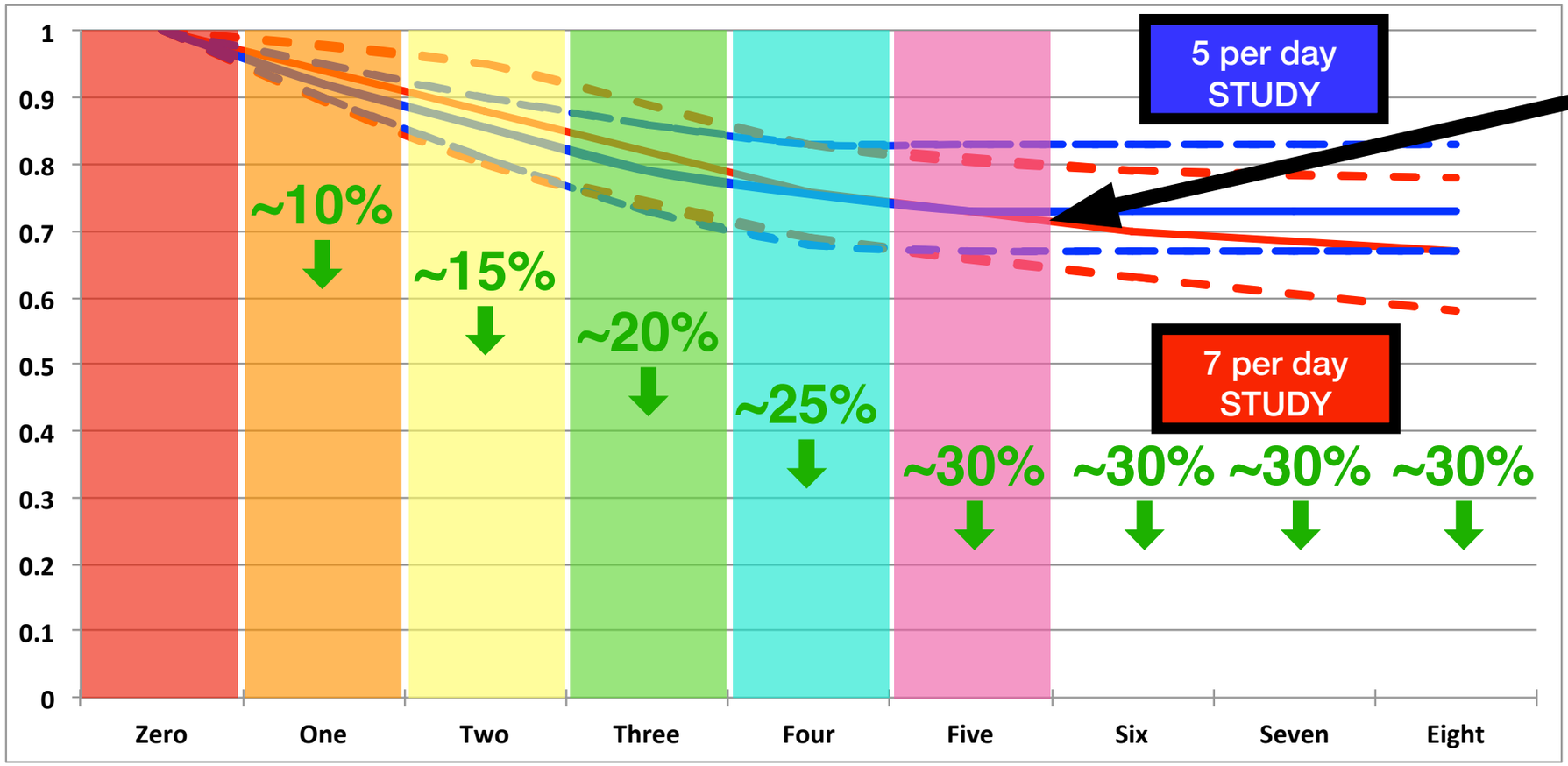
Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies

5 per day

BMJ - June 2014

Fruits and Vegetable Servings
- it's about what you "see"

The association between overall mortality and daily intake of fruit and vegetables



Servings of fruits and vegetables

Ultra-processed food

The NOVA classification outlines 4 food categories

1. Unprocessed and minimally processed food
2. Processed culinary ingredients
3. Processed food
4. Ultra-processed food (UPF)

% of energy intake

US/UK ~50 to 60% from UPF

"eat the least" quintile still average 20-30%

Canada and Brazil ~50%

Spain and Portugal ~20%

Italy ~10%

Common examples are carbonated soft drinks, fatty or salty snacks, candies, pastries, cakes and cake mixes, margarine, sweetened cereals, fruit yogurt, pasta, pizza, poultry or fish nuggets, sausages, burgers, hot dogs, powdered or instant soup, noodles, and desserts.

