

WHEN IT COMES TO EVIDENCE-BASED PRACTICE

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therapeuticseducation.org

Some of this talk was made better (I think) by using AI
I am responsible for all the content



THE UNIVERSITY OF
BRITISH COLUMBIA

James McCormack



Employee at the University of British Columbia –
Faculty of Pharmaceutical Sciences



Do a weekly podcast (BS Medicine) and we have
a **premium subscription plan**



A book on Amazon – **The Nutrition Proposition**



No grants, no patents, no memberships
on advisory boards



Member of **PEER** – non-profit



Part of the **MEME group** – non-profit



Many of my images are **AI generated**



Evidence-driven

Grounded in science
and critical thinking.



Curious

Always asking
better questions.



Purposeful

Focused on real
impact and solutions.

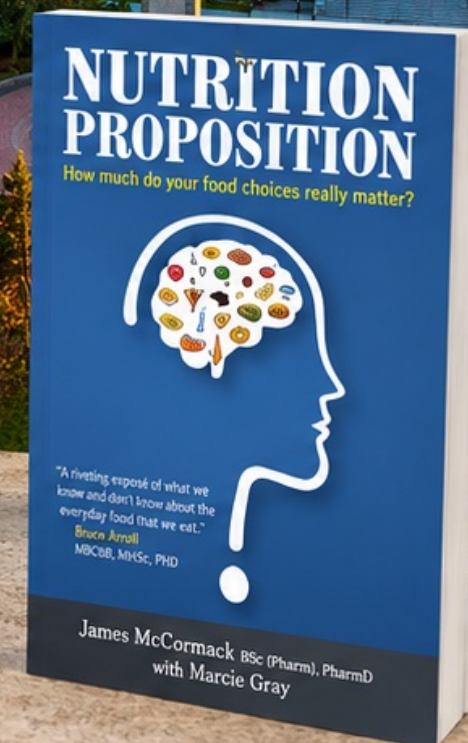


Health-focused

Helping people make
better choices.



Curious., Evidence-driven, Purposeful.



What we will try to cover today

What I do

Philosophical thoughts

Shared decision-making

Using guidelines and moving beyond them

Dealing with uncertainty in medicine and legal stuff

Communicating with patients about evidence - as part of shared decision-making

Antibiotic common sense

Using VERY low doses

Reducing lab test stress

Cool AI stuff

What you will do today

PLEASE

Interact as much as you want

Ask questions

Challenge the ideas if you like

Bring up concerns for sure

Bring up other ideas - you may have better ones



Medical BS



Nutrition BS



Social Media BS

General BS

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

James McCormack, Trisha Greenhalgh

BMJ - 25 years ago



Medical BS

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

James McCormack, Trisha Greenhalgh

BMJ 2000;320:1720-3

10 year trial

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

	Any diabetes related end	Microvascular end	Individual macrovascular end	
Insulin/sulfonylureas lowered A1c by 0.7-1.2% Difference in retinal photocoagulation (2.4%) and NOTHING else				
Relative risk reduction	8.2	22.6	Difference between the groups for any of the individual end points‡	
Absolute risk reduction	3.2§	2.4	Significantly lower for all drugs compared with dietary advice	
No needed to treat for 10 years to prevent one event	31	42		

Table 2 Effect of 10 years' treatment with metformin or chlorpropamide, glibenclamide, or insulin in overweight patients with newly diagnosed type 2 diabetes

Any							
Insulin/sulfonylureas lowered A1c by the same amount as metformin Only metformin showed a difference in macrovascular events (5-7%) but no microvascular differences							(%)
Relative risk reduction (metformin v dietary advice)	26.2	38.8	32.7	36.0	44.4§	NS	Significantly lower for all drugs compared with dietary advice
Absolute risk reduction (metformin v dietary advice)	10.2	5.2	7.1	6.4	2.8§	NS	
No needed to treat for 10 years to prevent one event (metformin v dietary advice)	10	19	14	16	36§	NS	

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

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

“We’ve shown something here” bias

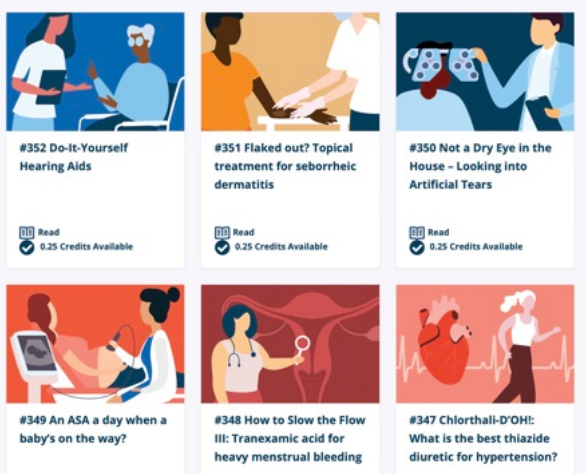
“The result we’ve all been waiting for” bias

“Just keep taking the tablets” bias

“What the hell can we tell the public?” bias

“If enough people say it, it becomes true” bias

Tools For Practice BS Medicine Podcast



300 word primary-care synopses
<https://cfpclearn.ca/tools-for-practice-library>

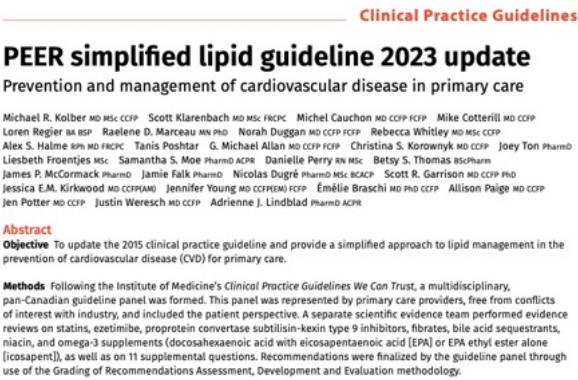
Since 2009
~410 to-date
Each sent to ~40K people



<https://therapeuticseducation.org>

Since 2008
~610 to-date
5K-10K
listens/month

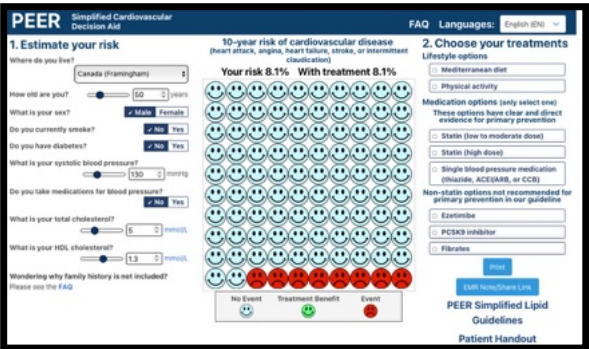
Simplified Lipid Guideline



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

2023
175K+ downloads
Total accesses for all 5 guidelines: ~3/4M

Simplified CVD Decision Aid



<https://decisionaid.ca/cvd>

Over the last year
170K users



You are not alone!

Clinicians in many health services around the world
(at least in resource well off countries like US UK Europe Canada)
are feeling under pressure...to do more and more

To follow myriads of guidelines often written for other contexts

To meet increasing expectations from the public/health management/ regulators

To manage personal expectations of being “a perfect clinician” and “getting it right every time”

To work with IT systems for extensive record keeping, without time allocated for this work.

The result .. many clinicians are unhappy - clinical work is becoming less satisfying for all/many people



TOPICS

Workload

Continuity

Lab tests

Lifestyle advice

Access to good evidence

Litigation

Screening

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 MPH 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

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

PEER Simplified Cardiovascular Decision Aid

FAQ Languages: English (EN)

1. Estimate your risk

Where do you live? Canada (Interim)
How old are you? 50 years
What is your sex? Male Female
Do you currently smoke? No Yes
Do you have diabetes? No Yes
What is your systolic blood pressure? 130 mmHg
Do you take medications for blood pressure? No Yes
What is your total cholesterol? 5 mmol/L
What is your HDL cholesterol? 1.3 mmol/L

2. Choose your treatments

Lifestyle options
Mediterranean diet
Physical activity
Medication options (only select one)
Statin (low to moderate dose)
Statin (high dose)
Ezetimibe
PCSK9 inhibitor
Fibrates
Single blood pressure medication (thiazide, ACEI/ARB, or CCB)

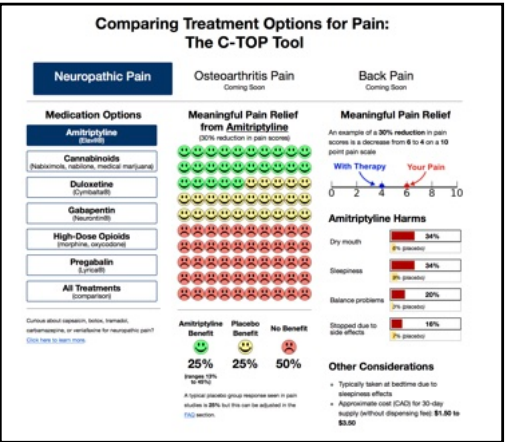
10-year risk of cardiovascular disease

Your risk 8.1% With treatment 8.1%

No Event Treatment Benefit Event

PEER Simplified Lipid Guidelines

Patient Handout



CVD decision aid

PEER Simplified Cardiovascular Decision Aid

FAQ Languages: English (EN) ▼

1. Estimate your risk

Where do you live?
Canada (Framingham)

How old are you?
50 years

What is your sex?
✓ Male Female

Do you currently smoke?
✓ No Yes

Do you have diabetes?
✓ No Yes

What is your systolic blood pressure?
130 mmHg

Do you take medications for blood pressure?
✓ No Yes

What is your total cholesterol?
5 mmol/L

What is your HDL cholesterol?
1.3 mmol/L

Wondering why family history is not included?
Please see the [FAQ](#)

10-year risk of cardiovascular disease (heart attack, angina, heart failure, stroke, or intermittent claudication)

Your risk 8.1% With treatment 8.1%

No Event	Treatment Benefit	Event

2. Choose your treatments

Lifestyle options

☐ Mediterranean diet

☐ Physical activity

Medication options (only select one)
These options have clear and direct evidence for primary prevention

☐ Statin (low to moderate dose)

☐ Statin (high dose)

☐ Single blood pressure medication (thiazide, ACEI/ARB, or CCB)

Non-statin options not recommended for primary prevention in our guideline

☐ Ezetimibe

☐ PCSK9 inhibitor

☐ Fibrates

[Print](#)

[EMR Note/Share Link](#)

PEER Simplified Lipid Guidelines

Patient Handout

Diabetes

PEER

Diabetes Medication Decision Aid

English (EN)

FAQCONTACT

Step 1

Calculate Risk

Sex

☒ Female

☐ Male

Age

years

Systolic Blood Pressure

mm Hg

Race/Ethnicity (if applicable)

☐ Black

☐ Hispanic

Current Medications

☐ Anticoagulant

☐ Antihypertensive (Including ACEI or ARB)

☐ Antihypertensive (Without ACEI or ARB)

☐ Oral diabetes drug (excluding semaglutide or flozin)

☐ Statin

Medical History

☐ Current smoker

☐ Prior myocardial infarction or stroke

Labs

Serum creatinine

umol/L

eGFR (2021 CKD-EPI equation)

ml/min/1.73 m²

Urine albumin-creatinine (ACR) ratio

mg/mmol

Total cholesterol

mmol/L

HDL cholesterol

mmol/L

Hemoglobin A1c

☒ %

mmol/mol

Risk of complications related to diabetes in the next 10 years

Death

4.9%

Heart attack/stroke

10.3%

Heart failure

2.2%

Kidney failure

6%

Severe vision loss

6.2%

Pressure sensation loss

6.4%

Estimated risk

NEXT

PEER

Simplified Diabetes Decision Aid

English (EN)

FAQ

1. Estimate your risk of diabetic complications (click to expand/collapse)

Where are you located?

☒ North America

☐ Other

Do you currently smoke?

☒ No

☐ Yes

How old are you?

years

What is your sex?

☒ Male

☐ Female

Do you take medications for blood pressure?

☒ No

☐ Yes

What is your systolic blood pressure?

mmHg

What is your race?

☒ Other

☐ Black

Are you currently taking a statin?

☒ No

☐ Yes

What is your eGFR?

ml/min/1.73²

What is your albumin-to-creatinine ratio?

mg/mmol

What is your HDL cholesterol?

mmol/L

What is your total cholesterol?

mmol/L

2. Choose your treatments

Lifestyle options

☐ Mediterranean diet

☐ Physical activity

Medication options

These options reduce 1 or more clinically important outcomes

☐ Single medication (thiazide, ACEI/ARB, or CCB) - blood pressure lowering

☐ Statin (low/moderate dose) - cholesterol lowering

☐ Statin (high dose) - cholesterol lowering

☒ GLPs - glucose lowering

☐ SGLT2i - glucose lowering

☐ Finerenone

These options lower glucose BUT do not reduce risk of clinically important outcomes

☐ Metformin - glucose lowering

☐ Sulfonylurea - glucose lowering

☐ Insulin - glucose lowering

☐ DPP4s - glucose lowering

3. Select an Outcome

Cardiovascular and Kidney Risk

10-year risk of cardiovascular disease (fatal or non-fatal heart attack/stroke or heart failure)

Your risk 9.3%

With treatment 2.2%

Cardiovascular and Kidney Risk

10-year risk of kidney failure (analysis on kidney transplant)

Your risk 2.6%

With treatment 2.2%

Other Risks

10-year risk of severe vision loss: 6.3%

10-year risk of pressure sensation loss: 7.6%

Glucose lowering treatments have NO evidence they reduce the risk of these important diabetic outcomes

Side Effects/Cost/Routine

GLP-1 receptor agonist

Risk of side effects over placebo: vomiting, major diarrhea (6.0%)

90-day cost: About \$500-900 for a 30-day supply (\$1800-3600/year)

Routine: Semaglutide: Available as a tablet (one tablet once a day) or injection (one injection once a week). Others: Once a day or once a week.

EMR Note/Share Link

Print

<https://decisionaid.ca/diabetes/>

Heart Failure

**SHARE-HF Decision Aid**

This tool is intended to facilitate shared decision-making discussions between patients and clinicians regarding medications for heart failure with reduced ejection fraction (HFrEF).

[FAQ](#) | [How to use](#)

Languages: English (EN)

1. Choose display

Individualized predictions

Population-level estimates

Estimate patient risk *(click to expand/collapse)*

Your current location

North America

Sex

Male

☒ Female

NYHA functional class

☒ 1 or 2

☐ 3 or 4

Prior heart failure hospitalization

☒ No

☐ Yes

Diabetes

☒ No

☐ Yes

Prior stroke or peripheral artery disease

☒ No

☐ Yes

Age (years)

70

Systolic BP (mmHg)

120

NT-proBNP (ng/L)

1300

Ejection fraction (%)

35

eGFR (mL/min/1.73²)

40

Current heart failure medications

☐ ACEI/ARB

☐ ARNI

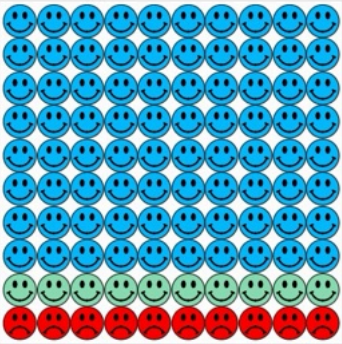
☐ Beta-blocker

☐ MRA

☐ SGLT2i

2. Know the benefits & harms of treatment:

5-year survival with additional medication(s):



80 Alive (with or without additional medications)

10 Alive due to additional medications

10 Not alive (with or without additional medications)

A. Your life expectancy:
With current medications: 83 years
With additional medications: Age 85 years or older (2 or more extra years added to your life)

B. Your risk of hospitalization for heart failure in the next year:
No medication: 15 in 100
With current and additional medications: 2 in 100

C. Quality of life:
With additional medications, 20 more people out of 100 will feel noticeably better.

3. Choose additional medication(s) to discuss

What are typical medication combinations?

Specific medications?

Choose an option to discuss
(click arrow in each button to see side-effects, costs, and routine)

4 medications (ARNI-based)

4 medications (ACEI/ARB-based)

3 medications

Print

EMR Note/Share Link

THE NUTRITION PROPOSITION

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RELEASED APRIL 2022

updated regularly

What does the
evidence really say
about your food
choices?

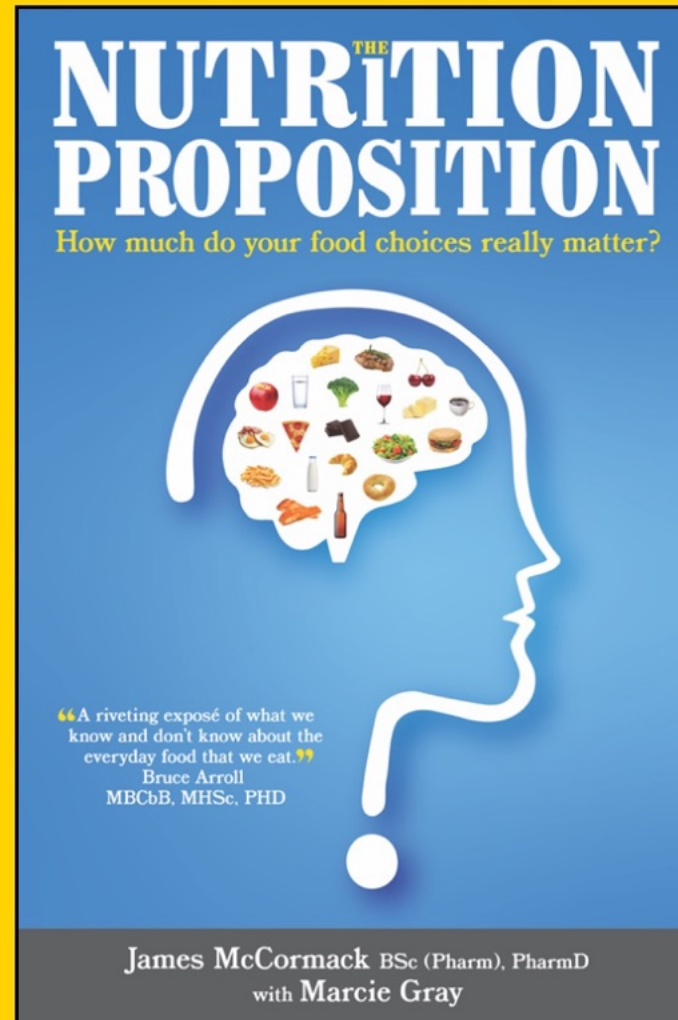
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"The Nutrition Proposition is a mammoth contribution to the world's understanding of the science behind nutritional hype. James McCormack helps strip the science of nutrition down to its bare essentials."

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



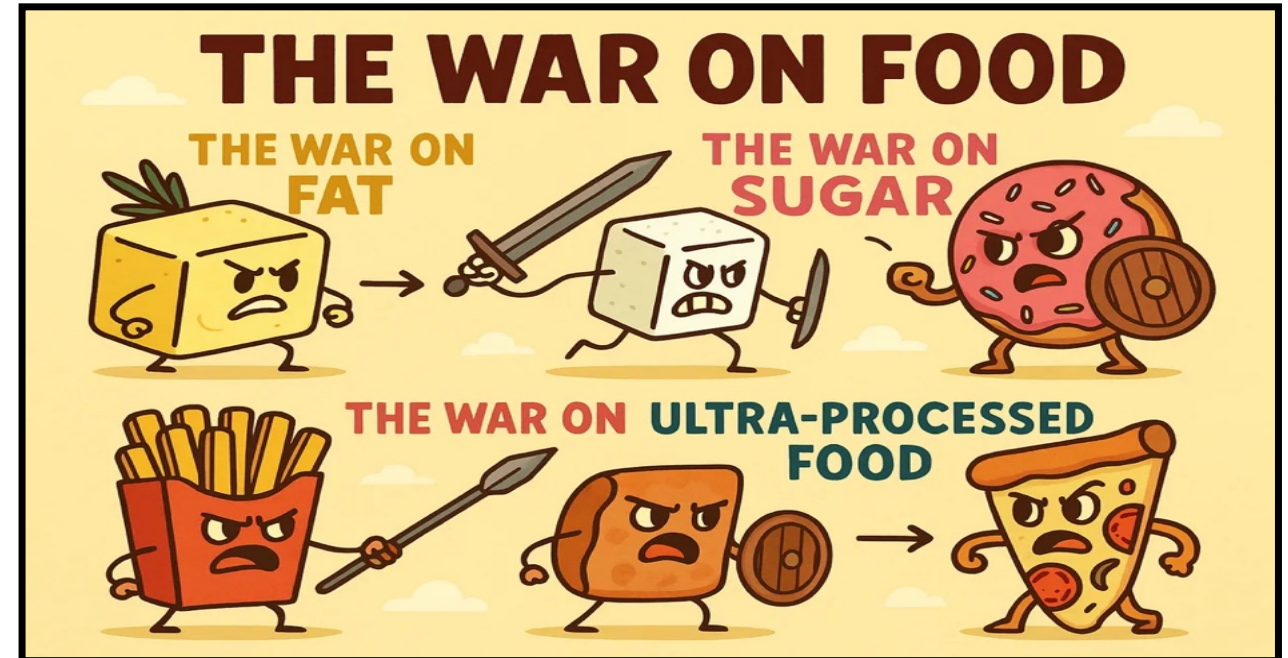
**The Only Nutrition Book That
Won't Tell You What To Eat!!
But It Will Tell You What We Know
And Don't Know About Food**

nutritionproposition.com

RFK - Secretary of the U.S. Department of Health and Human Services



**J McCormack - The 60+ Year Nutritional Cold War: Looking towards a truce - a three-part miniseries.
Sensible Medicine Substack**

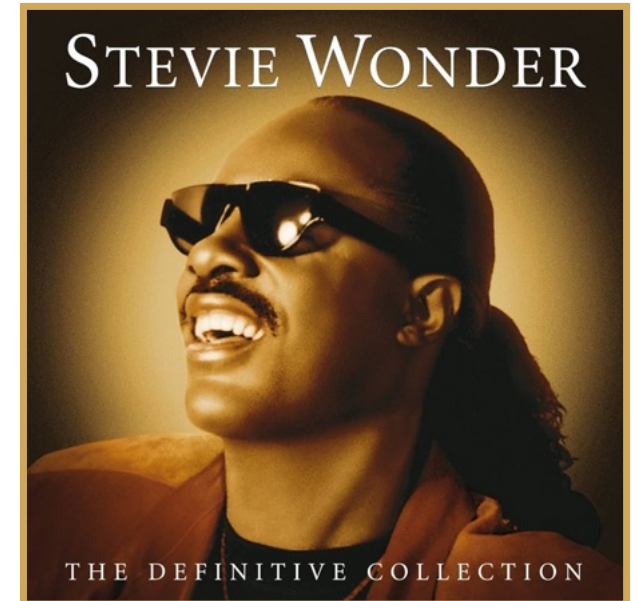


“ultra-processed foods are a primary cause of chronic disease”
“UPFs are ‘poison’”

“If you are eating less than 30-40% UPF and you enjoy what is presently being called UPF, great - eating should be a joy.”