A simple way to figure out if a product is ultra-processed is to see if its list of ingredients contains words such as:
hydrolysed proteins, soya protein isolate, gluten, casein, whey protein, mechanically separated meat, fructose, high-fructose corn syrup, fruit juice concentrate, invert sugar, maltodextrin, dextrose, lactose, soluble or insoluble fibre, hydrogenated or interesterified oil

Ultra-processed food and bad outcomes

% of energy intake
US/UK ~50 to 60% from UPF
Canada and Brazil ~50%
Spain and Portugal ~20%
Italy ~10%

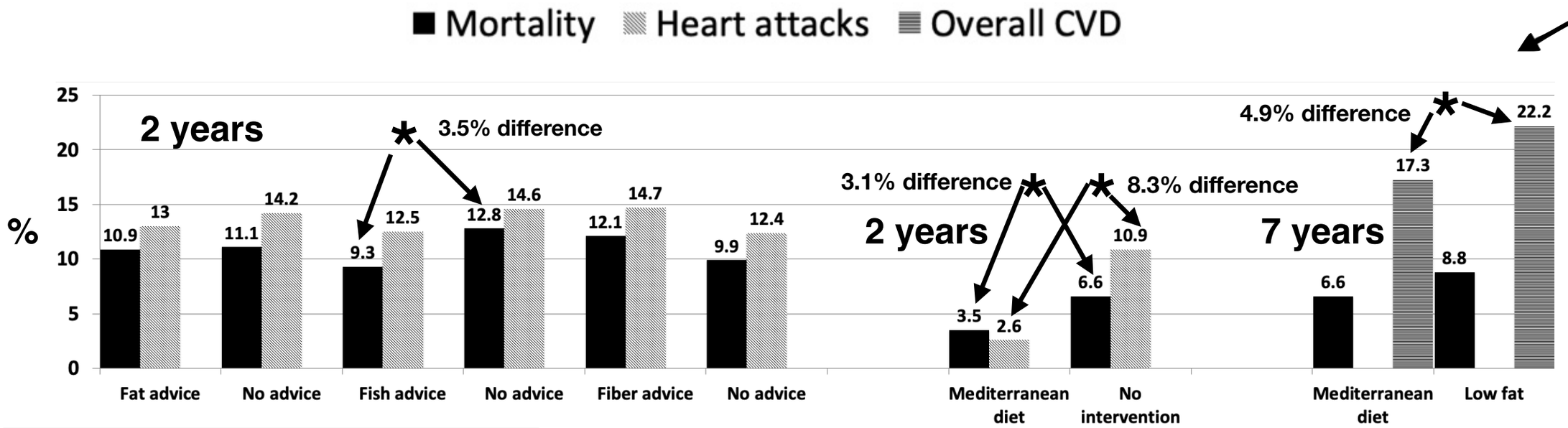
			QUANTILE				
			1 (reference)	2	3	4	5
	Years	**Outcome**	**~<25%* total daily energy, or ~<2 servings/day**	**~25-30% ~2-3.5**	**~30-40% ~3.5-4.5**	**~40-45% ~>4.5**	**~>45%**
Zhong 2021	13.5	CVD Mortality	1	NSS	NSS	NSS	**1.21 (1.07-1.37)**
Blanco-Rojo 2019	7.7	Mortality	1	NSS	NSS	**1.44 (1.01-2.07)**	
Schnabel 2019	7.1	Mortality	1	NSS	NSS	NSS	
Srour 2019	5.2	CVD	1	NSS	NSS	**1.23 (1.04-1.45)**	
Kim 2019	19	Mortality	1	NSS	NSS	**1.30 (1.08-1.57**	
		CVD mortality	1	NSS	NSS	NSS	
Rico-Campa 2019	200,432 persons years	Mortality	1	NSS	NSS	**1.44 (1.01-2.05)**	
		CVD mortality	1	NSS	NSS	NSS	

*** numbers rounded**

The 5 large RCTs of nutrition intervention

these numbers were reported as statistical different, everything else was not statistically different

People with previous history of heart attacks/strokes



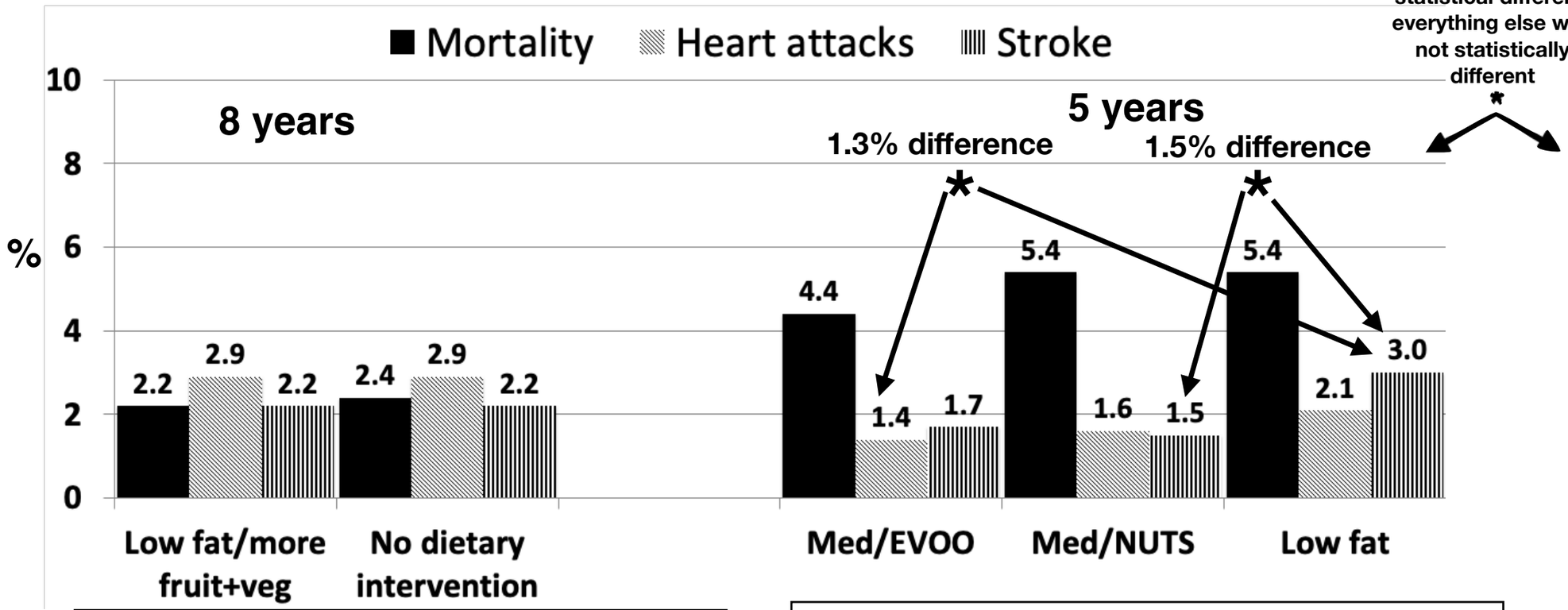
1989 - DART - Wales 2033 subjects, 100% male, 56 y/o, 62% smokers
ACTUAL NUTRITIONAL CHANGES MADE
⬆ fibre intake from ~10g/day to ~20g/day ⬆ polyunsaturated/saturated fat ratio from ~0.4 to ~0.8 fish intake - ⬆ EPA from ~0.7g/week to ~2.4g/week ⬇% fat energy from ~35 % to ~32%

1994 - Lyon - France 605 subjects, 90% male, 53 y/o, ~15-20% smokers
ACTUAL NUTRITIONAL CHANGES MADE
⬌ polyunsaturated/saturated fat ratio ⬇ cholesterol 318 mg/day vs 217 mg/day ⬇ calories ~2100 vs ~1900 ⬇ saturated fat ~12% of total calories vs ~8% significantly ⬆ intake of bread, fruit, and margarine; and a ⬇ intake of butter, cream, meat, ham, sausage, and offal

2022 - CORDIOPREV - Spain 1002 subjects, 83% male, 60 y/o, ~10% smokers
ACTUAL NUTRITIONAL CHANGES MADE
Med diet ⬆ total fat from 37% to 41% ⬆ amount of extra virgin olive oil/nuts/oily fish ⬇ carbs from 41% to 37% **Low fat diet** ⬇ total fat from 37% to 32% ⬆ carbs from 42% to 46%

People with NO previous history of heart attacks/strokes

these numbers were reported as statistical different, everything else was not statistically different *



2006 - WHI - USA
48,835 subjects, 100% female,
62 y/o, 7% smokers

ACTUAL NUTRITIONAL CHANGES MADE

~10% ⬇ in energy from fat
⬆ one more serving a day of vegetables/fruit
~1.4 ⬇ in servings a week of meat

2018 - PREDIMED - Spain
7447 subjects, 57% female,
62 y/o,14% smokers

ACTUAL NUTRITIONAL CHANGES MADE

⬆ weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings)

used 1 litre/week of extra virgin olive oil
or took 30 gm of mixed nuts/day

Important things I haven’t touched on

Food allergies and intolerance

Animal rights

Environmental issues

Nutrition advice to which pretty much everyone agrees

1. Eat a greater percentage of whole foods (food that has not been overly processed or refined as little as possible)
2. Eat more vegetables
3. Eat less food that has added sugars
4. Eat more whole grains
5. Eat in a style that fits your food preferences, tolerances, and lifestyle
6. Eat in a style you can sustain
7. When it comes to weight, how much you consume is the KEY issue
8. The “best” weight is the weight you are when living the healthiest life you can enjoy
9. Avoid any food that has, for you, been shown to consistently cause unacceptable intolerances

BUT THERE ARE BIG CAVEATS

Almost all the nutrition "benefits and harms" evidence comes from cohort studies

there is a real possibility of important publication bias because 100s to 1000s of researchers are looking at 100s of different databases

there are many potential confounders - let alone data collection issues

many of the associations seen in cohort studies are quite small (<10% relative) and principally only seen when you compare "lots quantiles" to "not much at all quantiles"

in general - single cohorts - unless that is all you have - should not be used as solid evidence

Much of nutrition research is on surrogate markers (blood pressure, lipids, glucose)

the changes seen **IF** they translated into effects on clinical outcomes would only amount to a 1% (at most 2%) absolute change in CVD risk over 10 years