“when it comes to UPF, sugar-sweetened beverages and processed meat are the main, if not the only, subtypes associated with significant health problems.”

“When you believe in things
That you don't understand,
Then you suffer,
Superstition ain't the way”
Stevie Wonder 1972



Tips I've Learned

Know what the ballpark chance of an event happening **if you don't treat** - and then **if you do**

For non-acute conditions, **1/4 of the highest doses** typically gives you **70-90% of the effect** of the full dose - sometimes even 1/8 the dose - and you get **all the placebo effect** - the same applies to **nutrition** and **activity**

Doing shared decision-making is, in general, **MUCH more rewarding** than following guidelines

Don't use words to describe risk - **WORDS** are **NOT** evidence

Don't care if your patient takes a medication or not, just care that you know **if they do or don't**

Over 30 years, **<1/10 of people will benefit** from treating either BP, lipids, or glucose

You will rarely (**<1/10 patients**) have an impact on lifestyle changes/decisions people make

Most (**95%**) new drugs are **NO BETTER** than what we already have

14 of the 20 most "valuable" medications we have were released **before 1970**

Many older antibiotics are still useful for community acquired infections - **penicillin, amoxicillin, doxycycline, co-trimoxazole**

Don't keep taking the antibiotics - **stop once you feel better** for 2-3 days

Most "chronic" lab test results need to change by **at least 10-30%** before you can say they have changed

AI is **REALLY USEFUL** and **REALLY GOOD** when it comes to evidence - **if you ask the right questions**

My Simple Philosophy on Treatments



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

We don't care **HOW** treatments work,
we care **IF** treatments work

HOW IT WORKS



IF IT WORKS

Does it improve
important outcomes?

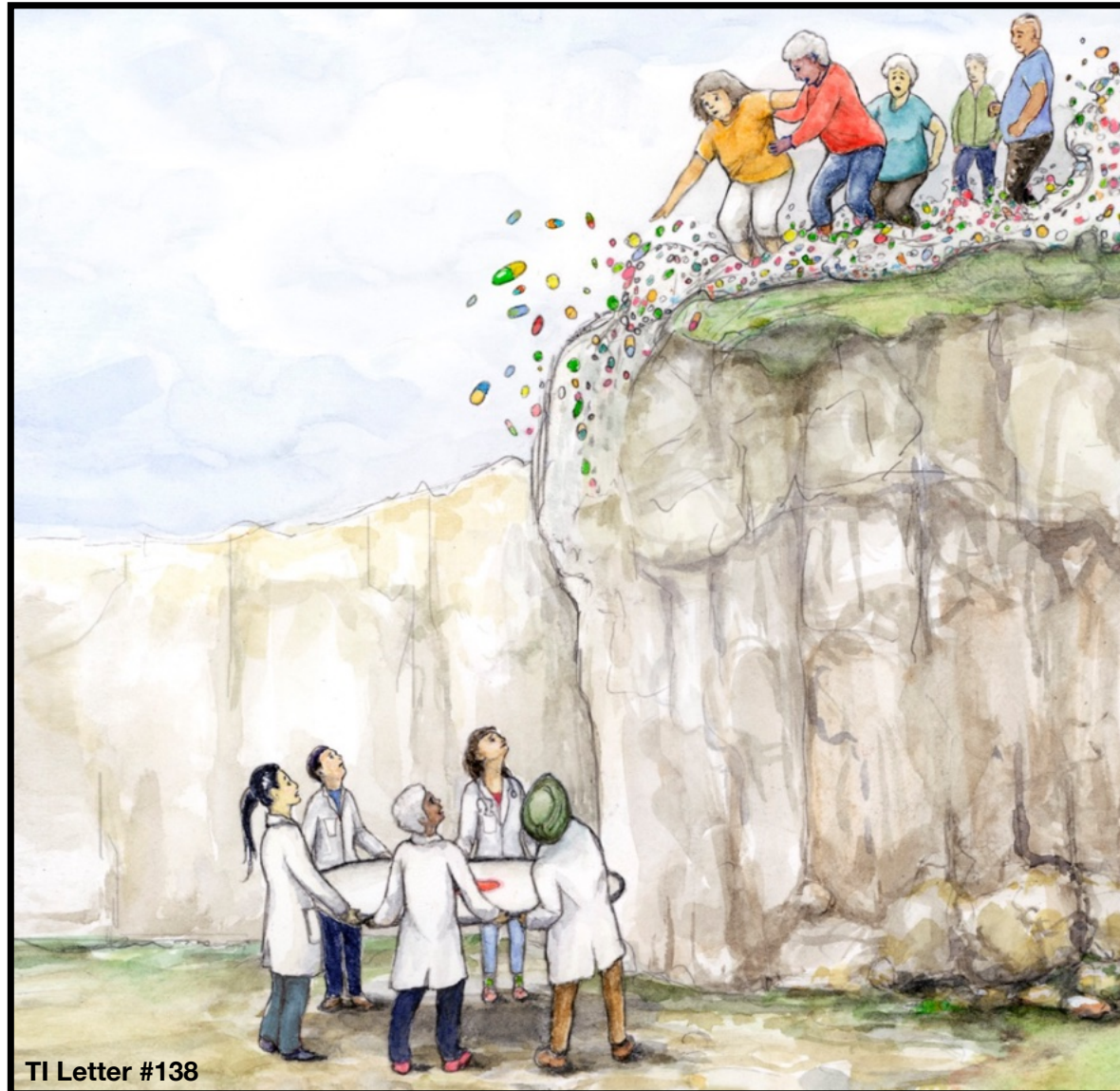
- ✓ Symptoms
- ✓ Function
- ✓ Quality of life
- ✓ Survival
- ✓ Safety



CLINICAL TRIAL
RESULTS
**TREATMENT
SHOWN TO IMPROVE
IMPORTANT OUTCOMES**

Conclusion:
Focus on what
matters most:
Does it work?

The proportion of people over 65 taking prescription medications



COUGH & COLD MEDICINES: OLD INGREDIENTS, NEW PACKAGING

Most active ingredients on pharmacy shelves today were introduced before **the Kefauver-Harris Amendment of 1962**.

PHENYLEPHRINE Nasal Decongestant	PSEUDOEPHEDRINE Nasal Decongestant	DIPHENHYDRAMINE Antihistamine	GUAIFENESIN Expectorant	BROMPHENIRAMINE Antihistamine	ACETAMINOPHEN Pain Reliever / Fever Reducer	DEXTROMETHORPHAN Cough Suppressant	OXYMETAZOLINE Topical Nasal Decongestant
							
FIRST INTRODUCED 1930s	FIRST INTRODUCED 1940s	FIRST INTRODUCED 1946	FIRST INTRODUCED 1952	FIRST INTRODUCED 1955	FIRST INTRODUCED 1955	FIRST INTRODUCED 1958	FIRST INTRODUCED 1960s

BEFORE 1962



Manufacturers only had to demonstrate **SAFETY**.
Drugs could be marketed with limited or no proof of effectiveness.

1962

THE KEFAUVER-HARRIS AMENDMENT



AFTER 1962



Manufacturers had to demonstrate **BOTH SAFETY AND EFFICACY** through adequate and well-controlled clinical trials.

This marked the beginning of modern FDA drug approval standards.



MOST COUGH-AND-COLD INGREDIENTS STILL SOLD TODAY ENTERED THE MARKET BEFORE **PROOF OF EFFECTIVENESS** BECAME A REGULATORY REQUIREMENT.

INFANT COUGH/COLD PRODUCTS

Still available for 4-6 y/o+



A popular decongestant has been deemed ineffective. Here's what it means for Canadians

Phenylephrine doesn't work any better than a placebo, U.S. panel finds

Sep 13, 2023



Sudafed PE, Vicks Nyquil, Sinex Nighttime Sinus Relief, Benadryl Allergy Plus Congestion, Tylenol Cold + Flu Severe Medicine, Walgreens Sinus Relief Congestion Day Caplets, and Mucinex Sinus-Max Severe Congestion Relief Caplets, among others.



Acetaminophen Products Promise Relief for Back Pain

Common over-the-counter products with acetaminophen market relief for backache and minor aches and pains.



TYLENOL®
Extra Strength
Acetaminophen
“For Backache”**



CVS Health®
Extra Strength
Acetaminophen 500 mg
“Backache” listed



Equate™
Extra Strength
Acetaminophen 500 mg
“Backache” listed



Kirkland Signature™
Extra Strength
Acetaminophen 500 mg
“Backache” listed



Walgreens®
Extra Strength
Acetaminophen 500 mg
“Backache” listed



GoodSense®
Extra Strength
Acetaminophen 500 mg
“Backache” listed

*Use as directed. Read and keep carton for complete warnings and information.



Acetaminophen was introduced in 1955—seven years before the Kefauver-Harris Amendment required proof of efficacy for drug approval.

A TIMELINE: ACETAMINOPHEN, BACK PAIN & REGULATION

1955

Acetaminophen approved in the U.S. (as an analgesic and antipyretic)



1962

Kefauver-Harris Amendment passed—manufacturers must prove both safety and efficacy.



2014

PACE Trial (Lancet) found acetaminophen no better than placebo for acute low back pain.

THE 1962 MILESTONE

1962

Kefauver-Harris Amendment



Enacted October 10, 1962

The Kefauver-Harris Amendment required drug manufacturers to demonstrate both safety AND efficacy through adequate and well-controlled clinical trials before marketing their products.



Acetaminophen is still sold in thousands of products today for back pain—decades after modern studies showed little to no benefit over placebo.

ACETAMINOPHEN: WHAT DOES MODERN EVIDENCE SHOW?

Acetaminophen (paracetamol) is one of the most widely used pain relievers.

EXAMPLES OF ACETAMINOPHEN PRODUCTS THAT MENTION ARTHRITIS



WHAT DOES MODERN EVIDENCE SHOW?

A high-quality systematic review and meta-analysis evaluated acetaminophen for two common musculoskeletal conditions:



Low back pain

The review found acetaminophen is not more effective than placebo for reducing pain or improving function.



Osteoarthritis (knee or hip)

The review found acetaminophen provides a statistically significant improvement in pain compared with placebo, but the improvement is not clinically important.



Overall conclusion: Acetaminophen has little to no clinically important benefit for low back pain and only a small benefit for osteoarthritis.

KEY FINDINGS FROM THE EVIDENCE



For low back pain, acetaminophen does not provide meaningful pain relief or functional improvement compared with placebo.



For osteoarthritis, acetaminophen improves pain scores compared with placebo, but the improvement is smaller than what most patients would consider meaningful.



These findings come from a systematic review and meta-analysis of randomized, placebo-controlled trials using high-quality methodology.



Source: Machado GC, Maher CG, Ferreira PH, et al.

Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015;350:h1225.

<https://www.bmj.com/content/350/bmj.h1225>



Golden Pill Award

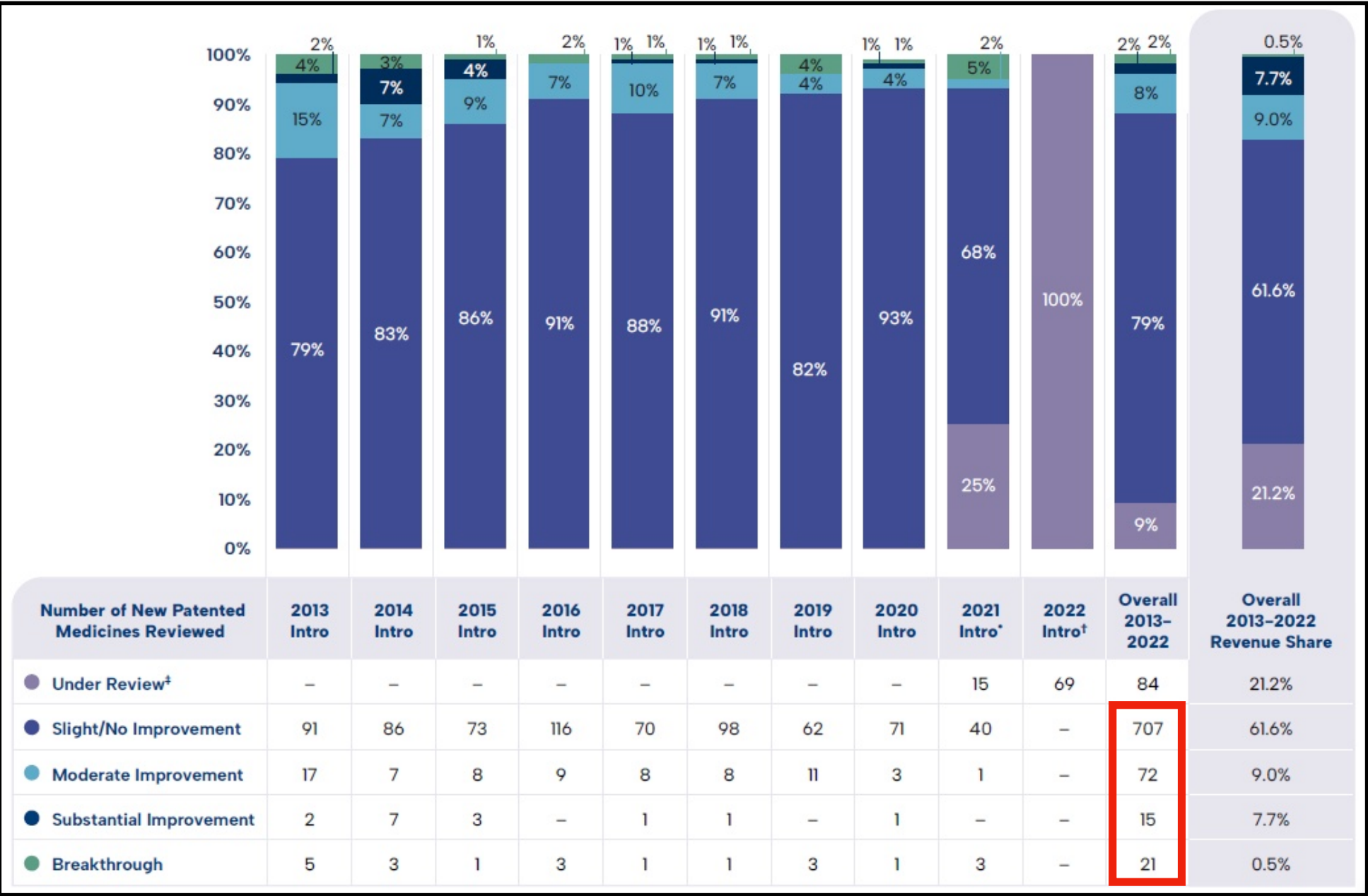
PRESCRIBE AWARDS

	Major advance		Clear advance		Modest improvement	
2011	0		0		0	
2012	0		0		2	abiraterone (prostate CA), boceprevir (Hep C)
2013	0		0		1	meningococcal conjugate vaccine (infant immunization)
2014	1	cholic acid (hereditary bile acid deficiency)	3	imatinib (ALL), artesunate (malaria), sofosbuvir (HepC)	1	sodium phenylbutyrate coated granules (urea cycle disorders)
2015	0		1	propranolol (severe infantile hemangioma)	2	permethrin (scabies), ketoconazole HRA (endogenous Cushing's syndrome)
2016	0		0		2	nivolumab (inoperable melanoma), trametinib (inoperable melanoma)
2017	0		1	asfotase alfa (perinatal and infantile forms of hypophosphatasia)	2	pertuzumab (metastatic breast cancer), emtricitabine/tenofovir (HIV transmission)
2018	0		2	sebelipase alfa (lysosomal acid lipase deficiency), naloxone nasal spray (emergency treatment of opioid overdose)	3	lidocaine + prilocaine combination (primary premature ejaculation), naloxone IM kit (emergency treatment of opioid overdose), arsenic trioxide (acute promyelocytic leukaemia)
2019	0		3	emicizumab (prophylaxis of bleeding episodes in patients with haemophilia A and "factor VIII inhibitors"), tisagenlecleucel (B-cell acute lymphoblastic leukaemia), axicabtagene ciloleucel (large B-cell lymphomas)	3	ruxolitinib (symptomatic myelofibrosis), trastuzumab emtansine (HER2-positive inoperable breast cancer), pembrolizumab (metastatic non-small cell lung cancer)
2020	1	Ebola vaccine rVSV	2	fexinidazole (human African trypanosomiasis sleeping sickness), tafamidis (transthyretin amyloid cardiomyopathy)	0	
2021	2	Pfizer Vaccine/Moderna Vaccine (COVID)	5	nasal glucagon (severe hypoglycaemia in diabetics), Janssen Vaccine (COVID), givosiran (acute hepatic porphyria), rituximab (pemphigus vulgaris), ChAdOx1-S Vaccine (COVID)	2	budesonide orodispersible tablets (eosinophilic oesophagitis), ivacaftor + tezacaftor + elexacaftor (cystic fibrosis)
2022	0		1	Paxlovid (nirmatrelvir + ritonavir) COVID	1	azacitidine (CMML)
2023	0		1	blinatumomab (In high-risk first-relapse acute lymphoblastic leukaemia in children)	0	
2024	1	fexinidazole (sleeping sickness)	0		1	sodium bicarbonate (metabolic acidosis due to chronic kidney disease)
TOTAL	5	~1 every 3 years	19	~1.5 every year	20	~1.5 every year

<https://english.prescrire.org/>

Figure 1. Percentage and Number of New Patented Medicines Reviewed, by Therapeutic Benefit

87%
9%
2%
3%



Our Top 20 Medications by “patented” year

Medication	Indication	Made/Patented
Morphine (oral, parenteral)	Pain	1827
ASA	Pain	1899
Epinephrine	Hormone	1904
Insulin	Hormone	1920
Diphenhydramine (oral, topical, parenteral)	Antihistamine	1946
Dexamethasone (oral, topical, inhaler,	Steroid	1957
Levothyroxine	Hormone	1958
Birth control pill	Contraception	1960
Metronidazole (oral, topical, parenteral)	Antibiotic	1960
Furosemide (oral, parenteral)	HF	1962
Lorazepam (oral, parenteral)	Anxiety	1963
Doxycycline (oral, topical, parenteral)	Antibiotic	1967
Salbutamol (inhaler, oral, parenteral)	Asthma/COPD	1968
Metoprolol (oral, parenteral)	HF/angina/PostMI	1969
Amoxicillin/clavulanate (oral, parenteral)	Antibiotic	1985
Omeprazole (least expensive PPI)	Heartburn	1989
Fluconazole (oral, topical, parenteral)	Antifungal	1990
Losartan (least expensive ARB)	CVD risk/HF	1995
Quetiapine	Antipsychotic/	1997
Polyethylene glycol	Laxative	??