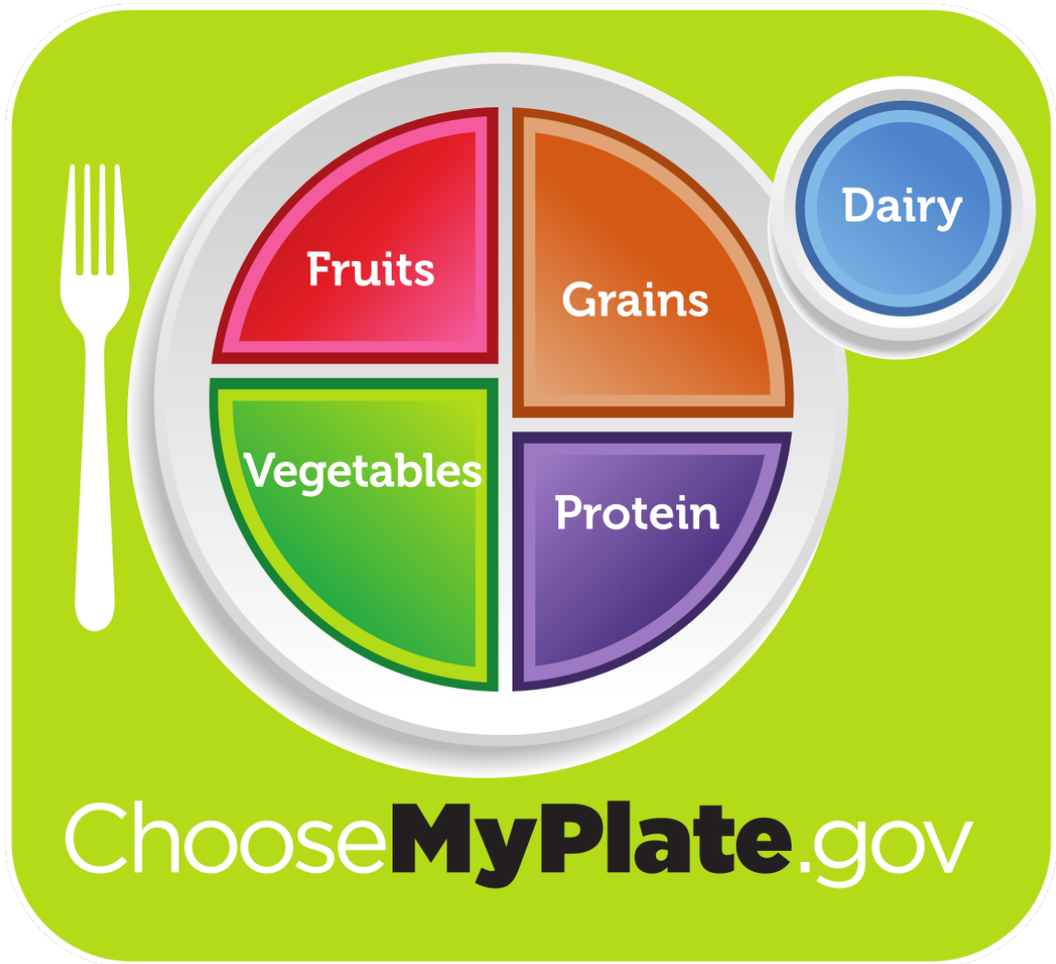
in general - single RCTs of surrogates - should not be considered high quality evidence

There are only 5 large RCTs (2+years) that have looked at important clinical outcomes

the "best evidence" is for the "Mediterranean Diet" and it only showed a 1-2% absolute difference in stroke over 5 years - more (3-8%) if secondary prevention

THESE ARE ACTUALLY PRETTY REASONABLE CONSIDERING THE EVIDENCE

CANADA

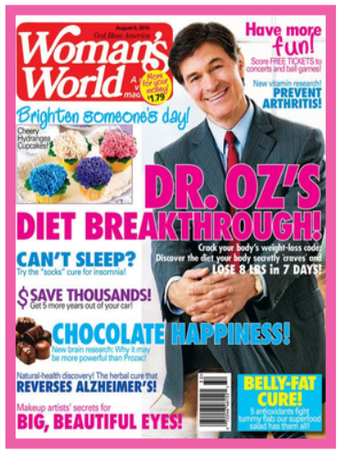


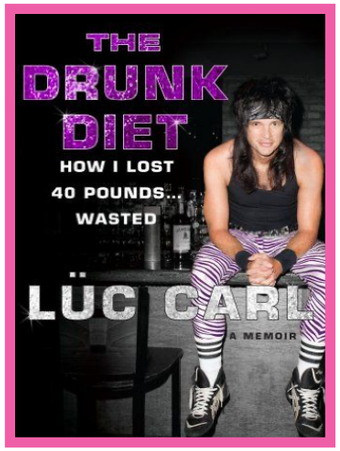
USA

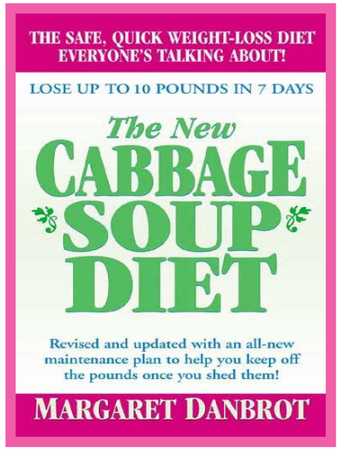

“Everything in moderation, including moderation.”
Oscar Wilde, Horace Porter, and Petronius, Socrates and many more

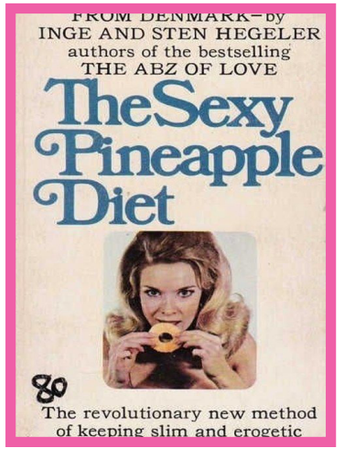
Assuming you wish your eating to be informed by the best available evidence