Average year
of “patenting”
1956

2 -1800s

1-1900s

1-1920s

1-1940s

3-1950s

7-1960s

2-1980s

3-1990

Shared Decision-Making



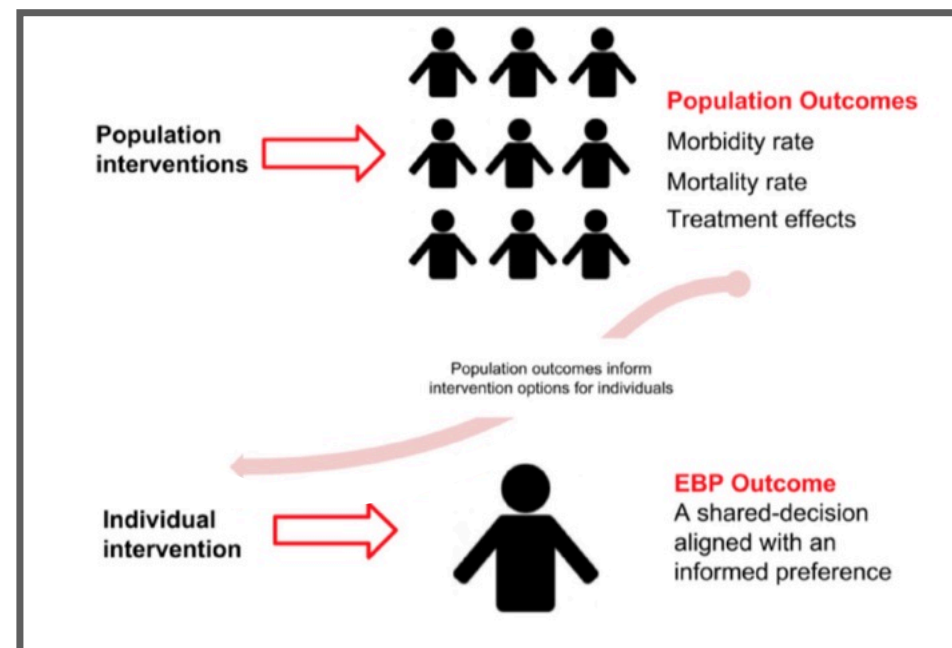
EBM analysis

**OPEN ACCESS**

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

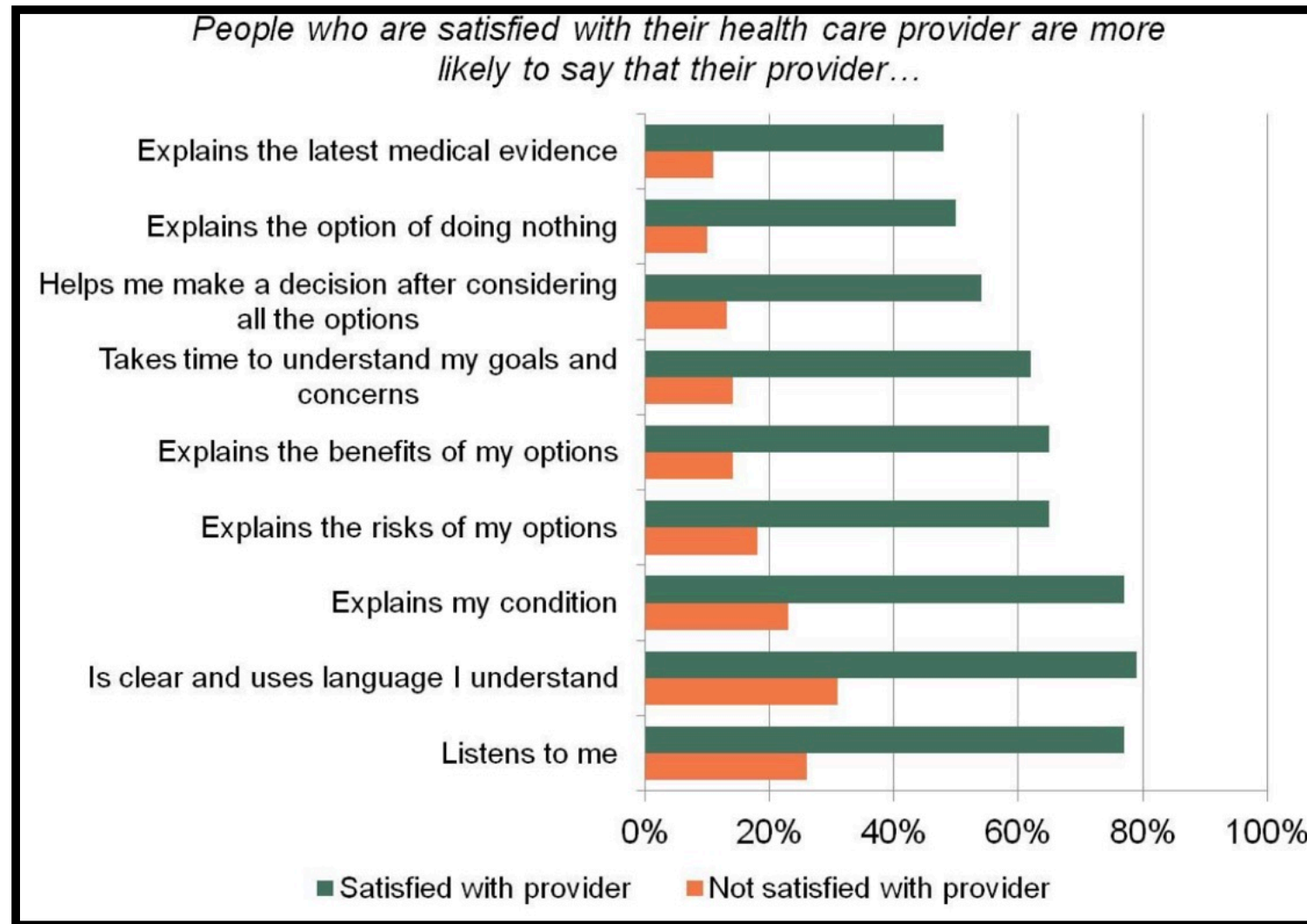
James McCormack,¹ Glyn Elwyn²

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



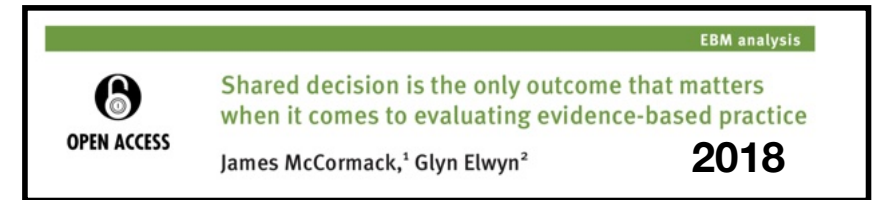
doi:10.1136/ bmjebm-2018-110922

Satisfaction is linked to shared decisions



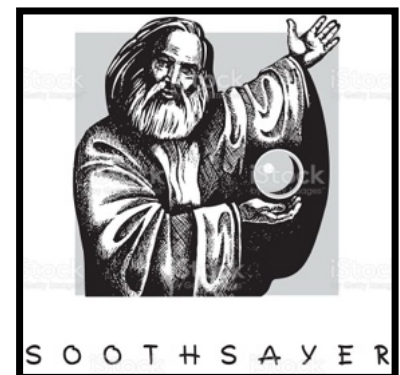
Communicating with patients on health care evidence.
Discussion Paper, Institute of Medicine, Washington, DC 2012

Where SDM may not work



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

If you know the ballpark evidence



Knowing, and being able to use, the
best available evidence is...



rewarding

interesting

enjoyable

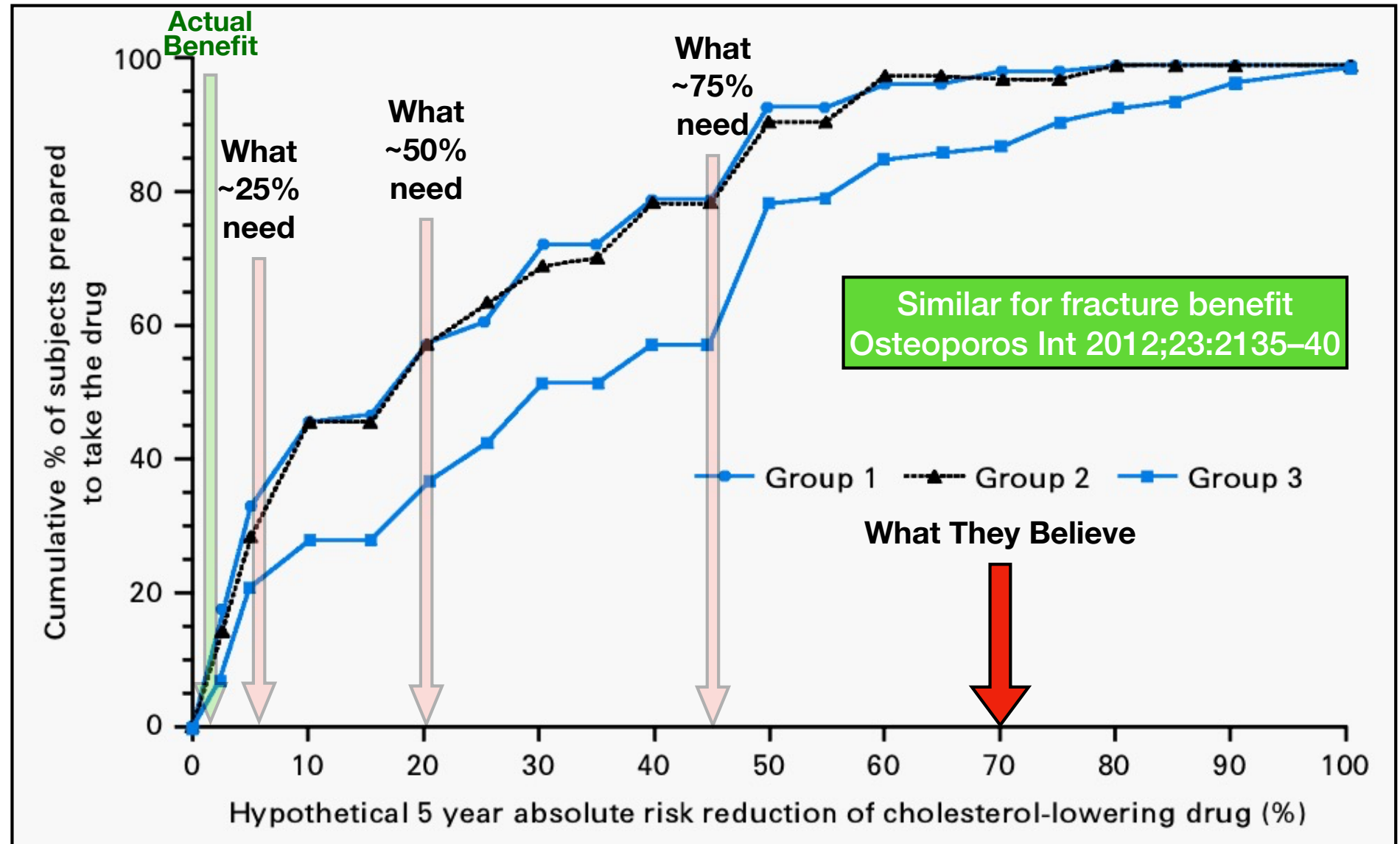
empowering

fun

Patient Expectation's are **NOT** close to what we can offer

Belief about
benefiting from
their CVD drug over
the next 5 years

~70%
**ABSOLUTE
BENEFIT**



People often ignore how **MUCH** an intervention **HELPS** (or **HARMS**) because they're fixated on how **CERTAIN** they are about **SOME** effect

INTERVENTIONS

- Drug A
- Program B
- Policy C
- Treatment D
- Device E
- Strategy F
- Therapy G

What really matters?





All of this is
exacerbated by
**The
Magnitudinous
Problem**

AVOID

Misleading Terminology

“Significant”

“Use with caution”

“Use with extreme caution”

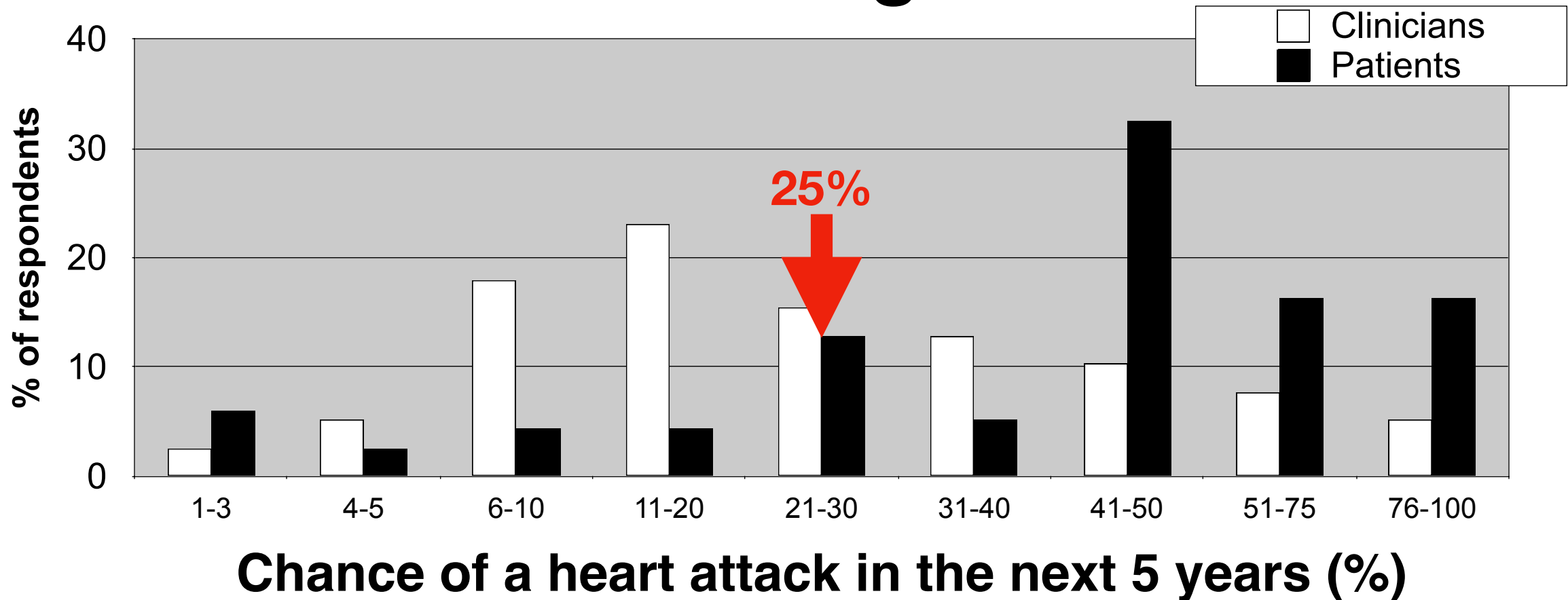
“Monitor closely”

“High risk”

“Very high risk”

“Really !@#\$\$% high risk”

What is "High Risk"



**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
Superior
Rare
Important

Considerable
Strong
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

NUMERICALLY ELASTIC

SAME WORD.

STRETCHED MEANING.

DIFFERENT IMPACT.

MOST

MANY

MAJORITY

SMALL

MORE
INCLUSIVE

LESS
INCLUSIVE

Examples that probably require quantification clarification

Your salary will be **INCREASED**

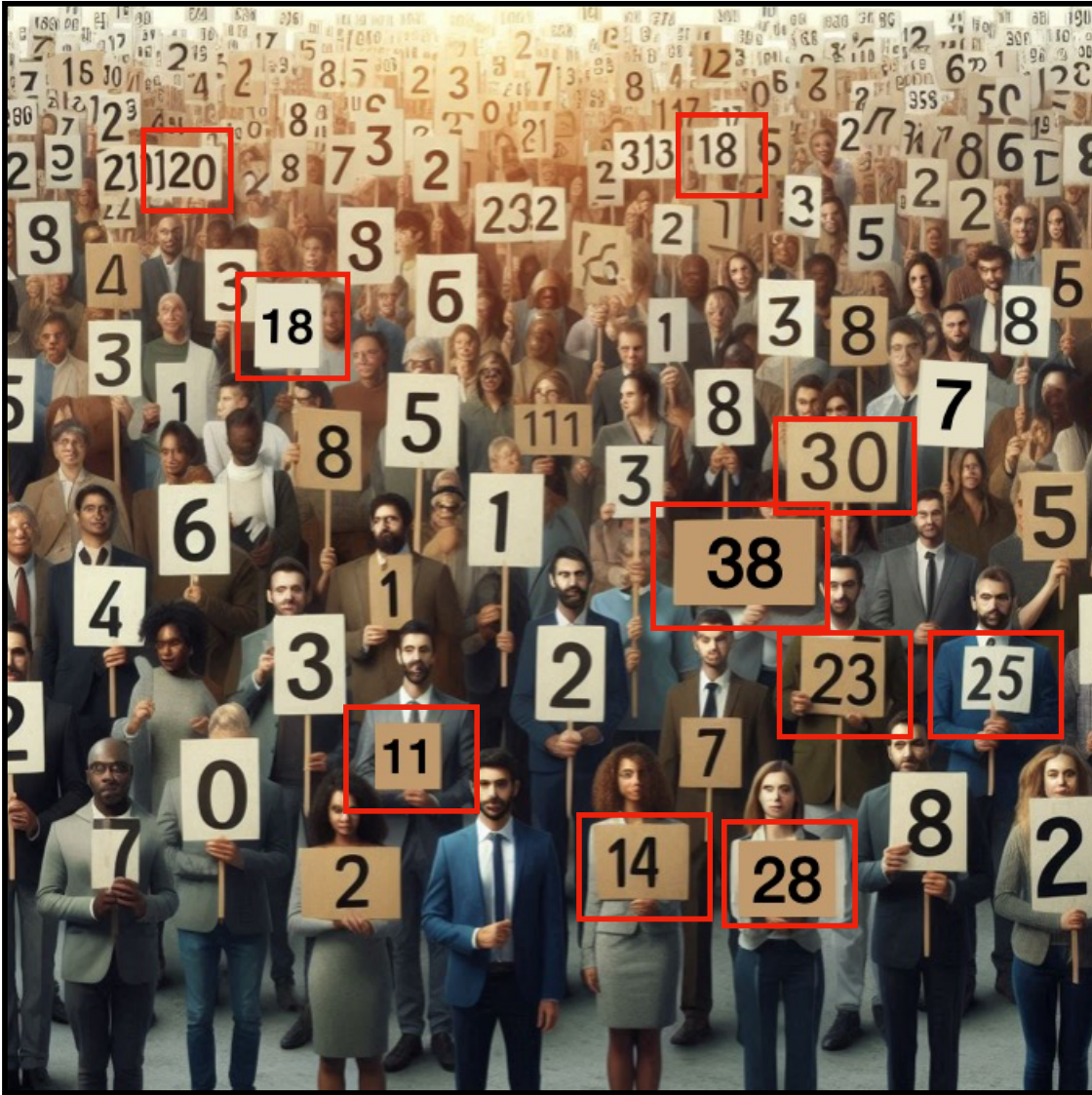
You will be getting a **SHORT** jail sentence

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

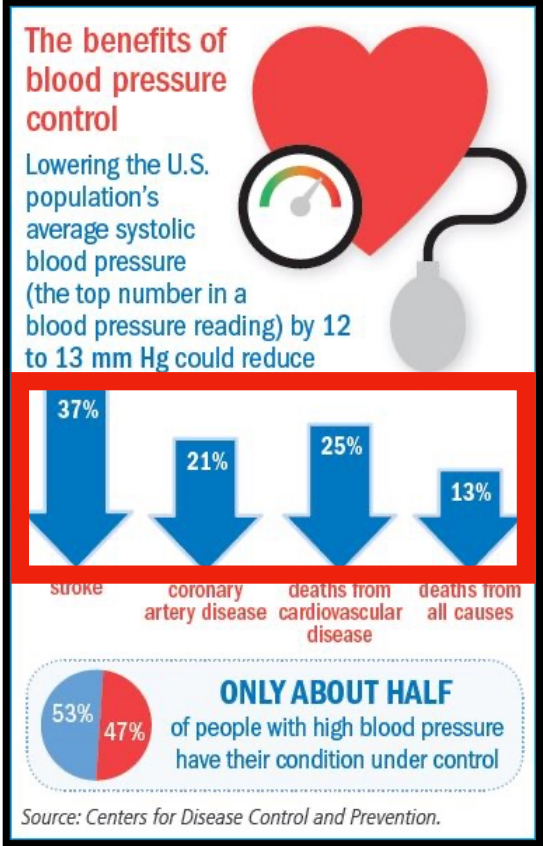
You have a **SIGNIFICANT** chance of a heart attack

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

Numbers are essential, BUT they can also be misleading



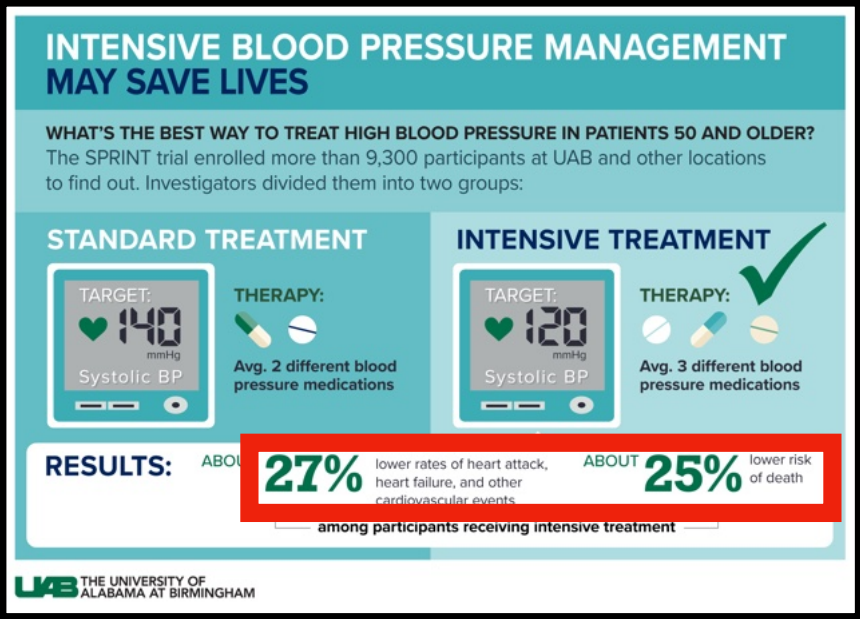
When you see/hear
CVD benefit
NUMBERS
greater than **10%**
they are almost always
relative numbers and these
can be
misleading unless
they are put into
the **proper context**



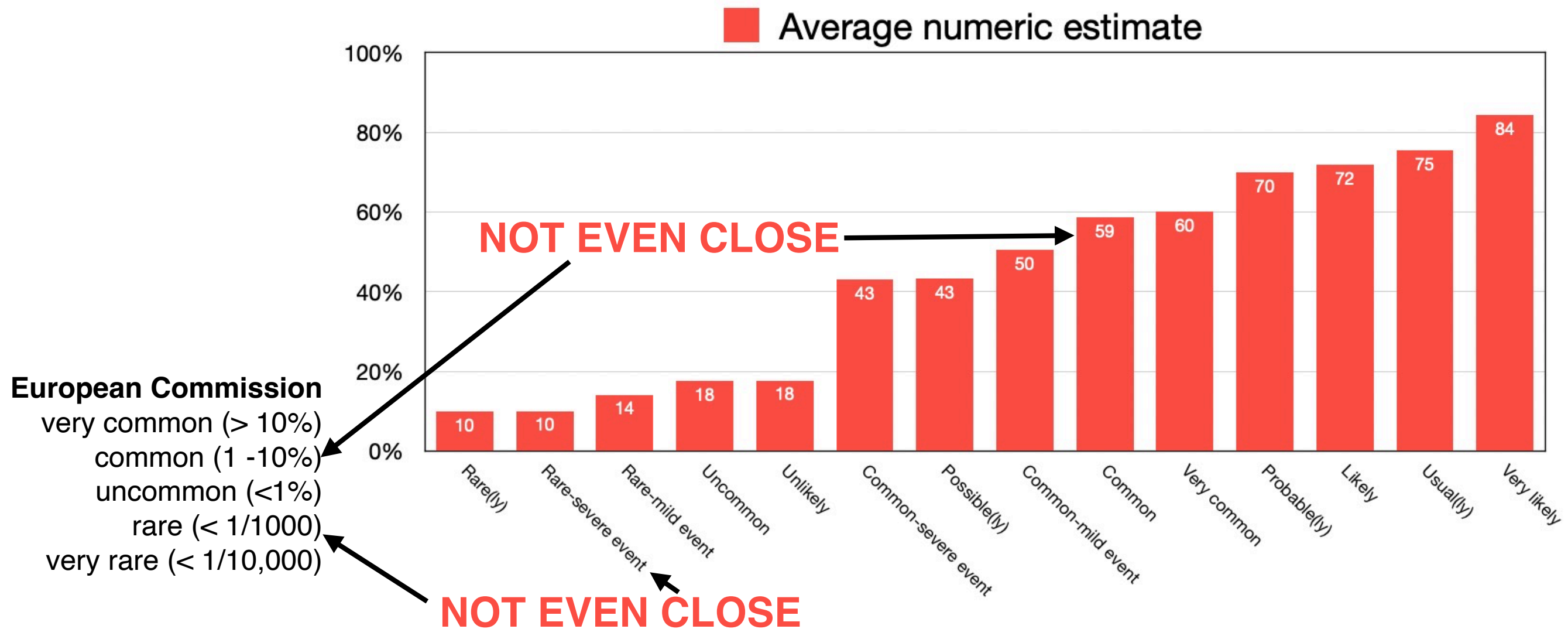
These #s are all relative and all misleading



NONE of these are **DRUG COMPANY** ads!



Using Words to Communicate Harms



1966

One of the first
blood pressure trials

Avg BP = **200/110** mmHg



EFFECT OF PROPRANOLOL IN **MILD** HYPERTENSION

J. W. PATERSON
M.B., B.Sc. Lond., M.R.C.P.
MEDICAL REGISTRAR

C. T. DOLLERY
M.B., B.Sc. Birm., M.R.C.P.

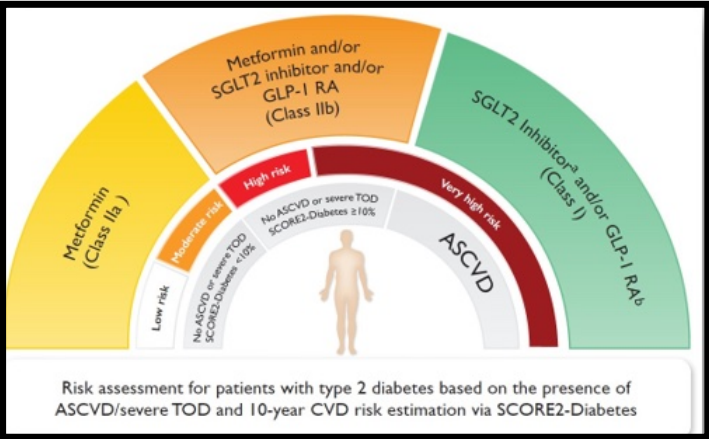
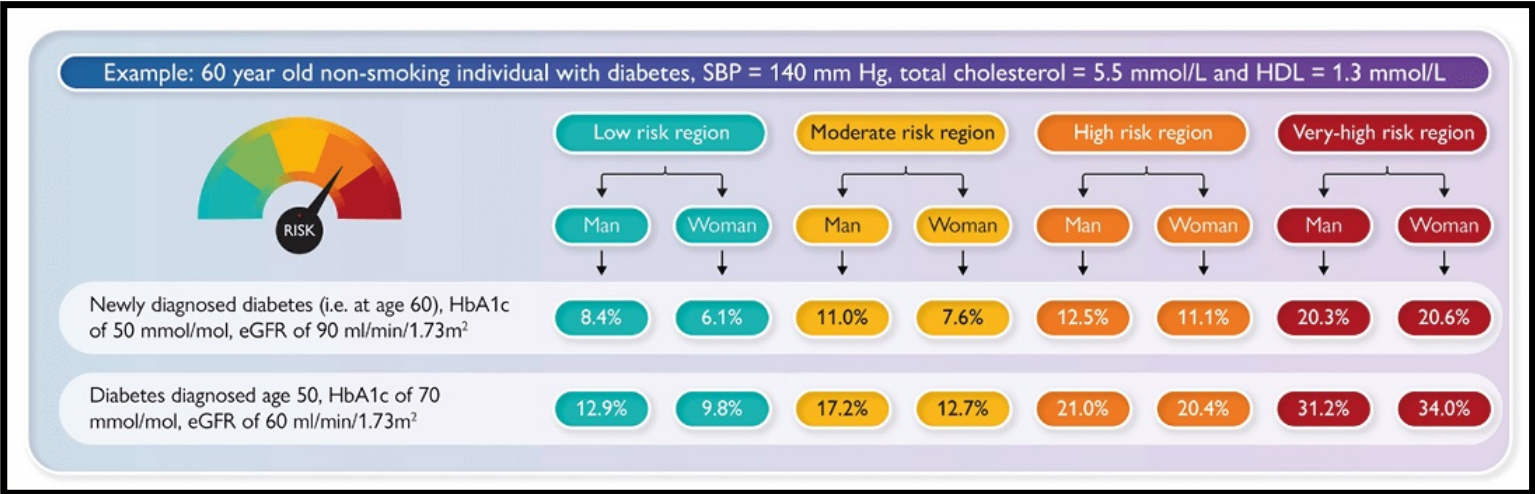
LECTURER IN CLINICAL THERAPEUTICS

DEPARTMENT OF MEDICINE, ROYAL POSTGRADUATE MEDICAL
SCHOOL, DUCANE ROAD, LONDON W.12, ENGLAND

Lancet 1966;2:1148-50



High
Low
Intermediate
Desirable



Normal
High to very high
Nearly optimal
Borderline high

Low to moderate
High Normal
Moderate
Moderate to high
Optimal

Blood Cholesterol Levels and Heart Disease Risk

Total Cholesterol Level	Category
Less than 200 mg/dL*	Desirable
200-239 mg/dL	Borderline High
240 mg/dL and above	High

LDL Cholesterol Level	Category
Less than 100 mg/dL	Optimal (Ideal)
100-129 mg/dL	Nearly Optimal
130-159 mg/dL	Borderline High
160-189 mg/dL	High
190 mg/dL and above	Very High

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

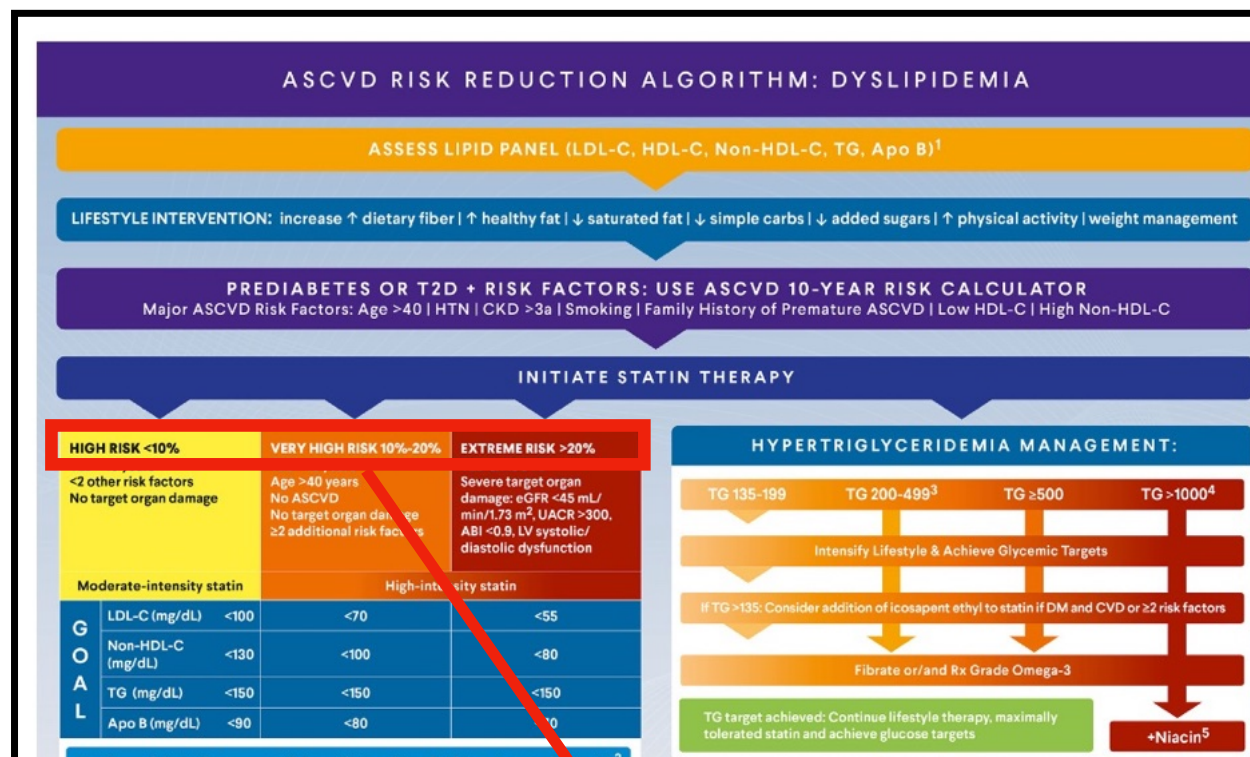
Very high

THESE
“CATEGORIES”
ARE BASICALLY
MADE UP

PRIMARY PREVENTION†		
Low-Risk* FRS <10%	Intermediate-Risk* FRS 10-19.9% and LDL-C ≥3.5 mmol/L or Non-HDL-C ≥4.2 mmol/L or ApoB ≥1.05 g/L or Men ≥50 yrs and women ≥60 yrs with one additional risk factor: low HDL-C, IFG, high waist circumference, smoker, or HTN or with presence of other risk modifiers: hsCRP ≥2.0 mg/L, CAC >0 AU, family history of premature CAD, Lp(a) ≥50 mg/dL (100 nmol/L)	High-Risk* FRS ≥20%



If your risk is 0% you are at “high” risk?



American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update

HIGH RISK <10%

VERY HIGH RISK 10%-20%

EXTREME RISK >20%

STOP CALLING WORDS EVIDENCE



WHY LANGUAGE MATTERS
AND PATIENTS DESERVE BETTER

JAMES P MCCORMACK

STOP CALLING WORDS EVIDENCE.



Words inform.
Evidence transforms.
Let's raise the standard.

Words
are clues.
Evidence
is proof.

The right
numbers
don't
mislead.

CHAPTER 3

FROM WORDS TO EVIDENCE: WE NEED **NUMBERS**.

Anecdotes may start the conversation,
but numbers tell the truth.
To represent actual evidence,
we need **data**.



WORDS describe what is claimed.



NUMBERS show what was measured.



EVIDENCE is demonstrated,
reproducible, and testable.

If you can count it, you can trust it.
If you can't, be careful.

42

*The right numbers don't mislead.
They illuminate the truth.*



STOP CALLING WORDS EVIDENCE.

WORDS ARE CLUES.
EVIDENCE IS PROOF.

TO REPRESENT ACTUAL EVIDENCE,
WE NEED **NUMBERS**.



Words can suggest.
Numbers can't.



Words persuade.
Numbers demonstrate.



Numbers reveal.
Evidence proves.

Count it. Measure it.
Prove it. Believe it.

CASE NOTES

1. Symptoms reported
2. Observations made
3. Data collected
4. Analysis performed
5. Evidence established

SEE THE DIFFERENCE

NOT EVIDENCE

He said
It think
It seems
Possibly
Maybe

EVIDENCE

25.6%
 $P = 0.003$
 $N = 512$
CI 95%
 $RR = 0.72$



Since last year, Trump has asserted that he has cut or will cut prescription drug prices by numbers like “500%,” “600%,” “1,000%,” “1,400%” and “1,500%.”

CNN April 24 2026

Trump’s prescription drug math makes no sense. RFK Jr. and Dr. Oz have defended it



Kennedy: “President Trump has a different way of calculating”

“President Trump has a different way of calculating. If – there’s two ways of calculating percentage. If you have a \$600 drug and you reduce it to \$10, that’s a 600% reduction.”



Trump added moments later that while he has taken “a lot of heat” for claiming 500%, 600% and 700% reductions, “We also say sometimes 50%, 60%; different kind of calculation – 70, 80 and 90%.” He conceded, “And people understand that better.” But he added, wrongly: “But there are two ways of calculating it.”



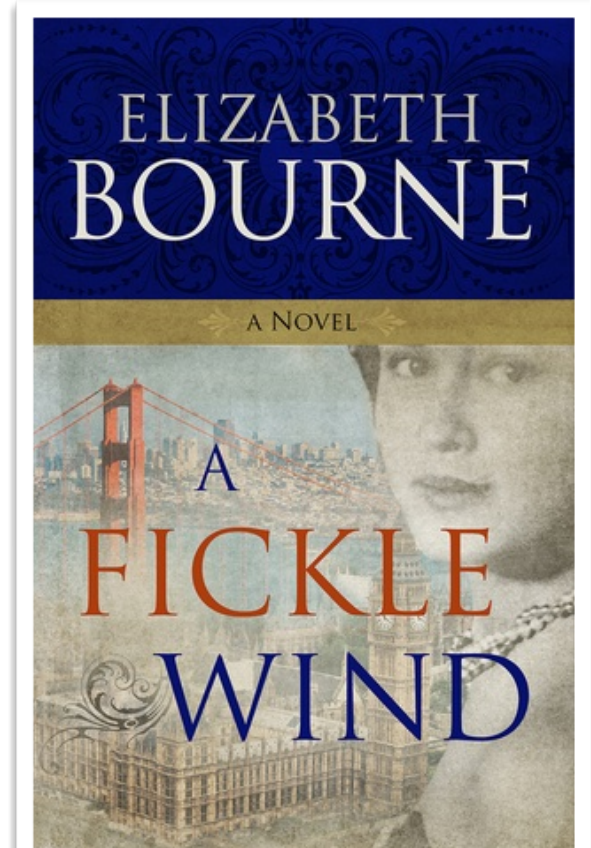
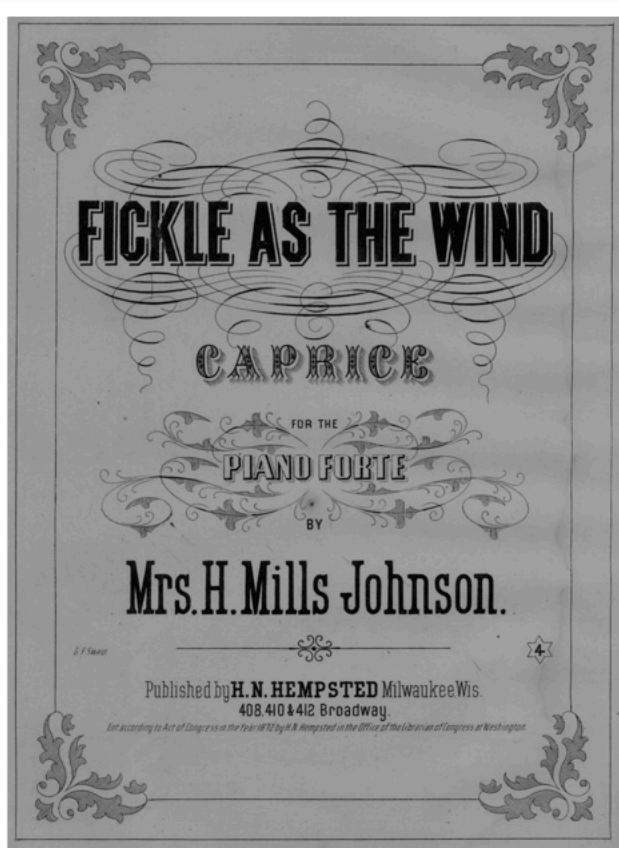
Oz: “It’s too high to calculate without a more studied approach”

Oz made a claim about the price of one common fertility drug being reduced from \$242 to \$10, then said, “I don’t know what the math is on that. We can’t even calculate it. It’s a lot. It’s too high to calculate without a more studied approach.”

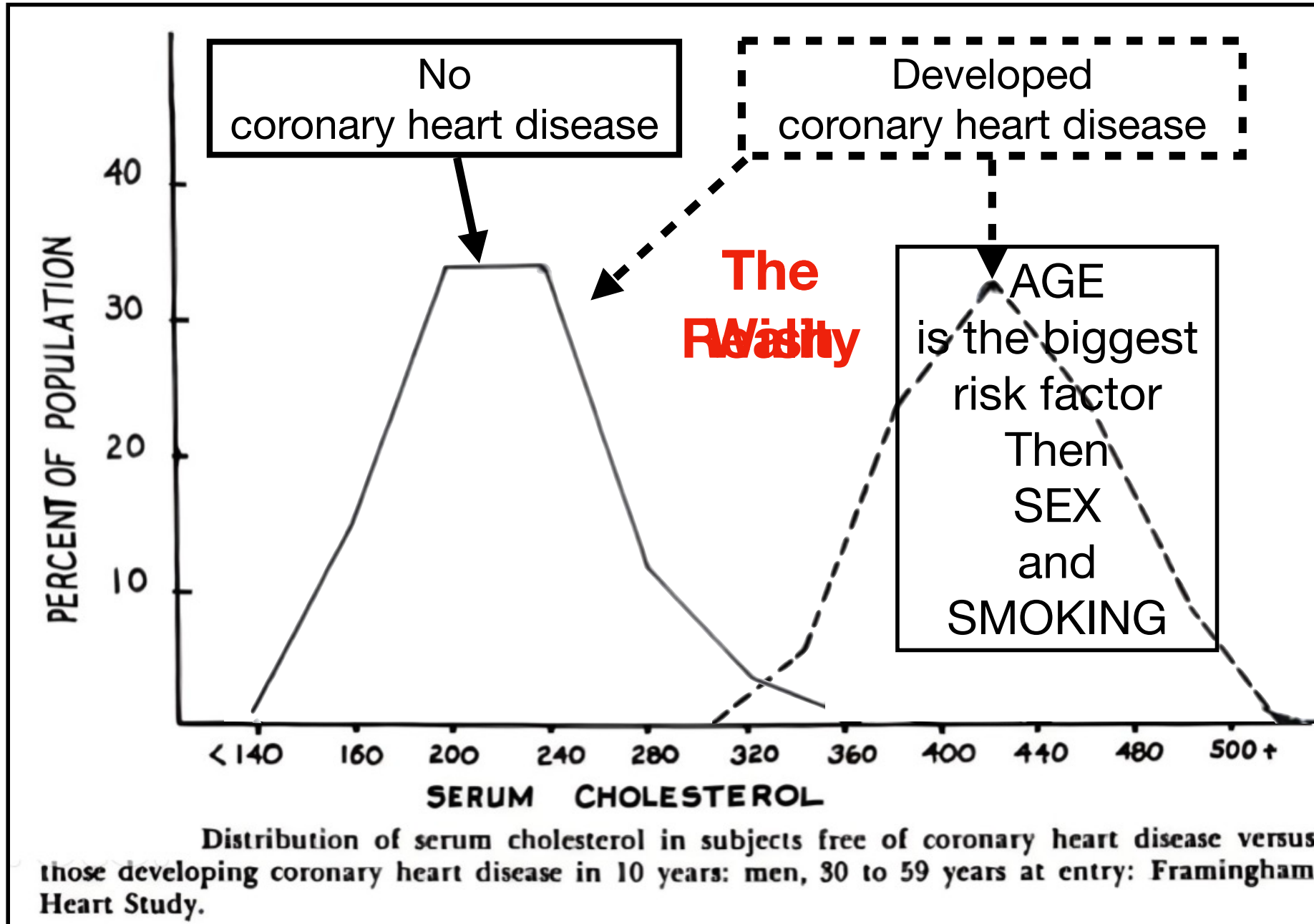
“Well, if the drug was \$100, and it raised the price to \$600, that would be a 600% rise. Well, if it drops from \$600 to \$100, that’s a 600% savings.”

“The president does the calculation by saying, ‘Okay, if a drug was \$100 and you reduce it to \$50, it’s 100% cheaper, because you’re taking \$50 off and left with only \$50. So the amount you took off the price is equal to the amount that’s left. They’re equal, so it’s 100%.’”