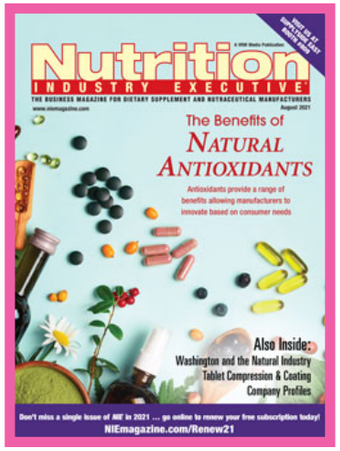
Anything else is likely…





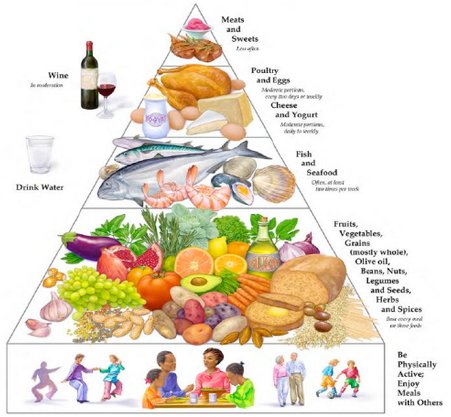


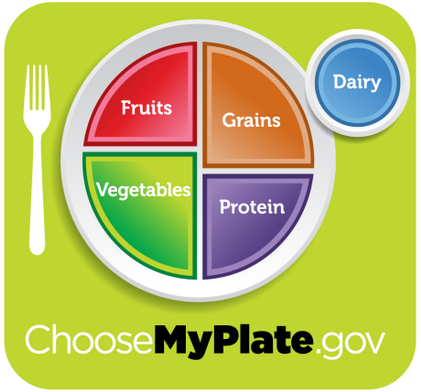




1. ENJOY EATING

2. Differences in outcomes are typically found from **“extremes”** and are **“small”**
3. The **Mediterranean diet** (whatever it is) seems reasonable - also CFG/USDA/DASH
4. Eat in **moderation/moderation/moderation**
5. Avoid **“ultra” processed food** - within reason
6. You can easily justify some red meat, butter etc
7. Eggs, coffee, salt, and alcohol in moderation seem fine
8. **Saturated fats - OK** - trans-fat?
9. **Added sugars at the high end** seem to increase risk of obesity
10. It is **VERY unlikely** a single “nutrient” would have an important effect
11. Animal rights/environmental issues are a whole other topic





Activity examples

Activity

150 minutes of moderate to high intensity exercise per week, or 30-60 minutes most days of the week (includes brisk walking)

Exercise for secondary prevention (RCTs)

Death at 4 years - NNT= 32

Heart failure admissions at 2 years - NNT = 14

Similar to medications?

Tools for Practice #145

Exercise for primary prevention (Cohorts)

Going from inactivity to current recommendations

CVD - RR = 0.83 (0.77-0.89)

J Am Heart Assoc. 2016;5:e002495 doi: 10.1161/JAHA.115.002495

Exercise for patients with major depression: a systematic review with meta-analysis and trial sequential analysis

Jesper Krogh,[1] Carsten Hjorthøj,[1] Helene Speyer,[1] Christian Gluud,[2] Merete Nordentoft[1]

BMJ Open 2017;7:e014820.

"There is currently no evidence in favour of exercise for patients with depression with a view to ameliorate depressive symptoms"
Low vs high risk for bias issue

Effects of Physical Activity in Knee and Hip Osteoarthritis: A Systematic Umbrella Review

VIRGINIA B. KRAUS[1], KYLE SPROW[2], KENNETH E. POWELL[3], DAVID BUCHNER[4], BONNY BLOODGOOD[5], KATRINA PIERCY[6], STEPHANIE M. GEORGE[7], and WILLIAM E. KRAUS[1], FOR THE 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE*

Medicine & Science in Sports & Exercise 2019;51:1324-39

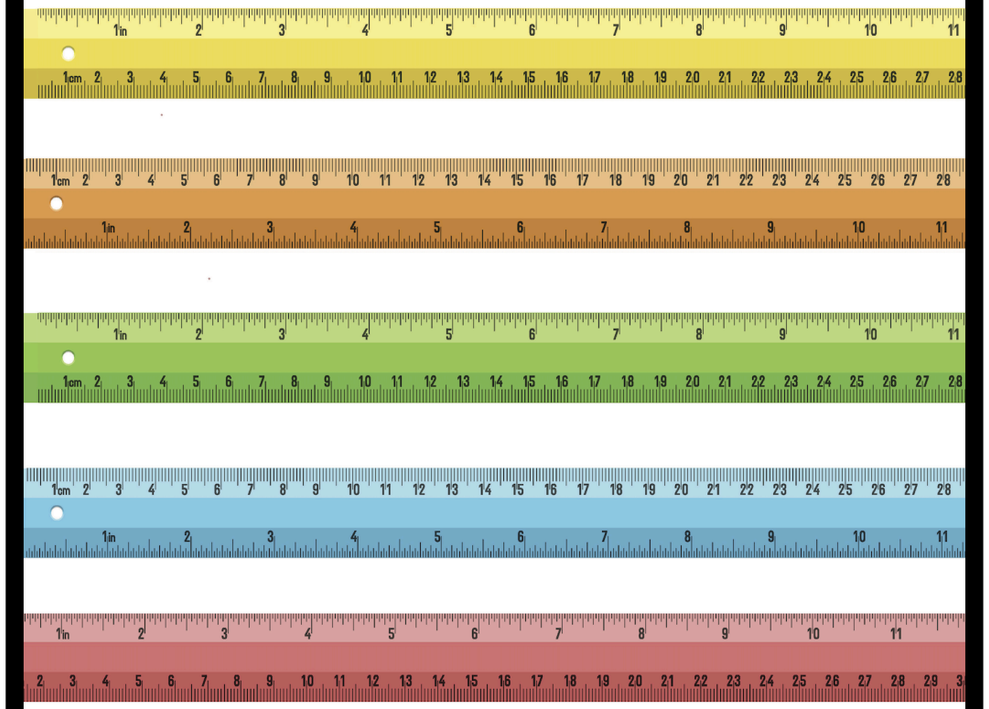
"Physical activity decreases pain, improves physical function and HRQoL among people with hip and/or knee OA relative to less active adults with OA"

Lab Test Examples

DO I HAVE TIME?