The Fickle Nature of Chronic “Disease” Guidelines



Risk Factor Context



The association between cholesterol and heart disease

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**

Wrong guidelines: why and how often they occur

**Primiano Iannone,¹ Nicola Montano,² Monica Minardi,³
James Doyle,³ Paolo Cavagnaro,⁴ Antonino Cartabellotta⁵**

“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

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, MS¹; Nathalia Celini Leite-Santos, BS¹; Franciele Cordeiro Gabriel, MS¹; [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



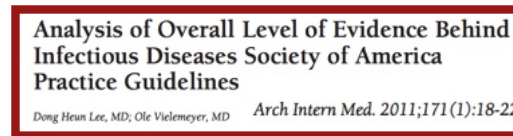
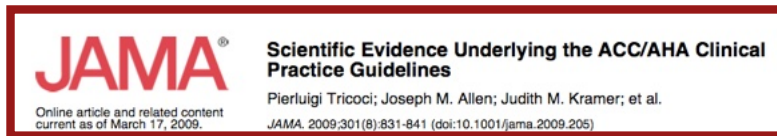
421 CPGs (July 2011-August 2017) for the management of common non-communicable disease in primary care

24% were rated as high quality

lowest median domain scores

applicability (22%) and rigour of development (33%)

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%

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 $\frac{2}{3}$ are
being developed
by groups with
a clear potential for
important biases

Original Investigation | Cardiology

Incorporation of Shared Decision-Making in International Cardiovascular Guidelines, 2012-2022

Blair J. MacDonald, BA, PharmD; Ricky D. Turgeon, BSc(Pharm), PharmD

Looked at 65 cardiovascular guidelines from 2012-2022

American College of Cardiology, Canadian Cardiovascular Society, and European Society of Cardiology

Only ~50% of these guidelines had a statement expressing the importance of shared decision-making

~2700 medication recommendations

only 6% incorporated shared decision-making

only 3% explicitly and impartially recommended shared decision-making

“But, the problem isn’t just bad guidelines.
It’s that good guidelines can disagree.”

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



GUIDELINE WRITERS

Words and Hypertension

Varying Word Definitions

			
Guideline Differences	2017/2015 ACC/AHA	2023 ESH	2025 Canada
Hypertension Definition	$\geq 130/80$	$\geq 140/90$	$\geq 130/80$
Optimal		$<120/80$	
Normal	$< 120/80$	120–129/80–84	
High normal (used to be prehypertension)		130–139/85–89	
Elevated	120–129/ <80		
Stage 1/Grade 1	130–139/80–89	140–159/90–99	
Stage 2/Grade 2	$\geq 140/90$	160–179/100–109	
Grade 3		$\geq 180/110$	

2025 Primary Care Hypertension Guidelines - CMAJ

Guideline

Hypertension Canada guideline for the diagnosis and treatment of hypertension in adults in primary care

Rémi Goupil MD MSc, Ross T. Tsuyuki PharmD MSc, Nancy Santesso RD PhD, Kristin A. Terenzi MD, Jeffrey Habert MD, Gemma Cheng MD, Stephanie C. Gysel BScPharm PharmD, Jill Bruneau NP PhD, Alexander A. Leung MD MPH, Norman R.C. Campbell MD, Ernesto L. Schiffrin MD PhD, Gregory L. Hundemer MD MPH

■ Cite as: CMAJ 2025 May 26;197:Exxx-x. doi: 10.1503/cmaj.241770

Single definition hypertension
BP $\geq$ 130/80 mm Hg

THE GOOD

A uniform hypertension definition and diagnosis approach, emphasizing healthy lifestyle changes and a manageable document size (16 pages) are useful improvements.

THE BAD

No information/evidence provided that would allow you to discuss the patient specific benefits and harms of treatment with the patient

The values and preferences sections primarily and almost exclusively focus on the values and preferences of the committee rather than the values and preferences of patients

CLINICAL GUIDELINES | 6 MARCH 2018

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

“Clinicians should aim to achieve an HbA_{1c} level **between 7% and 8% in most patients** with type 2 diabetes”

Because of harms - primarily internists

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2018 EXECUTIVE SUMMARY*

“**An A1C level of $\leq 6.5\%$ is considered optimal** if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.”

Because of benefits - primarily endocrinologists

Glucose



Tight control of A1c

Tight typically = getting to an A1c of less than 7% versus staying between 7 and 8%
before SGLT2 and GLPs

At least 5 trials looked at tighter control

NO impact on patient-important microvascular risks (kidney, eye, or sensory outcomes/neuropathy)

YET - 77%–100% of published statements and 100% of guidelines **endorsed microvascular benefit**

NO effect on all-cause mortality, cardiovascular mortality, or stroke **BUT** a consistent 15% relative risk reduction of nonfatal MI

YET - between 2006 and 2008 47%–59% of statements endorsed the benefits - also after 2008 (ACCORD) still 21%–36% **endorsed a macrovascular benefit**

Circ Cardiovasc Qual Outcomes 2016;9:504-512

Continuous monitoring



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.

Do higher doses of statins cause more side effects?

Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses

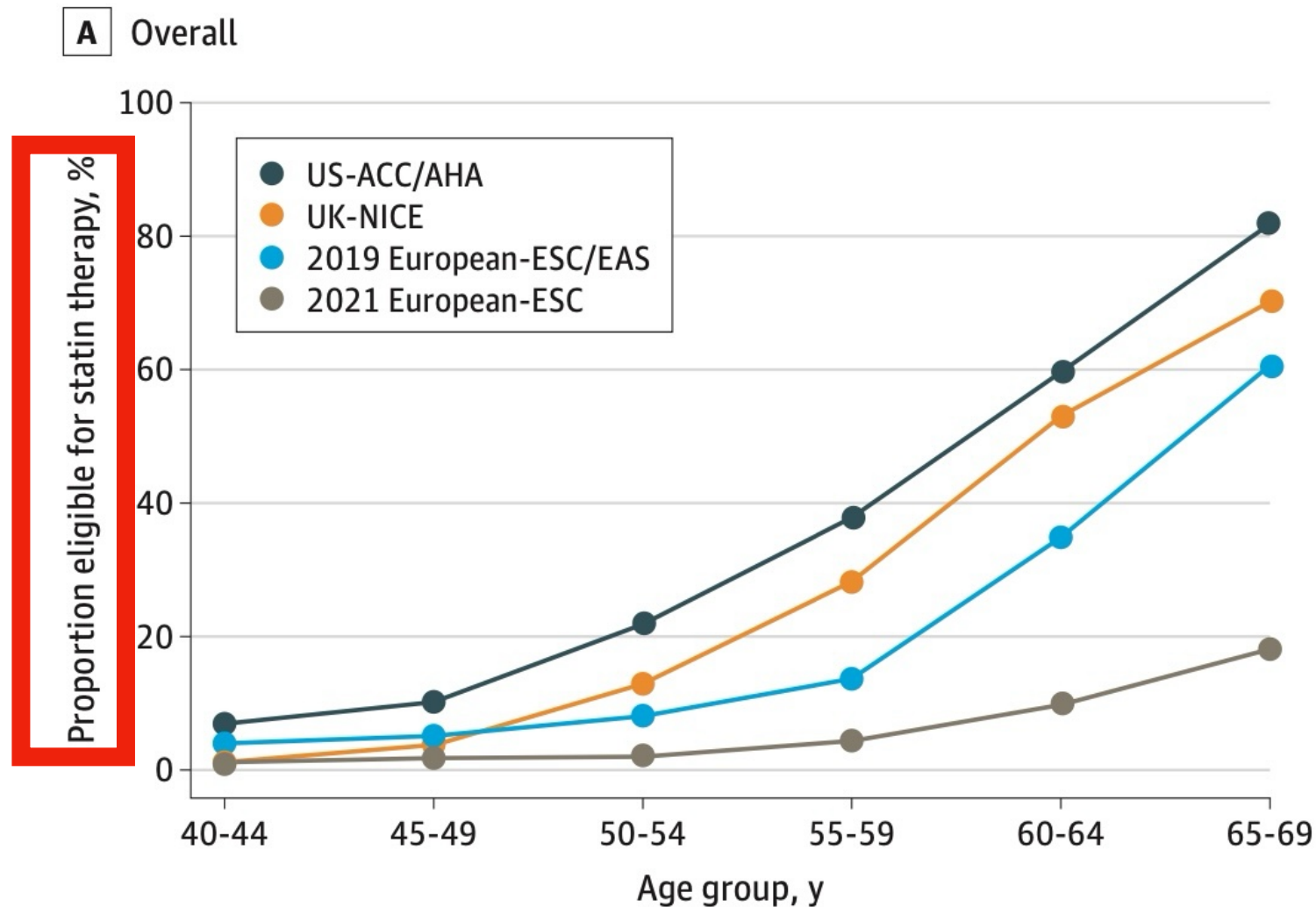
Statin Intensity			
Statin (mg)	Low	Moderate	High
Atorvastatin	5	10-20	40-80
Pravastatin	10-20	40-80	-
Rosuvastatin	2.5	5-10	20-40
Simvastatin	5-10	20-40	-

Table 3 Estimated maximum adverse effects of individual statins from E _{max} dose-response models*						
Statin	Muscle symptoms	Muscle disorders	Liver dysfunction	Renal insufficiency	Diabetes	Eye conditions
Atorvastatin	1.35 (0.92 to 4.46)	0.89 (0.47 to 1.67)	2.03 (1.03 to 12.64)	1.35 (0.61 to 12.83)	1.18 (0.37 to 4.39)	1.32 (0.36 to 6.10)
Fluvastatin	1.10 (0.61 to 5.12)	1.12 (0.49 to 2.79)	1.02 (0.34 to 33.99)	No data	No data	No data
Lovastatin	1.25 (0.79 to 5.00)	0.85 (0.46 to 1.46)	3.29 (0.95 to 40.24)	No data	0.98 (0.14 to 5.63)	1.09 (0.38 to 2.83)
Pitavastatin	0.85 (0.43 to 2.01)	0.94 (0.27 to 2.62)	1.50 (0.41 to 100.85)	0.94 (0.27 to 4.70)	0.74 (0.19 to 3.34)	No data
Pravastatin	1.18 (0.79 to 4.84)	1.02 (0.58 to 1.76)	1.13 (0.59 to 14.72)	1.33 (0.60 to 4.57)	0.95 (0.25 to 3.77)	0.91 (0.26 to 3.33)
Rosuvastatin	1.26 (0.97 to 2.82)	0.92 (0.45 to 1.63)	1.61 (0.75 to 16.82)	1.39 (0.84 to 11.03)	1.16 (0.22 to 4.33)	1.36 (0.56 to 4.22)
Simvastatin	0.83 (0.44 to 2.58)	0.94 (0.44 to 2.06)	1.59 (0.60 to 21.95)	1.17 (0.48 to 5.20)	No data	No data

E_{max}=asymptotic maximum drug effect.
*The maximum odds ratio (OR_{max}) with 95% credible interval (CrI) in each cell is the maximum effect of each statin on the adverse event compared with non-statin controls (that is, the dose of the statin is 0), which is the natural exponential form of the estimated parameter, E_{max}, in each model.

ONLY ONE high dose difference - atorvastatin - liver dysfunction (3x AST/ALT) - 2% vs 1%

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**

Typical GRADE Statin Recommendations

THE NUMBERS		THE RECOMENDATION		THE GRADE DEFINITION	
10-year CVD risk %*	Absolute statin benefit over 10 years**	Primary/Secondary	Typical Recommendation	Typical GRADE recommendation language	Phrases used to describe recommendation
5	~1-2%	Primary prevention	Conditional/weak	“Not all individuals will be best served”	“The majority of individuals would want but many would not”
10	~3%	Primary prevention	Conditional/weak		
15	~4-5%	Primary/secondary prevention	Conditional/Strong		
20	~5-6%	Secondary prevention	Strong	“Most or all individuals will be best served”	“Most individuals would want and only a small proportion would not want”
30	~8-9%	Secondary prevention	Strong		
40	~10-12%	Secondary prevention	Strong		

* GRADE does not have explicit risk thresholds

** assuming 25% relative benefit

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

I've done this to you

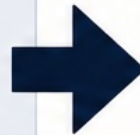
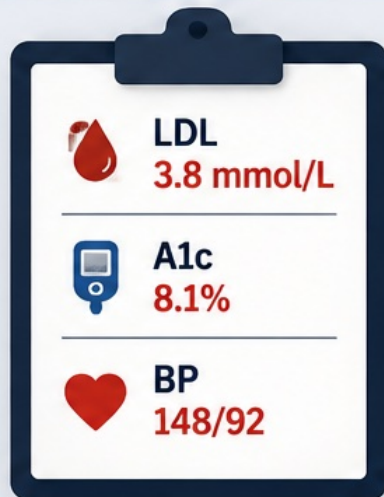
SO NOW WHAT??



Stop Treating Numbers. Start Discussing Numbers.

Patients don't care about reaching **targets**.
Patients care about **what those targets mean**.

Stop treating numbers



Start discussing numbers

-  Heart attacks prevented
-  Strokes prevented
-  Symptoms improved
-  Treatment burden
-  Patient preferences



Tomorrow morning, I don't want you to ignore numbers.
I want you to **stop treating them as the endpoint** of the conversation
and **start using them as the beginning** of the conversation.

Ballpark Lifetime Risks

These are the starting points for a person's risk

Lifetime Risk	CVD 2/3 heart, 1/3 brain		Cancer	
	Developing	Dying From	Developing	Dying From
Men	~50%	~25-30%	~40%	~20%
Women	~30-35%	~20-25%	~40%	~20%

Other Risk of Death - Accidents 10%, Respiratory 10%, Alzheimer's 5%, Kidney, Liver

Risk Factors

Blood pressure, lipid, and glucose numbers
are simply
a measure of
3 of Risk Factors

Some call these conditions chronic diseases - but this is misleading

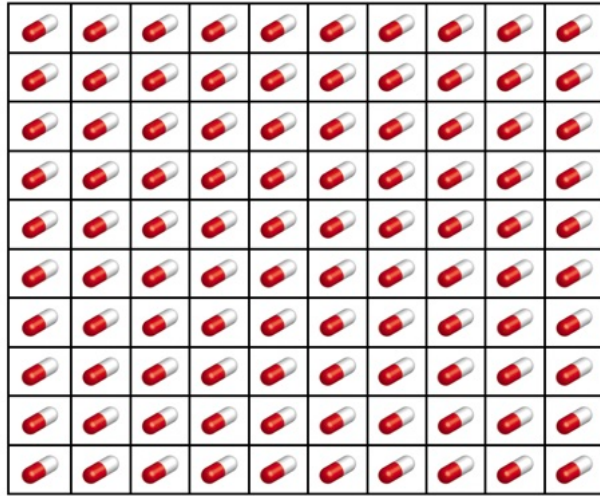
Other key Risk Factors
Age, Smoking, Sex, and Family History

RISKS - death/heart attacks/strokes/kidney problems



So here are the “NUMBERS” you should know

100 people on a medication
daily for 10 years

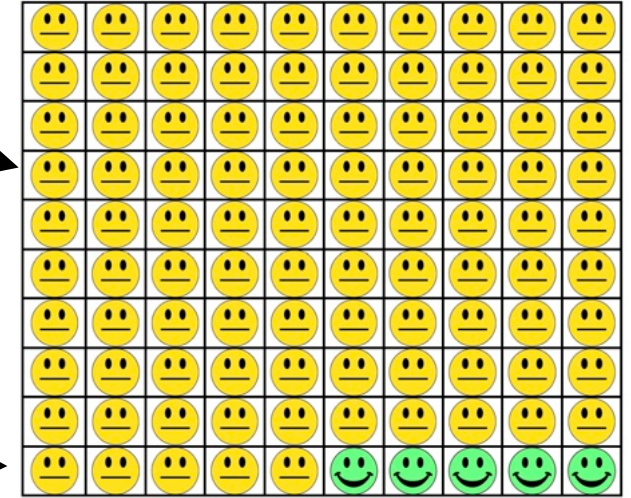


100 people take a
medication daily
for 10 years for their
“HIGH” blood
pressure/cholesterol/
glucose

Almost all will get a
decrease in their
“measurable numbers”
BP, cholesterol, glucose

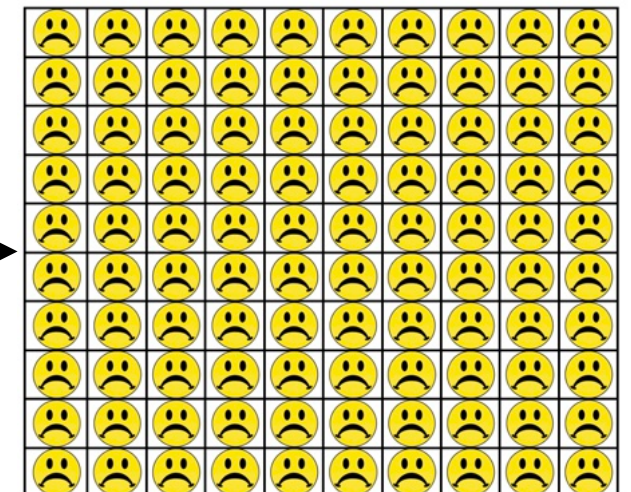
At least **95**
get no CVD
benefit

5 out of
100 get a benefit

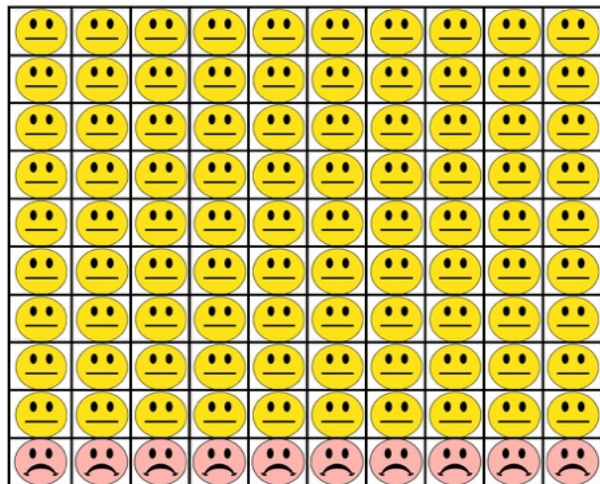


At most,
5 get a
clinical
benefit

100 get the cost and
inconvenience



5-10 won't tolerate them



5-10 won't
tolerate them

100 get the
inconvenience
and cost

CVD decision aid

PEER Simplified Cardiovascular Decision Aid

FAQ Languages: English (EN) ▼

1. Estimate your risk

Where do you live?
Canada (Framingham)

How old are you?
50 years

What is your sex?
✓ Male Female

Do you currently smoke?
✓ No Yes

Do you have diabetes?
✓ No Yes

What is your systolic blood pressure?
130 mmHg

Do you take medications for blood pressure?
✓ No Yes

What is your total cholesterol?
5 mmol/L

What is your HDL cholesterol?
1.3 mmol/L

Wondering why family history is not included?
Please see the [FAQ](#)

10-year risk of cardiovascular disease (heart attack, angina, heart failure, stroke, or intermittent claudication)

Your risk 8.1% With treatment 8.1%

No Event Treatment Benefit Event

2. Choose your treatments

Lifestyle options

☐ Mediterranean diet

☐ Physical activity

Medication options (only select one)
These options have clear and direct evidence for primary prevention

☐ Statin (low to moderate dose)

☐ Statin (high dose)

☐ Single blood pressure medication (thiazide, ACEI/ARB, or CCB)

Non-statin options not recommended for primary prevention in our guideline

☐ Ezetimibe

☐ PCSK9 inhibitor

☐ Fibrates

Print

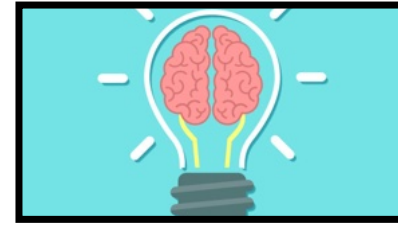
EMR Note/Share Link

PEER Simplified Lipid Guidelines

Patient Handout

They Aren't Actually Sick

A condition vs a disease



When these numbers are “high” we often refer to them as chronic “diseases”

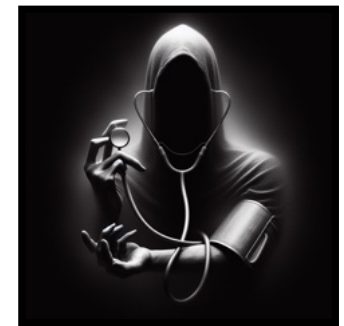
HOWEVER - in general, people with:

“high” blood pressure have **NO** symptoms

“high” cholesterol have **NO** symptoms

Type 2 diabetes (“high” glucose) - most have **NO** symptoms (unless your glucose is really high then you might experience peeing more frequently, increased thirst, feel tired, recurrent skin/bladder infections)

Silent Killers



A much more informative way is to think of these **simply as RISK factors**

Importantly

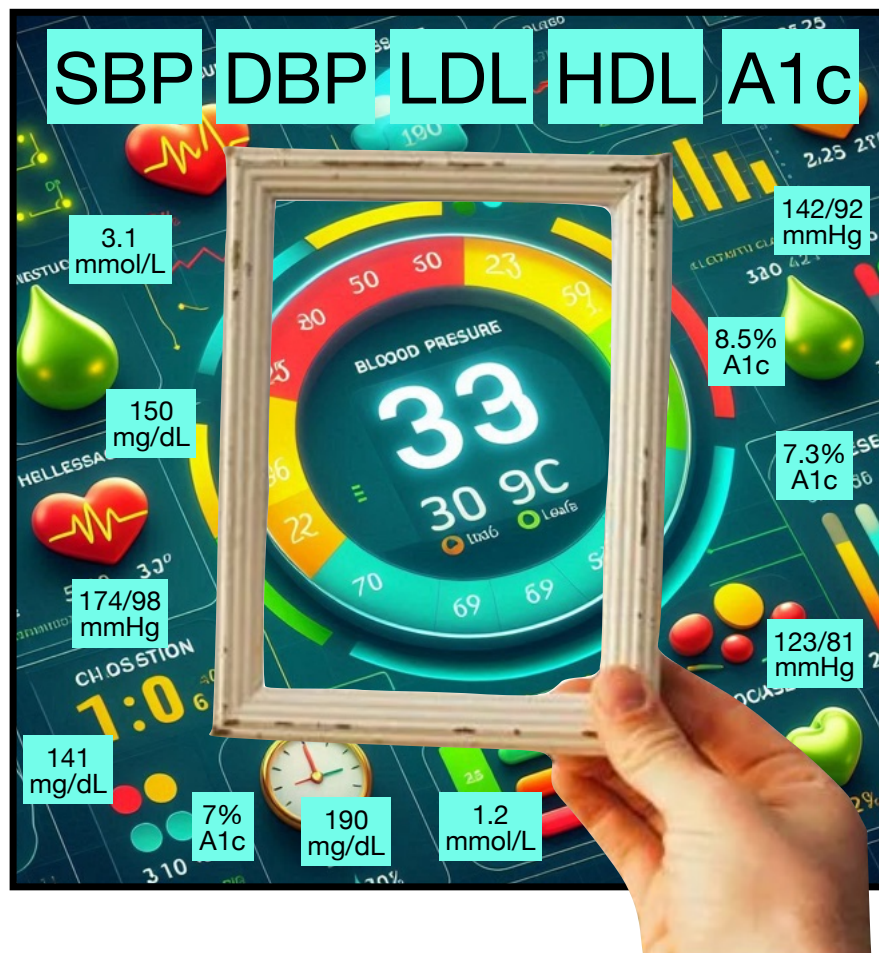
- 1) it's difficult to make a person with no symptoms feel better
- 2) if your blood pressure and/or cholesterol and/or glucose was ZERO, you would be DEAD