22 February 2020
368:261-302 No 8234 | ISSN 1759-2151

thebmj



YOUR RESULTS MAY VARY

The imprecision of medical measurements

James P. McCormack and Daniel T. Holmes
February 22, 2020

thebmj

BMJ 2020;368:m149 doi: 10.1136/bmj.m149 (Published 20 February 2020)

Check for updates

PRACTICE

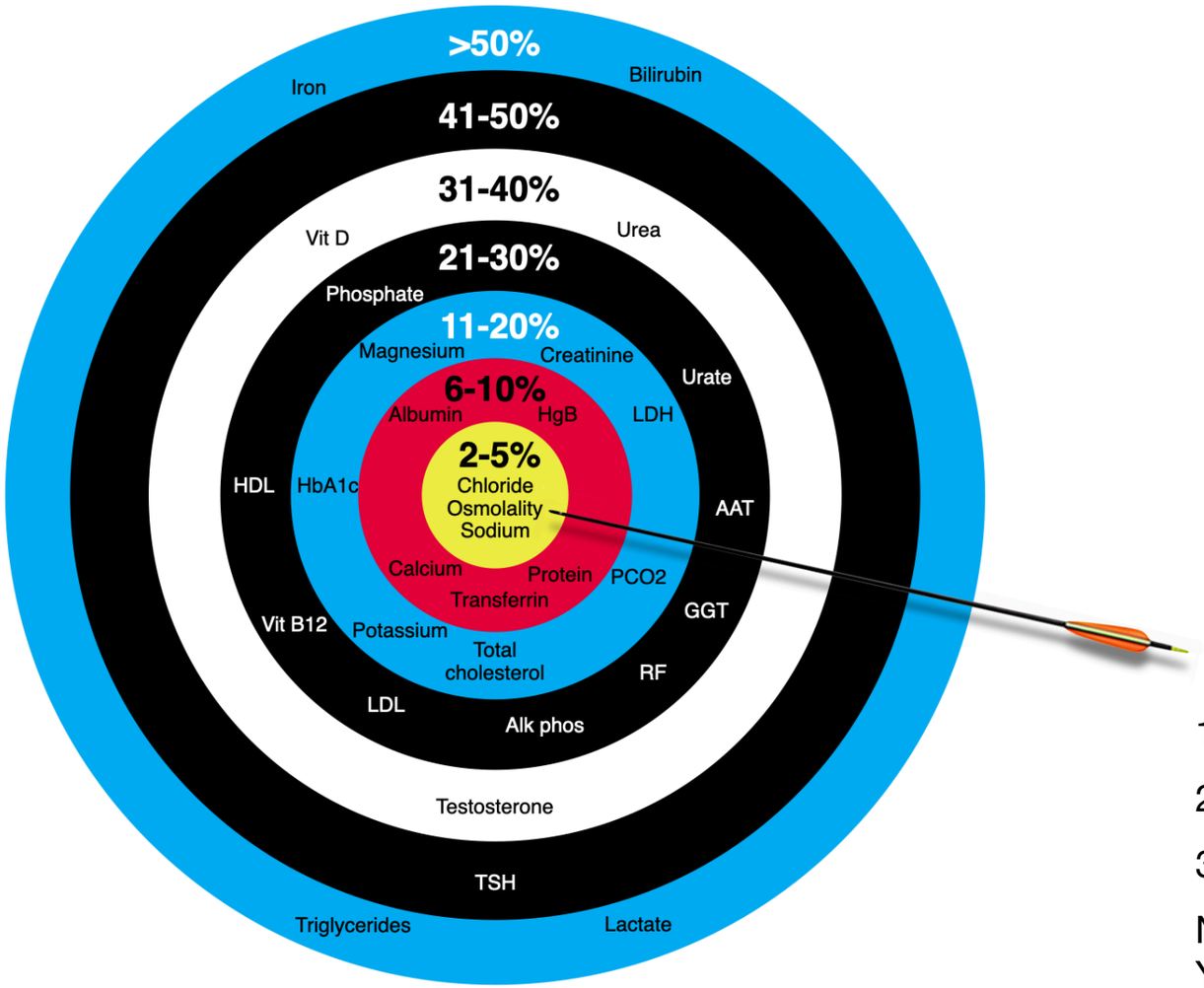
PRACTICE POINTER

Your results may vary: the imprecision of medical measurements

James P McCormack *professor*[1], Daniel T Holmes *clinical professor*[2 3]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; [2]St Paul's Hospital, Department of Pathology and Laboratory Medicine, Vancouver, BC, Canada; [3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada.

The change in a lab test that is needed to be confident there is a change



Repeat levels are next to useless unless you expect a change of at least

1) Cholesterol - 20-30% - 10-20% - total cholesterol - statins lower LDL by 25-30% - but increasing doses of statins only lower by 10%

2) Vitamin D - 30-40%

3) A1C - 10-20% - meds lower A1c by ~10%

4) Bone density - never recheck

5) Blood pressure - 40 office measurements before and after treatment to be REASONABLY confident that a 5 mmHg change has occurred

Yearly tests

1) Cholesterol ~ 0.5-1% increase per year

2) Blood pressure ~ 0.5-0.8 mmHg increase per year

3) Bone ~ 0.6% decrease in bone density per year

NONE OF THESE CHANGES CAN BE PICKED UP BY YEARLY TESTS - need to wait ~5-10 YEARS

the bmj Interactive

Your results may vary

A tool for visualising the variability of lab test results

Version 1.0
19 Feb 2020

Interpreting results can be challenging for patients and clinicians alike. Results can be affected by measurement uncertainty, and by variation caused by biological processes. This tool (based on data in the article below) is designed to help you decide if two consecutive results can be considered truly different after these kinds of variation have been taken into account.

1 Choose a test

HbA1c Healthy NGSP (%)

2 Adjust variables

These boxes are automatically populated with reasonable estimates of the analytic variation (authors' lab) and biologic variation (published research). These can be adjusted as needed.

HbA1c Healthy NGSP (%)

Analytic variation	Biologic variation	Normal range (reference interval)	
		Low	High
2.5%	1.6%	4.0	5.6

3 Enter lab results

Enter one or, if available, two serial lab results

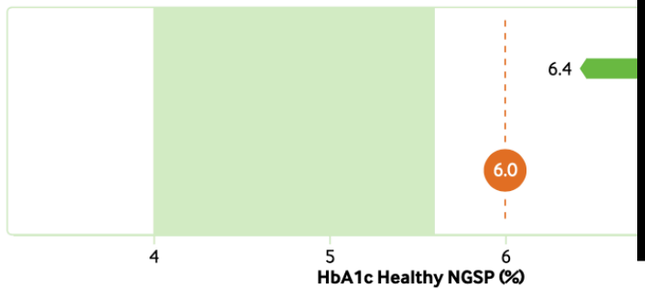
Result 1: 7.0

Result 2: 6.0

Show

4 View estimates

The minimum change required to conclude that two serial measurements are like
"reference change value" (RCV). Arrows to the left and right of your first result sho
For serial results, measurements can be considered different if the second is outs

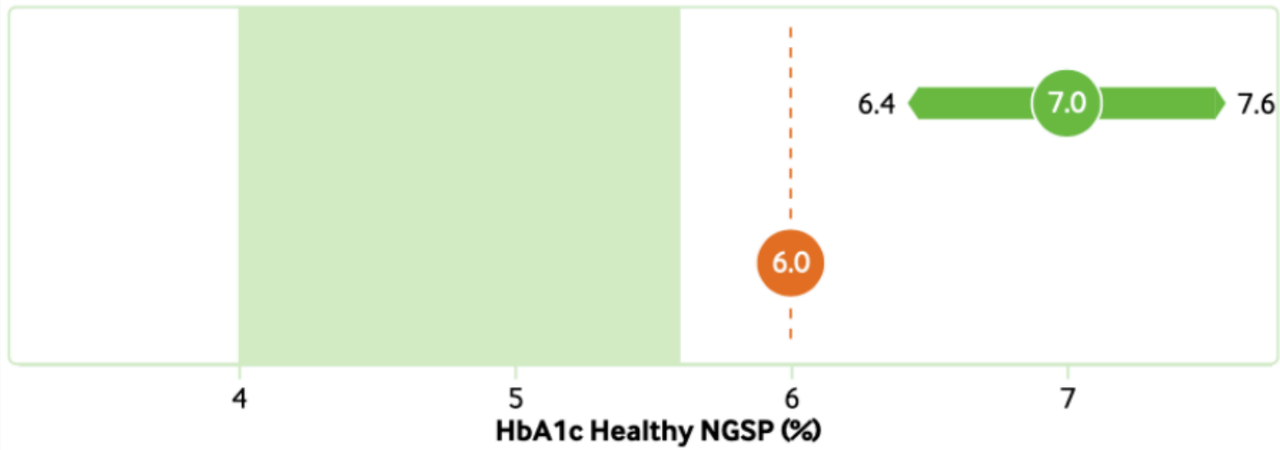


Normal range

Outside normal range

Result 2 is outside the RCV, so the difference is unlikely to be due to the combined effects of analytic and biological variation

The minimum change required to conclude that two serial measurements are likely different is called the "reference change value" (RCV). Arrows to the left and right of your first result show the RCV for this test. For serial results, measurements can be considered different if the second is outside the RCV of the first.