Reframe What You Think About Numbers

Blood pressure, lipids, and glucose

What Really Matters

What doesn't matter as much



QUALITY OF LIFE

Reduced chance
of heart attacks

Reduced chance
of strokes

Minimize testing

Minimize side effects

Minimize worry

Minimize inconvenience

Minimize
cost

ABSOLUTE Benefit on CVD risk over 10 years

Typically based on a 10-year risk of 15%

THE GOLDEN RULE

BENEFIT NEVER >10%

Mainly LESS than 5%

Typically AROUND 2-3%

Often as LOW as 1%

PRIMARY PREVENTION

SBP 180 ~ 4-5%

SBP 160 ~ 3-4%

SBP 140 ~ 2-3%

SBP 130 ~ 1-2%

Statins (primary) ~ 2-3%

Statins (post MI) ~ 5-6% - high dose + ~ 2%

A1c 8% - insulin, SU, DPP4 ~ 0%

A1c 8% - SGLT-2, GLP ~ 2% - SGLT-2 for renal ~ 1-2%

If A1c 10% ~ 3%

A fib - DOACs ~ 2-3% PER YEAR (for stroke only)

Treatments that have decent evidence of benefit

in people who have never had a cardiovascular event

Lifestyle and their relative benefits *		Medications and their relative benefit *					
Lifestyle	Heart attack/ stroke benefit	Blood pressure	Heart attack/ stroke benefit	Lipids	Heart attack/ stroke benefit	Glucose	Heart attack/ stroke/kidney benefit
Mediterranean diet	30% ↓	Salt substitute 75%Na/25%K	10-15% ↓	Statins lower dose	25% ↓	Metformin	? only 1 trial
Moderate physical activity	25% ↓	Thiazide lower dose	25% ↓	Statins higher dose	an extra 10 % ↓	SGLT2's **	15% ↓
		ACE/ARB lower dose	25% ↓	Ezetimibe **	5% ↓	GLP's **	15% ↓
		Betablockers, calcium channel blockers	Some but less than those above	PCSK9 Inhibitors **	15% ↓	Sulfonylureas Insulin DPP4s	0%

*Regardless of their effect on the specific risk factor and all numbers are rounded

** Much, and in some cases all, of the evidence is in secondary prevention

Lp(a): How Much Does It Change Your Risk?

Lp(a) is a genetically determined lipoprotein.
Higher levels are associated with higher risk of cardiovascular disease.

HOW MUCH DOES Lp(a) CHANGE RISK? (Compared with average ~35 nmol/L)					
Lp(a) (nmol/L)	Approx % of People	Multiplier (relative to ~35 nmol/L)	ADJUSTED 10-YEAR RISK		
			5% baseline risk	10% baseline risk	20% baseline risk
5 nmol/L	~10%	0.9x	4.5%	9.0%	18.0%
20–30 nmol/L	~30%	0.95x	4.8%	9.5%	19.0%
35 nmol/L (median)	~10%	1.0x	5.0%	10.0%	20.0%
75–100 nmol/L	~15%	1.1x	5.5%	11.0%	22.0%
125 nmol/L	~15%	1.2x	6.0%	12.0%	24.0%
180–200 nmol/L (≈200 nmol/L)	~10%	1.4x	7.0%	14.0%	28.0%
250 nmol/L	~7%	1.6x	8.0%	16.0%	32.0%
400 nmol/L	~2%	2.1x	10.5%	21.0%	42.0%
500 nmol/L	~1%	2.4x	12.0%	24.0%	48.0%

Values are approximate based on population percentiles and current evidence.

KEY TAKEAWAYS



Most people have little change in risk from Lp(a).



Meaningful risk increase occurs in the ~5% of people with Lp(a) >250 nmol/L.



Very high levels (≥400 nmol/L) carry a large increase in risk but are rare.

WHY IS Lp(a) HARD TO PREDICT?



High Lp(a) is surprisingly difficult to predict from traditional risk factors, family history, and lipid levels alone.

WHAT DO GUIDELINES RECOMMEND?



CCS (Canada)

If Lp(a) is elevated (≥100 nmol/L), the main recommendation is:

More intensive risk factor modification.



ACC/AHA (United States)

Lp(a) is a risk-enhancing factor (≥125 nmol/L).

A high Lp(a) may push clinicians toward:

- Starting a statin
- Using a higher-intensity statin
- Considering additional LDL lowering



ESC/EAS (Europe)

Use Lp(a) in overall risk assessment.

High Lp(a) can justify:

- More intensive LDL-C lowering
- Earlier intervention in younger people with very high Lp(a).



INTERESTINGLY: While randomized trials evaluating therapies that lower Lp(a) by 20–30% (including niacin and CETP inhibitors) have not provided evidence that lowering Lp(a) reduces the risk of ASCVD beyond that which would be expected from the observed reduction in ApoB-containing lipoproteins, recent data with PCSK9 inhibitors have suggested a possible role for Lp(a) lowering in reducing cardiovascular risk.



The ONLY GUARANTEED RISK is Treatment Burden



TREATMENT BURDEN AFFECTS EVERYONE

Health care visits

Dietary restrictions

Taking pills

Side effects

Lab visits

Measuring

Worrying

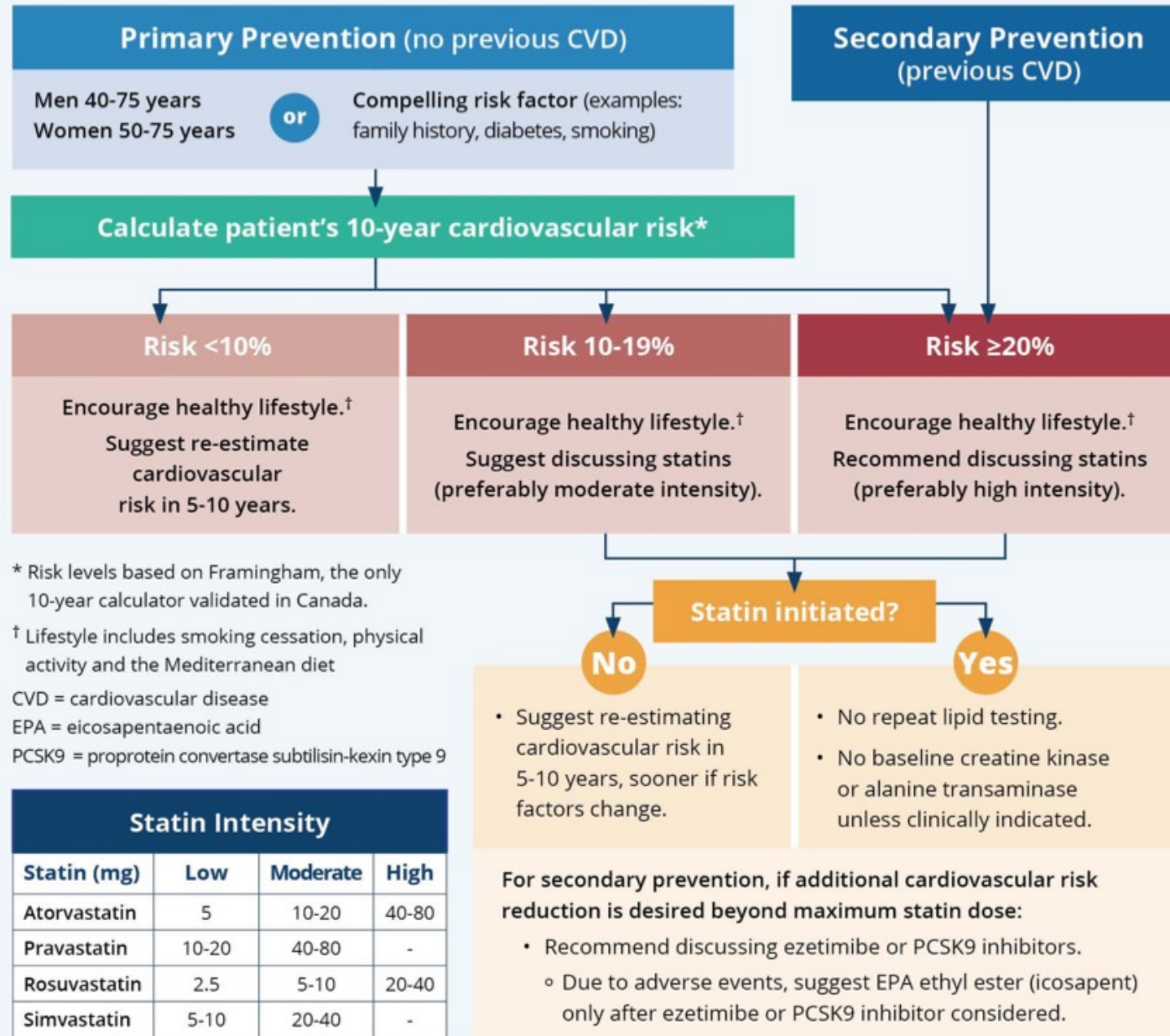
Costs

Inconvenience



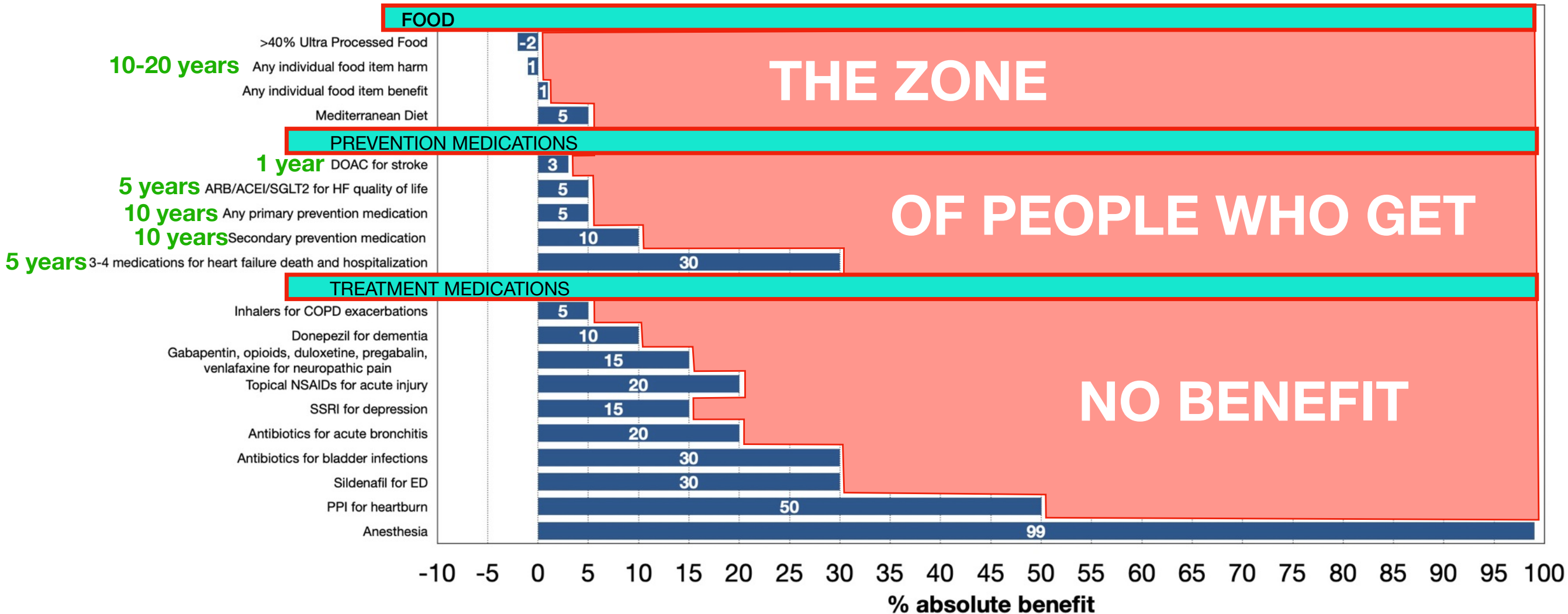
Treatment Algorithm

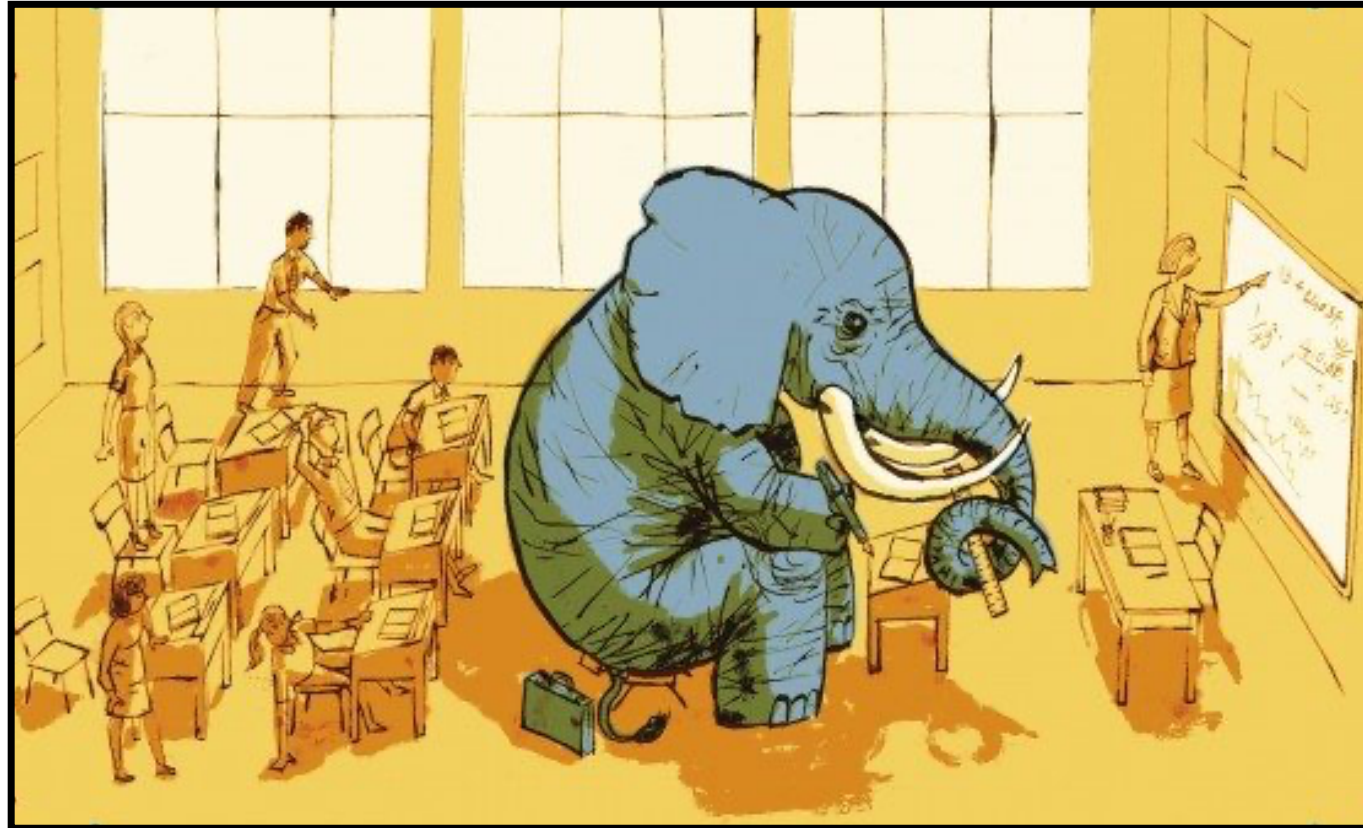
(Excludes familial hypercholesterolemia)



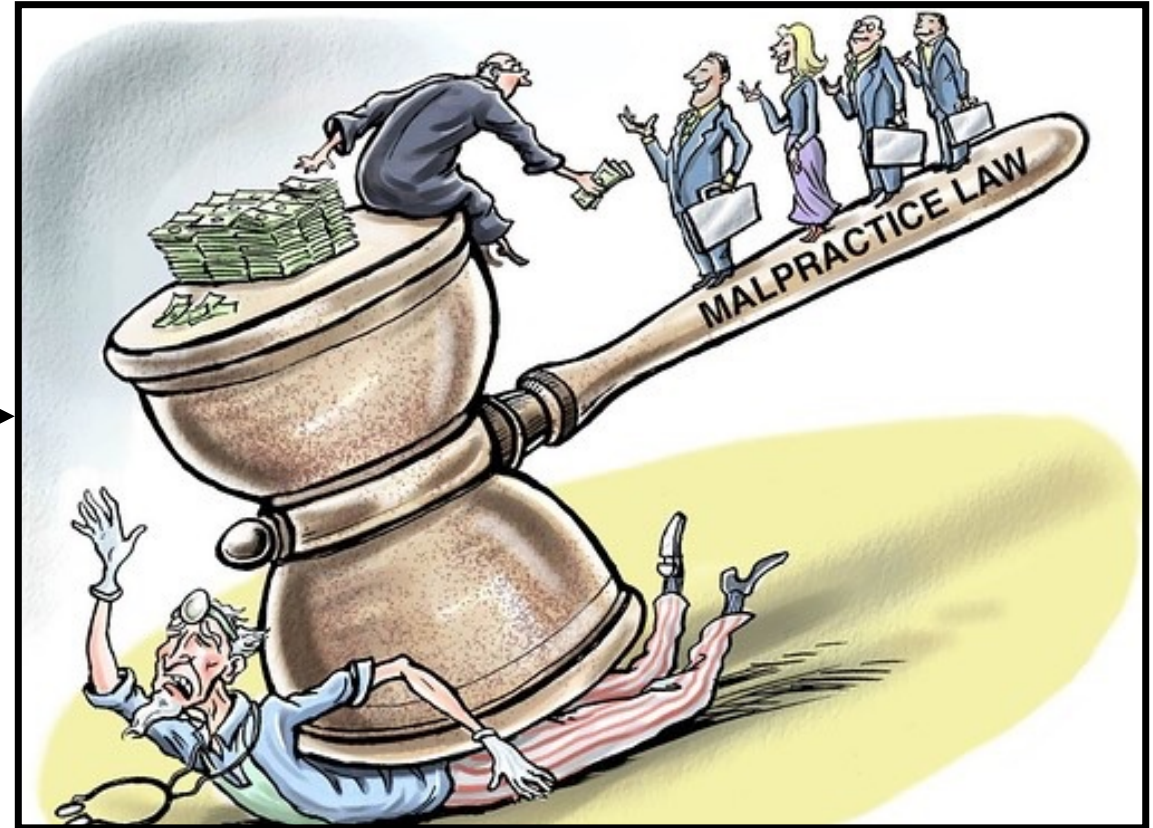
**Discussion Thresholds
NOT
Treatment thresholds**

The Benefit/No Benefit Zone





The Elephant In The Room



**I'll get sued if I don't
follow guidelines**

Most Docs Practice
**Defensive
Medicine**



“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.**”

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**”

**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

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 Cockle², Mala Mann⁶ 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



Litigation anxiety, particularly in the context of the INEVITABLE uncertainty inherent in clinical practice, can be paralyzing and demoralizing for many clinicians.

**CANADA
INVOLVED IN A LAWSUIT**

In Canada ~1%/yr

~2% in the USA

32% in career to date

Emerg med and Surgery 45-50%

Radiology 40%

Primary care 32%

8 out of 10 the physicians
ultimately prevail

UK

GMC REFERRALS

2-3% get an enquiry/year

85% - are closed immediately

2% of the 85% - end up in a
tribunal

25% of those 2% - get struck off
or suspended

So 1 in 1,800 go to a tribunal/yr

1 in 7,000 get struck off or
suspended/yr

Top Tips

Many complaints arise from poor communication and perceived lack of caring rather than lack of knowledge or failure to stick to guideline

Improved consultation listening and explaining skills across the board increases clinical accuracy, increases trust and reduces litigation

Complaints about medications... more because of too much medication, poor monitoring, etc not the other way around

Be clear about informed conversations with patients about drugs, remembering to review and stop treatments, and adjust dose to the lowest that works

Top Tips

Complaints about delayed diagnoses... ask “what else is this likely to be based on what I know right now?”

Build continuity by ensuring you know the results of your own tests, investigations and referrals

When things are vague or unclear be curious...what is going on for this person? Debt, domestic abuse, gambling, alcohol problems may present very indirectly.

Explain your clinical reasoning to patients so they know your thinking and you can work things out together

Top Tips

MANAGE your litigation anxiety by frequent informal discussion with colleagues to keep things in perspective about what a reasonable clinician does (not a perfect one!!).

Document appropriately with your thinking clearly explained - don't alter notes

Reasonable documentation should reduce your anxiety and show you did your best at the time - note all the times when things go well!

Remember parents know their kids and care even more than you do

Recognise and admit mistakes to yourself, don't do wacky stuff, don't think you know better than everyone else, accept feedback...and then ask yourself did I do my best?

Did I act with kindness and compassion?

GOOD MEDICINE. INFORMED PATIENTS. LEGAL PROTECTION.

It's not about hitting targets. It's about helping patients make informed choices.

WHAT GETS YOU IN TROUBLE

-  Missed diagnosis or untreated risk
-  Ignored warning signs or labs
-  No follow-up on uncontrolled risk
-  No discussion or documentation



WHAT PATIENTS REALLY WANT



WHAT PROTECTS YOU

-  Discuss risks, benefits, and alternatives
-  Use numbers patients can understand
-  Document the conversation
-  Plan follow-up together



FROM NUMBERS TO DECISIONS

1 STARTING RISK



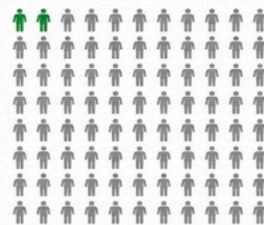
10 out of 100
may have an event

2 WITH TREATMENT



8 out of 100
may have an event

3 ABSOLUTE BENEFIT



About 2 fewer
out of 100

4 RELATIVE BENEFIT



Relative risk
reduction

5 WHAT MATTERS TO THIS PATIENT?



Values, preferences,
and trade-offs

6 SHARED DECISION



Document plan.
Revisit and adjust.
Continue together.



PERFECT NUMBERS AREN'T THE GOAL.

REASONABLE CARE + INFORMED PATIENTS + GOOD DOCUMENTATION = BETTER OUTCOMES FOR EVERYONE.

“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

Healthy Outpatient CAP

DRUGS OF CHOICE (2019)

amoxicillin 1g three times daily or

doxycycline 100 mg twice daily

azithromycin 500 mg on day 1, then 250 mg for 4 days

Mycoplasma pneumoniae
Chlamydophila pneumoniae
Legionella

Streptococcus pneumoniae percent susceptible

Amoxicillin 97%

Azithromycin 69%

BCCDC

β-Lactam Monotherapy vs β-Lactam-Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia

A Randomized Noninferiority Trial

580 immunocompetent Swiss adult patients hospitalized for moderately severe CAP

β-lactam and a macrolide or with a β-lactam alone (monotherapy arm)

If *Legionella* was found (3%) - given macrolide

Primary outcome - proportion of patients not reaching clinical stability

“We did not find noninferiority of β-lactam monotherapy”

Clinical stability after 7 days - combo 66% - mono 59%

Re admission- combo 3% - mono 8% - statistically different

ORIGINAL ARTICLE

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

CAP-START

2,283 adults with clinically suspected CAP in 7 hospitals in the Netherlands

β -lactam mono vs β -lactam–macrolide combo vs fluoroquinolone mono

Primary outcome was 90-day all-cause mortality - also length of stay and complications

NO DIFFERENCE IN OUTCOME

but 39% of β -lactam mono ended up getting a fluoroquinolone

Clinicians could deviate from the assigned strategy when they thought it was clinically necessary

“Most hospitalized ward CAP patients may not need routine upfront atypical coverage, provided clinicians can escalate therapy when necessary.”

The “Best” Ever Antibiotic Sensitivity Chart - MAY 2024

ANTIBIOTIC SENSITIVITY CHART																				
Created by James McCormack, BSc(Pharm), PharmD and Fawzieh Laif, BSc(Pharm), PharmD, with assistance from Drs. Tim Liu, Cecilia Nishi, Solomon Chow Faculty of Pharmaceutical Sciences, University of British Columbia, and Vancouver Hospital, Vancouver, BC																				
Bacteria	Gram Positive Cocci						Gram Negative Bacilli						Gram Negative Coccobacilli		Anaerobes			Atypicals		
	Streptococcus (pneumoniae / pyogenes / viridans group)	Enterococcus faecalis	Staphylococcus epidermidis (coagulase negative)	Staphylococcus aureus (Methicillin sensitive)	Community acquired (Methicillin resistant)	Hospital acquired (Methicillin resistant)	Non-beta-lactamase producing (Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae)	Beta-lactamase producing (Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae)	AmpC producing (HECK-Yes) (Hafnia alvei, Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes, Yersinia enterocolitica)	ESBL-E (Extended spectrum beta-lactamase producing) (Enterobacteriaceae)	CRE (Carbapenem-resistant Enterobacteriaceae)	Pseudomonas aeruginosa	Neisseria meningitidis	Neisseria gonorrhoeae	Above the diaphragm (Peptostreptococcus)	Below the diaphragm (Bacteroides spp)	Clostridioides difficile	Mycoplasma pneumoniae, Chlamydia pneumoniae	Legionella pneumophila	Chlamydia trachomatis
Site of infection	CNS, oral, respiratory tract, heart, skin	Intraabdominal, urinary tract	Skin, prosthetics	Oral, respiratory tract, heart, skin, bones/joint			Respiratory, intraabdominal, urinary tract, and others						Central nervous system	Pelvic inflammatory disease/STI	Oral, respiratory tract	Intraabdominal, pelvic inflammatory disease	Intraabdominal	Respiratory tract	Pelvic inflammatory disease/STI	
Penicillins	Penicillin V/G												Penicillin G-IV		Penicillin V/G					
	Amoxicillin/Ampicillin						Amoxicillin/Ampicillin						Ampicillin-IV		Amoxicillin/Ampicillin					
				Cloxacillin																
	Amoxicillin-clavulanate				Amoxicillin-clavulanate			Amoxicillin-clavulanate	Avoid in serious infections							Amoxicillin-clavulanate				
Cephalosporins	Piperacillin-tazobactam						Piperacillin-tazobactam	Avoid in serious infections				Piperacillin-tazobactam			Piperacillin-tazobactam					
	Cefazolin/Cephalexin			Cefazolin/Cephalexin			Cefazolin/Cephalexin								Cefazolin/Cephalexin					
	Cefuroxime			Cefuroxime			Cefuroxime								Cefuroxime					
	Cefoxitin			Cefoxitin			Cefoxitin								Cefoxitin					
	Ceftriaxone/Cefotaxime			Ceftriaxone/Cefotaxime			Ceftriaxone/Cefotaxime						Ceftriaxone/Cefotaxime							
	Cefixime						Cefixime						Cefixime							
							Ceftazidime					Ceftazidime								
	Cefpime			Cefpime			Cefpime	Unpredictable activity				Cefpime			Cefpime					
							Ceftiderocol (SAP)													
							Ceftolozane-tazobactam					Ceftolozane-tazobactam			Ceftolozane-tazobactam					
Monobactams							Ceftazidime-avibactam (SAP)													
	Ceftaroline (SAP)			Ceftaroline (SAP)											Ceftaroline (SAP)					
Carbapenems	Cefbiprole			Cefbiprole											Cefbiprole					
	Meropenem/Imipenem						Aztreonam (SAP)						Aztreonam (SAP)							
	Ertapenem						Meropenem/Imipenem						Meropenem/Imipenem			Meropenem/Imipenem				
Macrolides	Imipenem-relebactam (SAP)						Ertapenem								Ertapenem					
	Imipenem-relebactam (SAP)						Imipenem-relebactam (SAP)								Imipenem-relebactam (SAP)					
Tetracyclines	Erythromycin																		Erythromycin	
	Clarithromycin/Azithromycin						Clarithromycin/Azithromycin (JUST H.R.)								Azithromycin				Clarithromycin/Azithromycin	Azithromycin
Fluoroquinolones	Tetracycline/Doxycycline/Minocycline						Tetracycline/Doxycycline/Minocycline (JUST H.R.)									Tetracycline/Doxycycline/Minocycline			Tetracycline/Doxycycline	
	Tigecycline														Tigecycline			Tigecycline		
Aminoglycosides							Ciprofloxacin/Norfloxacin (Only bladder infections for Norfloxacin)												Ciprofloxacin	
	Levofloxacin/Moxifloxacin						Levofloxacin/Moxifloxacin								Levofloxacin/Moxifloxacin	Moxifloxacin		Levofloxacin/Moxifloxacin		
Polymyxins							Gentamicin/Tobramycin/Amikacin					Amikacin								
							Colistin/Polymyxin B													
Lincosamides	Clindamycin				Clindamycin											Clindamycin			Clindamycin only	
	Vancomycin/Daptomycin/Dalbavancin														Vancomycin/Daptomycin/Dalbavancin			Vancomycin (PO)		
Oxazolidinones	Linezolid														Linezolid					
					Trimethoprim-sulfamethoxazole		Trimethoprim-sulfamethoxazole													
Chloramphenicol	Chloramphenicol						Chloramphenicol							Chloramphenicol						
																Metronidazole				
Nitrofurantoin/Fosfomicin		Nitrofurantoin/Fosfomicin					Nitrofurantoin/Fosfomicin	Unpredictable activity	Unpredictable activity											
				Rifampin									Rifampin							
Rifampin																				
																		Fidaxomicin		
Fidaxomicin																				
A/Vancomycin should not be used alone for Staphylococcal infections Enterococcus has two main species - Enterococcus faecalis and Enterococcus faecium; the antibiotics listed are active against E. faecalis, but have limited activity for E. faecium Ceftazidime as well as beta-lactamase inhibitor combinations have in-vitro activity for HECK-Yes organisms but may induce production of beta-lactamase Tigecycline is active against HECK-Yes organisms, but for Proteus spp it depends on local susceptibility data SAP = Special Access Program (i.e., not marketed but available from Health Canada)																				
MAY 2024																				

<https://therapeuticseducation.org/tools>

Belief – take the antibiotics until they are all gone or you will get ...?

Resistance

Super infection

Die



Belief – the longer you take antibiotics
the greater the chance of getting ...?

Resistance

Super infection

Die



Duration of antimicrobial therapy for common infections in primary care

Faculty of Medicine
This Changed My Practice (UBC CPD)

By [Dr. Kevin Afra](#), [Maggie Wong, PharmD](#), [Tim T.Y. Lau, PharmD](#), and [Dr. Victor Leung](#) on August 15, 2022

“Shorter treatment durations are just as effective as longer durations for a wide range of common infections.”

“Give Me Five”: The Case for 5 Days of Antibiotics as the Default Duration for Acute Respiratory Tract Infections

Table 1. Duration of Penicillin-Class Antibiotics for Treatment of Group A Streptococcal (GAS) Pharyngitis, Acute Otitis Media (AOM), and Acute Bacterial Rhinosinusitis (ABRS) in US Guidelines Compared to Select International Guidelines

Duration in Days	GAS Pharyngitis	AOM	ABRS
United States	10 d [3]	>6 y: 5–7 d 2–5 y: 7 d <2 y or severe symptoms: 10 d [4]	10–14 d (7 d from symptom resolution) [5–7] Redbook: 5–7 d [8]
United Kingdom (NICE) [9]	5 d for symptomatic cure 10 d for microbiologic cure	5–7 d	5 d
The Netherlands	Forego antibiotics If treating, 5–7 d to shorten symptom duration [10]	<2 y or perforation: 7 d >2 y: forego antibiotics [11]	Antibiotics only if severe course or immune compromised: “no reasons to recommend a longer than usual duration of use of the antibiotic” [12]
Australia	High-risk groups: 10 d Low-risk groups: forego antibiotics [13]	7 d [14]	5 d [15]
WHO [16]	High-risk groups: 10 d Low-risk groups: forego antibiotics. If treating: 5 d	5 d	5 d

J Pediatric Infect Dis Soc
2024 Jun 28;13(6):328–333.

Pneumonia

Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis

“3–5 days probably offers the optimal balance between efficacy and treatment burden for treating CAP in adults if they achieved clinical stability”

BMJ Open 2023;13:e061023

**Short-Course vs Long-Course Antibiotic Therapy for Children With Nonsevere Community-Acquired Pneumonia
A Systematic Review and Meta-analysis**

“A 3-day course ... was noninferior to a 5-day course for the outcome of treatment failure and a 5-day course was noninferior to a 10-day course”

JAMA Pediatr 2022;176:1199-1207

Comparison of a short versus long-course antibiotic therapy for ventilator-associated pneumonia: a systematic review and meta-analysis of randomized controlled trials

“short-course (≤ 8 days) antibiotic therapy did not result in increased number of recurrence and relapses of VAP, suggesting that short-course should be preferred to reduce the exposure to antibiotics”

eClinicalMedicine 2023;58: 101880

Bacteremia

Duration of antibiotic treatment for Gram-negative bacteremia – Systematic review and individual participant data (IPD) meta-analysis

“7 days as good as 14”

10.1016/j.eclinm.2022.101750

Community Acquired Pneumonia in Hospitalized Patients



Community Acquired Pneumonia (CAP): Duration of Antibiotic Therapy in Hospitalized Adults

Key Messages

- Three (3) days is sufficient to treat patients with CAP who meet clinical stability criteria
- Clinical stability criteria for discontinuation of antibiotics after 3 days of therapy in CAP include:
 1. Temperature $\leq 37.8^{\circ}\text{C}$ on day 3 of therapy ***AND***
 2. No CAP-associated sign of clinical instability on day 3 of therapy:
 - i. Systolic blood pressure < 90 mmHg
 - ii. Heart rate > 100 beats/minute
 - iii. Respiratory rate > 24 breaths/minute
 - iv. Oxygen saturation $< 90\%$ on room air (or on baseline home oxygen)
- Patients who are afebrile with no more than one CAP-associated sign of clinical instability by day 5 of therapy are also considered clinically stable and can have antibiotics discontinued.
- Patients who fail to meet clinical stability by day 5 of therapy should be evaluated for potential complications pneumonia as well as alternative etiologies for their respiratory or infectious syndrome.

Cellulitis

Route and duration of antibiotic therapy in acute cellulitis: A systematic review and meta-analysis of the effectiveness and harms of antibiotic treatment

“there is a striking lack of evidence that initial IV therapy or treatment beyond 5–7 days are more effective than initial oral or short course treatment”

Journal of Infection 2020;81;521–531

Pharyngitis

Short- vs. Long-Course Antibiotic Treatment for Acute Streptococcal Pharyngitis: Systematic Review and Meta-Analysis of Randomized Controlled Trials

“Overall, short-term antibiotic therapy was as effective as long antibiotic courses”

“Late clinical cure no difference overall”

Antibiotics 2020, 9, 733; doi:10.3390/antibiotics9110733

Issues - bacterial eradication and rheumatic fever

Cystitis

Single-dose antibiotic therapy for urinary infections during pregnancy: A systematic review and meta-analysis of randomized clinical trials

Studies of single dose cotrimoxazole, amoxicillin and fosfomycin (most studies)

Int J Gynecol Obstet. 2022;159:56–64.

Review of Published Studies on Single Dose Therapy of Urinary Tract Infections

“single dose antimicrobial therapy should now be considered as the treatment of choice for uncomplicated urinary tract infections presenting in general practice”

Infection 1990;18:S53–S56

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Cystitis - Nitrofurantoin 5 days

Cotrimoxazole, Quinolones, Cephalosporins/amox-clav 3 days

Fosfomycin single dose

Clinical Infectious Diseases 2011;52:e103–e120

Pyelonephritis

Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection— 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials

“Seven days of treatment for acute pyelonephritis is equivalent to longer treatment”

J Antimicrob Chemother 2013;68:2183–2191

Otitis Media

Shorter versus longer antibiotic therapy for children with acute otitis media: A systematic review

Conclusion: It cannot generally be assumed that a shorter antibiotic therapy leads to equivalent treatment results in children with AOM. However, new high-quality RCTs investigating treatment duration of commonly used antibiotics are highly needed. Shorter therapies offer economic benefits only when they are clinically as effective as longer ones.

Many guidelines now recommend antibiotic treatment durations tailored to age, for example, 10 days for children under 2 years of age, 7 days for children aged 2 to 6 years, and 5 to 7 days for children older than 6 years [20, 61].

Shorter Durations

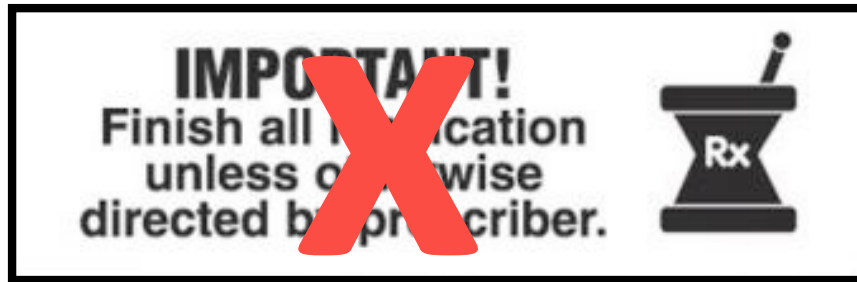
For most community acquired infections (not otitis media in children under 2) shorter courses of duration (3-5 days depending on the site) are as effective as longer durations and produce less side effects and reduced cost and inconvenience

CONTEXT

These are average results from different meta-analyses

“Individualizing treatment” should still be considered

Treating for 2-3 days after asymptomatic is also reasonable - and would lead to 5-7 days duration in most cases



BMJ **EDITORIALS**

A prescription for improving antibiotic prescribing in primary care

Comprehensive education programmes can reduce antibiotic prescriptions, but the impact on clinical outcomes is unclear

BMJ 2012;344:d7955 doi: 10.1136/bmj.d7955 (Published 2 February 2012)

James McCormack *professor*¹, G Michael Allan *associate professor*²

“a reasonable approach for most primary care infections would be to tell the patient to continue the antibiotic until they have been asymptomatic or afebrile for 72 hours and then to stop”

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



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

What is the preferred treatment regimen for uncomplicated urinary tract infections?

BOTTOM LINE

TFP April 2023

For symptom resolution, all antibiotics are similar. Based on limited evidence, best guidance for treatment durations for symptom resolution are nitrofurantoin 5-day; trimethoprim-sulfamethoxazole, beta-lactams, ciprofloxacin and norfloxacin 3-day, and fosfomycin 1-day. Treatment choice should be driven by patient preference, local resistance, side effects, and allergies.

MINI BOTTOM LINE

It really doesn't matter which antibiotic for symptoms

What is the efficacy of fosfomycin for uncomplicated cystitis in non-pregnant women?

Bottom Line: At best, single dose fosfomycin has similar efficacy to other antibiotics for uncomplicated cystitis. However, the best quality, publicly funded trial showed it was not as efficacious as nitrofurantoin, with 58% of cases clinically resolving at 28 days compared to 70% for nitrofurantoin.

TFP July 2020

MINI BOTTOM LINE
Nothing magical ~\$10 more?

Typical Oral Dosing

Nitrofurantoin (Macrobid) 100mg BID x 5 days

Nitrofurantoin (Macrochantin) 50mg QID x 5 days

SMX/TMP 1 DS 800mg/160mg BID x 3 days

Trimethoprim 200 mg daily x 3 days

Fosfomycin 3g sachet OD x 1 day

Amoxicillin 1000 mg BID x 3 days

Ciprofloxacin 250 mg BID x 3 days

Norfloxacin 400 mg BID x 3 days

**INTERNATIONAL
YEARBOOK OF
NEPHROLOGY1989**

edited by
Vittorio E. Andreucci

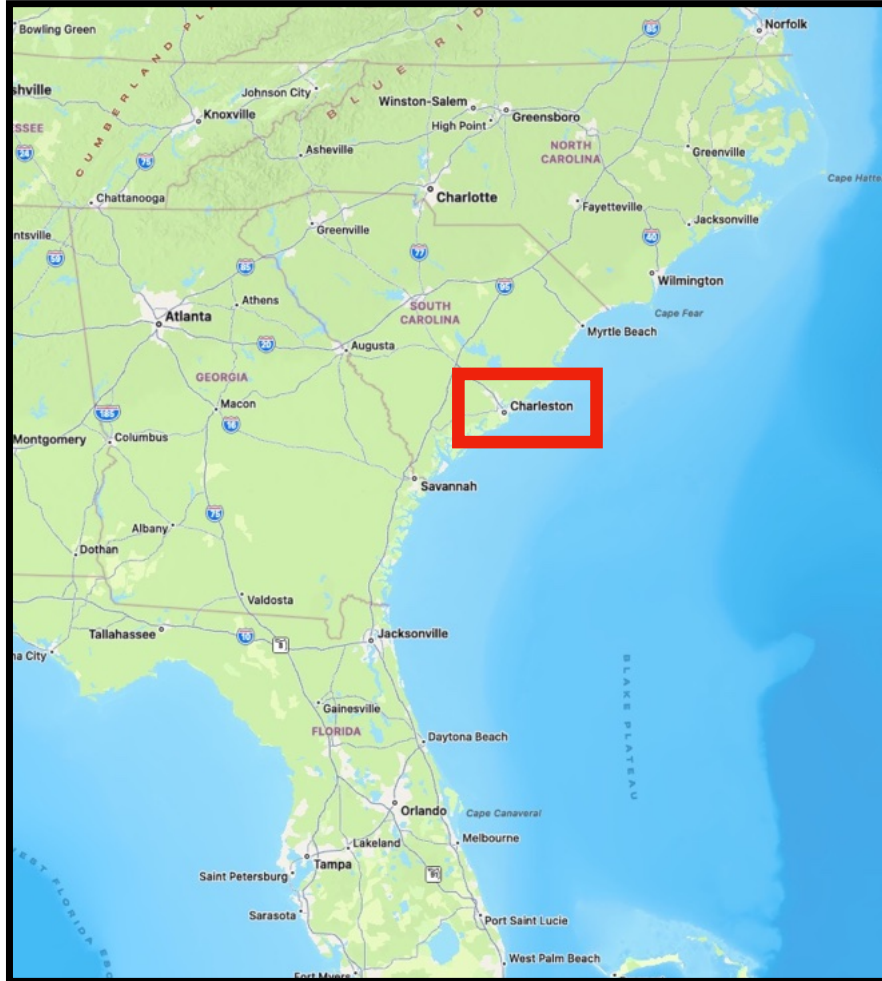
Dosing of antibiotics is somewhat/a lot magical

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).