Normal range

Outside normal range

Result 2 is outside the RCV, so the difference is unlikely to be due to the combined effects of analytic and biological variation

Approximate variability estimates for routine medical measurements

Test	Single measurement variability		Serial measurement variability
	Analytical variation†	Analytical and biological variation‡	Reference change value*
Bone density (spine, total hip)	<2%	2-5%	2-5%
Chloride	<2%	2-5%	2-5%
Osmolality	<2%	2-5%	2-5%
Sodium	<2%	<2%	2-5%
Bone density (femoral neck)	<2%	2-5%	6-10%
Albumin	2-5%	6-10%	6-10%
Calcium	2-5%	2-5%	6-10%
HbA_{1c} NGSP (%)	2-5%	6-10%	6-10%
Haemoglobin	2-5%	6-10%	6-10%
Total protein	2-5%	6-10%	6-10%
Transferrin	2-5%	6-10%	6-10%
Creatinine	2-5%	6-10%	11-20%
Glucose	2-5%	6-10%	11-20%
HbA_{1c} (diabetics) IFCC (mmol/mol)	2-5%	11-20%	11-20%
HbA_{1c} (diabetics) NGSP (%)	2-5%	6-10%	11-20%
HbA_{1c} IFCC (mmol/mol)	6-10%	6-10%	11-20%
Lactate dehydrogenase	2-5%	11-20%	11-20%
Magnesium	2-5%	6-10%	11-20%
PCO_2	2-5%	6-10%	11-20%
Potassium	2-5%	6-10%	11-20%
Total cholesterol	2-5%	11-20%	11-20%
Alanine aminotransferase	6-10%	11-20%	21-30%
Alkaline phosphatase	11-20%	11-20%	21-30%
Aspartate aminotransferase	6-10%	11-20%	21-30%
Gamma glutamyltransferase	6-10%	11-20%	21-30%
HDL cholesterol	2-5%	11-20%	21-30%
LDL cholesterol	2-5%	11-20%	21-30%
Phosphate	2-5%	11-20%	21-30%
Rheumatoid factor	11-20%	21-30%	21-30%
Uric acid	2-5%	11-20%	21-30%
Vitamin B_{12}	11-20%	11-20%	21-30%
25-hydroxy-vitamin D	6-10%	21-30%	31-40%
Holotranscobalamin	6-10%	21-30%	31-40%
Total testosterone (male)	6-10%	21-30%	31-40%
Urea	2-5%	21-30%	31-40%
Thyroid stimulating hormone	6-10%	31-40%	41-50%
Iron	2-5%	>50%	>50%
Lactate	2-5%	>50%	>50%
Total bilirubin	2-5%	41-50%	>50%
Triglycerides	2-5%	31-40%	>50%

*Change (%) required for two serial measurements to be considered different.
†Confidence interval (%) around a single measurement when only considering analytical variation.
‡Confidence interval (%) around a single measurement when considering both analytical and biological variation.
NGSP = National Glycated Haemoglobin Standardization. IFCC = International Federation of Clinical Chemistry.
HDL = high density lipoprotein. LDL = low density lipoprotein.

The calculations in the three columns help you interpret 3 different scenarios

1) Confidence interval (%) around **a single measurement** = analytic variation

2) Confidence interval (%) around **a single measurement of something that might be on-going** = analytic and biologic variation

3) Change (%) required for **two serial measurements** to be considered different

Test	Single measurement variability		Serial measurement variability
	Analytical variation†	Analytical and biological variation‡	Reference change value*
Bone density (spine, total hip)	<2%	2-5%	2-5%
Chloride	<2%	2-5%	2-5%
Osmolality	<2%	2-5%	2-5%
Sodium	<2%	<2%	2-5%
Bone density (femoral neck)	<2%	2-5%	6-10%
Albumin	2-5%	6-10%	6-10%
Calcium	2-5%	2-5%	6-10%
HbA_{1c} NGSP (%)	2-5%	6-10%	6-10%
Haemoglobin	2-5%	6-10%	6-10%
Total protein	2-5%	6-10%	6-10%
Transferrin	2-5%	6-10%	6-10%

Test	Single measurement variability		Serial measurement variability
	Analytical variation†	Analytical and biological variation‡	Reference change value*
Creatinine	2-5%	6-10%	11-20%
Glucose	2-5%	6-10%	11-20%
HbA_{1c} (diabetics) IFCC (mmol/mol)	2-5%	11-20%	11-20%
HbA_{1c} (diabetics) NGSP (%)	2-5%	6-10%	11-20%
HbA_{1c} IFCC (mmol/mol)	6-10%	6-10%	11-20%
Lactate dehydrogenase	2-5%	11-20%	11-20%
Magnesium	2-5%	6-10%	11-20%
PCO_2	2-5%	6-10%	11-20%
Potassium	2-5%	6-10%	11-20%
Total cholesterol	2-5%	11-20%	11-20%
Alanine aminotransferase	6-10%	11-20%	21-30%
Alkaline phosphatase	11-20%	11-20%	21-30%
Aspartate aminotransferase	6-10%	11-20%	21-30%
Gamma glutamyltransferase	6-10%	11-20%	21-30%
HDL cholesterol	2-5%	11-20%	21-30%
LDL cholesterol	2-5%	11-20%	21-30%
Phosphate	2-5%	11-20%	21-30%
Rheumatoid factor	11-20%	21-30%	21-30%
Uric acid	2-5%	11-20%	21-30%
Vitamin B_{12}	11-20%	11-20%	21-30%

Test	Single measurement variability		Serial measurement variability
	Analytical variation†	Analytical and biological variation‡	Reference change value*
25-hydroxy-vitamin D	6-10%	21-30%	31-40%
Holotranscobalamin	6-10%	21-30%	31-40%
Total testosterone (male)	6-10%	21-30%	31-40%
Urea	2-5%	21-30%	31-40%
Thyroid stimulating hormone	6-10%	31-40%	41-50%
Iron	2-5%	>50%	>50%
Lactate	2-5%	>50%	>50%
Total bilirubin	2-5%	41-50%	>50%
Triglycerides	2-5%	31-40%	>50%