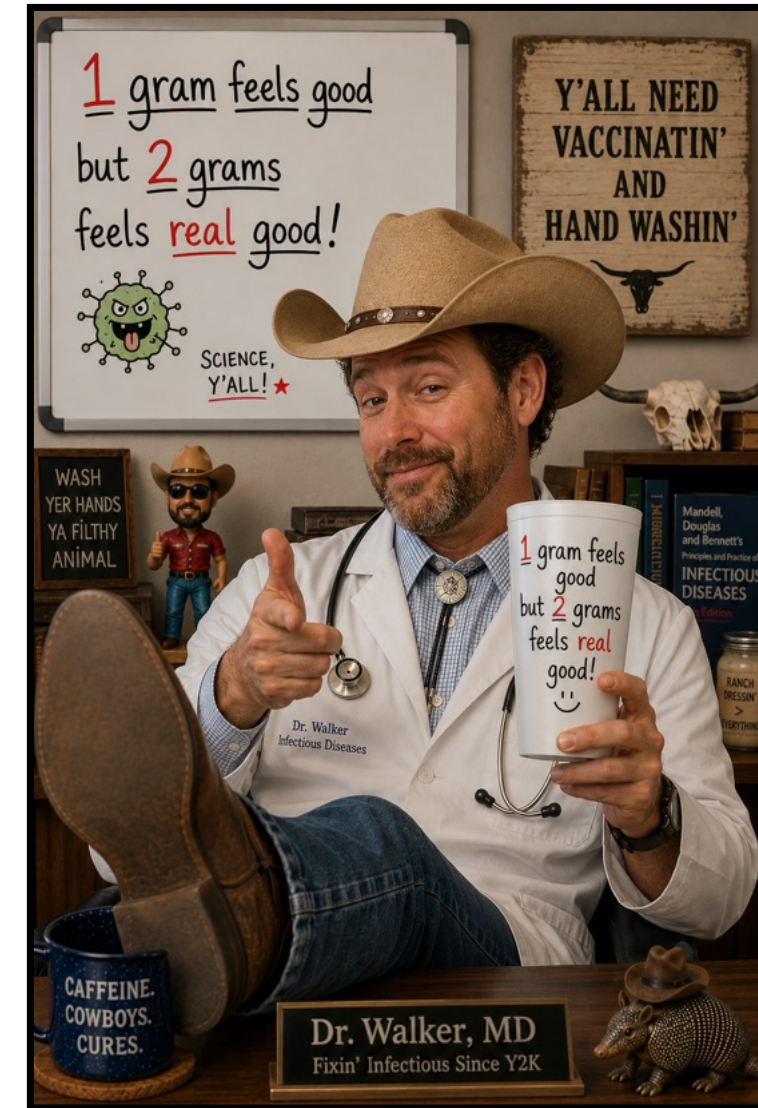
There are quite a few old (70s-80s) trials of single doses of amoxicillin, TMP/SMX, trimethoprim, nitrofurantoin, ciprofloxacin showing effectiveness

Empiric Antibiotic Dosing

Charleston, SC



Jaw osteomyelitis
Pseudomonas
Ceftazidime



Does increasing water intake prevent recurrent urinary tract infections?

Bottom Line: Based on 1 RCT in women with recurrent UTIs (average 3.3 per year) and low fluid intake (less than 1.5L/day), increasing water intake by an additional ~1.5 L/day results in 1.5 fewer UTIs and 1.7 fewer antibiotic prescriptions per patient after 1 year compared to those who don't change intake. Over 90% of women with increased water intake will have fewer than 3 episodes of UTIs per year.

TFP April 2019

MINI BOTTOM LINE

**An additional 1.5L/day reduces recurrent infections by 50%
~ 3/year down to 1.5/year**

Does cranberry juice or extract prevent recurrent urinary tract infections?

Bottom Line: Available evidence for cranberry products for reduction of UTIs is poor and inconsistent. Funding or selective reporting influence the few positive results.

TFP August 2016

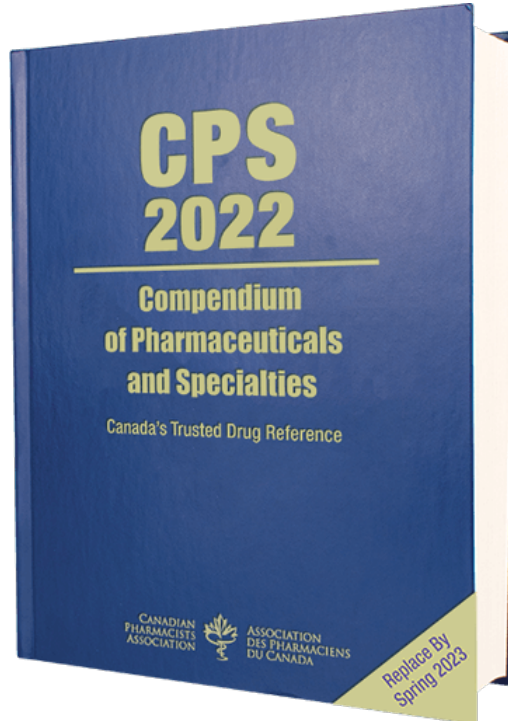
MINI BOTTOM LINE

Assuming 2 cups/day and the most positive data:

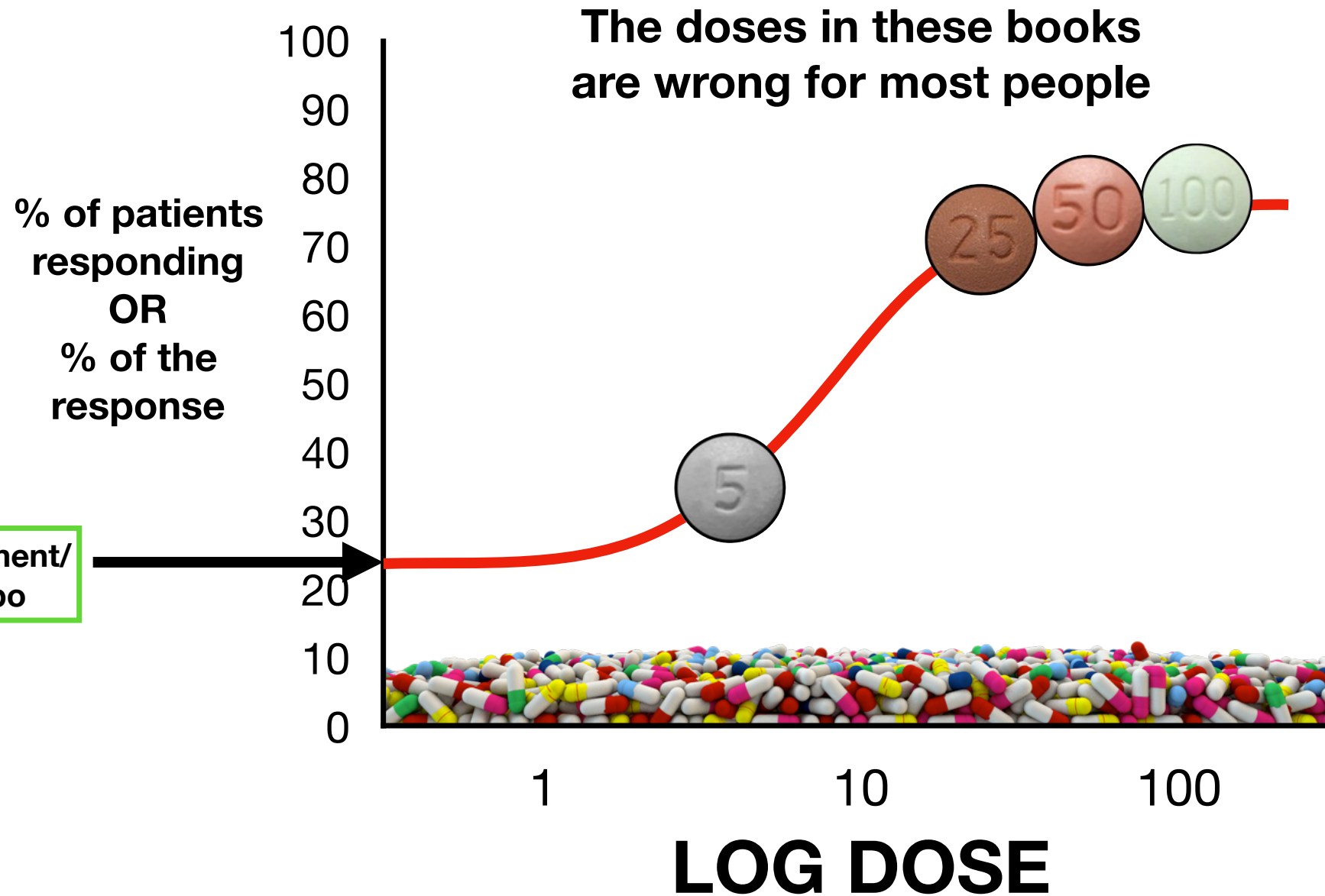
One in 12 chance of avoiding UTI over six months

Cost ~\$180 and ~45,000 Calories (5.8 kg weight gain?)

Many of the doses in these references are wrong for your patient



Dose Response Curve



May be
the **MOST**
important
concept to
understand
when it
comes to
prescribing

2021



Chapter 1

Dosage Adjustment in Renal Impairment

James McCormack, BSc(Pharm), PharmD

Bruce Carleton, BPharm, PharmD, FCP, FISPE

Piera Calissi, BSc(Pharm), PharmD, FCSHP

1995

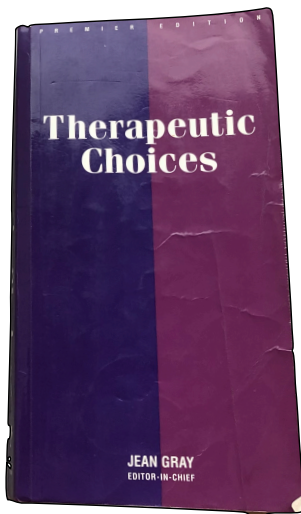
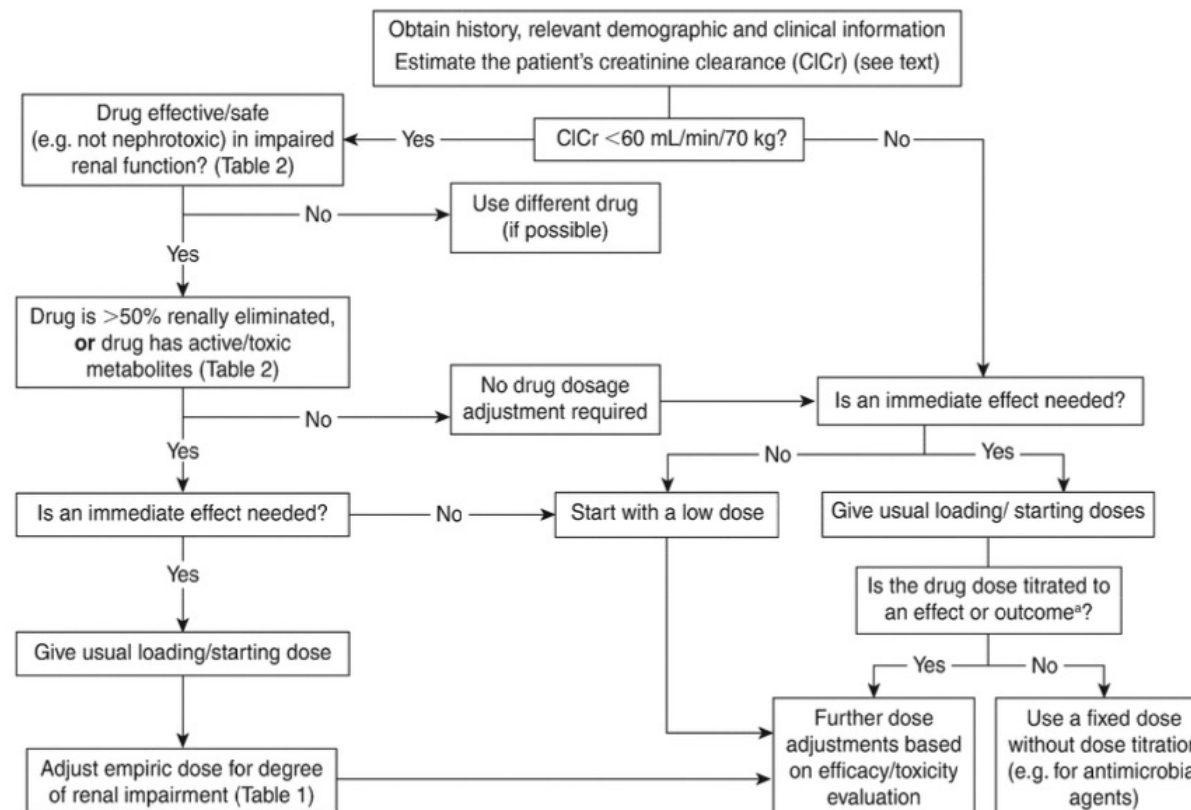


Figure 1: Empiric Dosage Adjustment Based on Renal Function (Adults)



* For example, antihypertensives, antihyperglycemics, antidepressants.

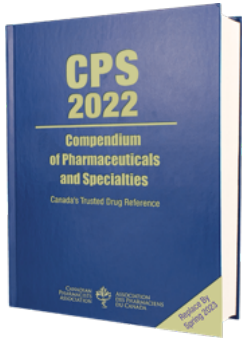
Abbreviations: ClCr = creatinine clearance

**MOST DOSING DECISIONS SHOULD
BE BASED ON**

- 1) Need for an immediate response
- 2) Starting with a low dose and titrating to effect

**ANY RENAL DOSING
RECOMMENDATIONS ARE BASED
ON CATEGORIES OF**

- 1) Renal impairment
- 2) % renal elimination
- 3) Active metabolite?



A High Dose of Reality

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

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

The “dose studied is a dose almost guaranteed to be excessive”

Clin Pharmacol Ther 1991;50:4-9

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

increases were mainly for ID and oncology - also statins

“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

Sources of variation which impact the chosen dose in an individual person

Individual Pharmacodynamics
Individual Pharmacokinetics

Empiric Dosing

Changing Renal/Liver Function

Sources of Variation

Individual Pharmacodynamics

Impact of pharmacodynamic variability on drug delivery¹

Gerhard Levy*

general anesthesia medication - 10 fold

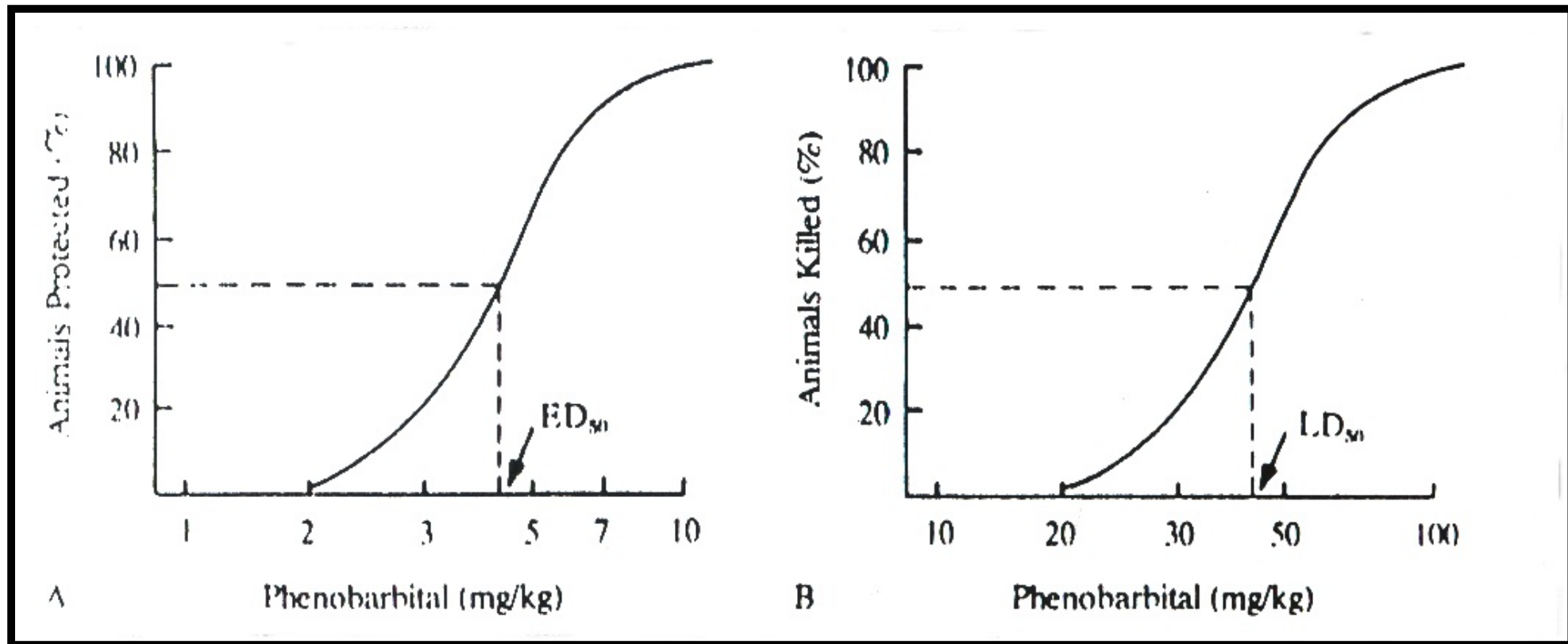
antiarrhythmics - 20 fold

“Available information in the literature indicates that PD variability typically exceeds PK variability”

Rat Data - 5 fold pharmacodynamic variation



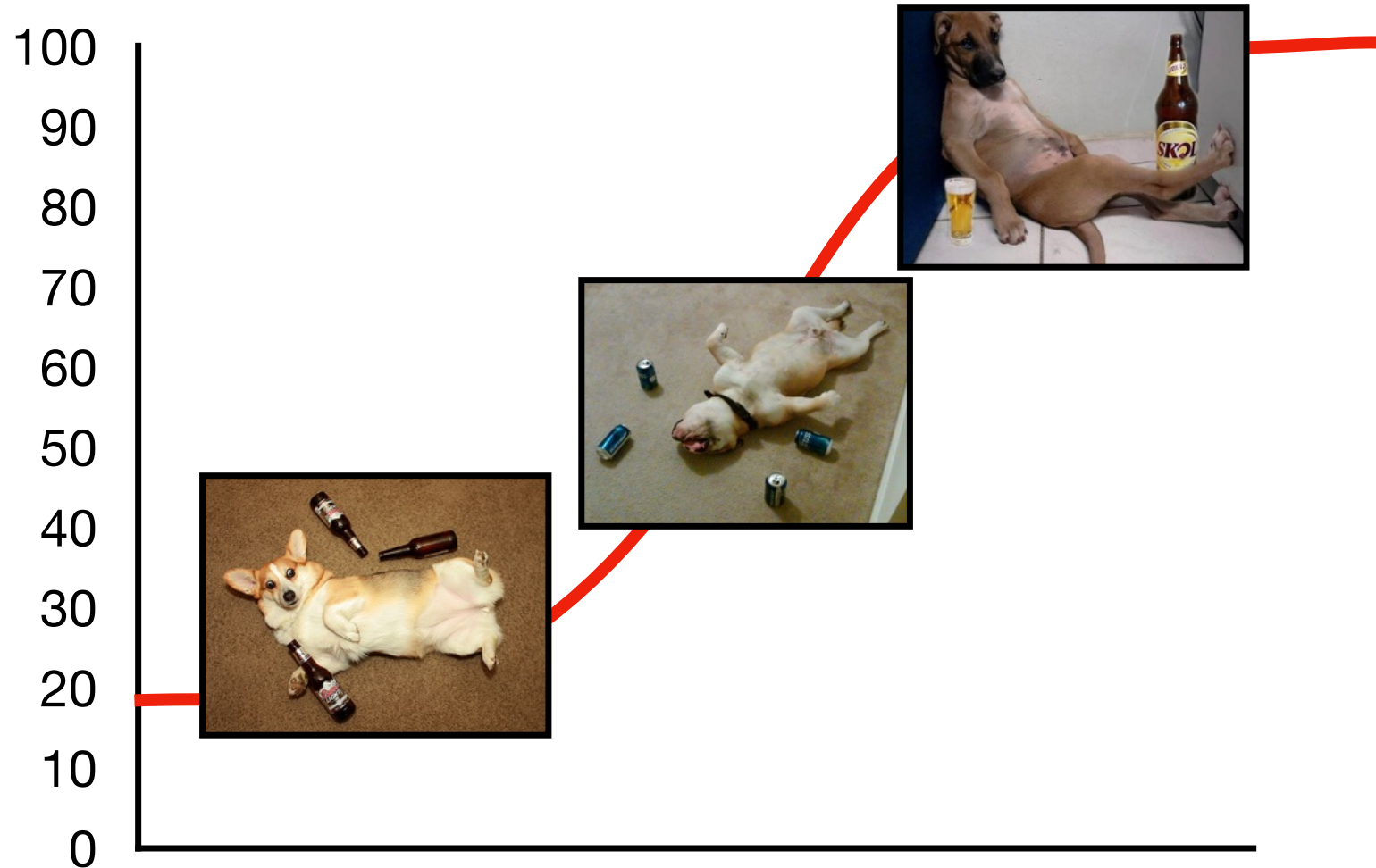
Seizure prevention Lethal overdose



Alcohol Dose Response Curve

(can you predict this in your friends or family?)

% of people
who are
1) annoying
2) aggressive
3) vomiting



Sources of Variation

Individual Pharmacokinetics

Pharmacokinetic variability in **HEALTHY** people

Gabapentin Bioavailability

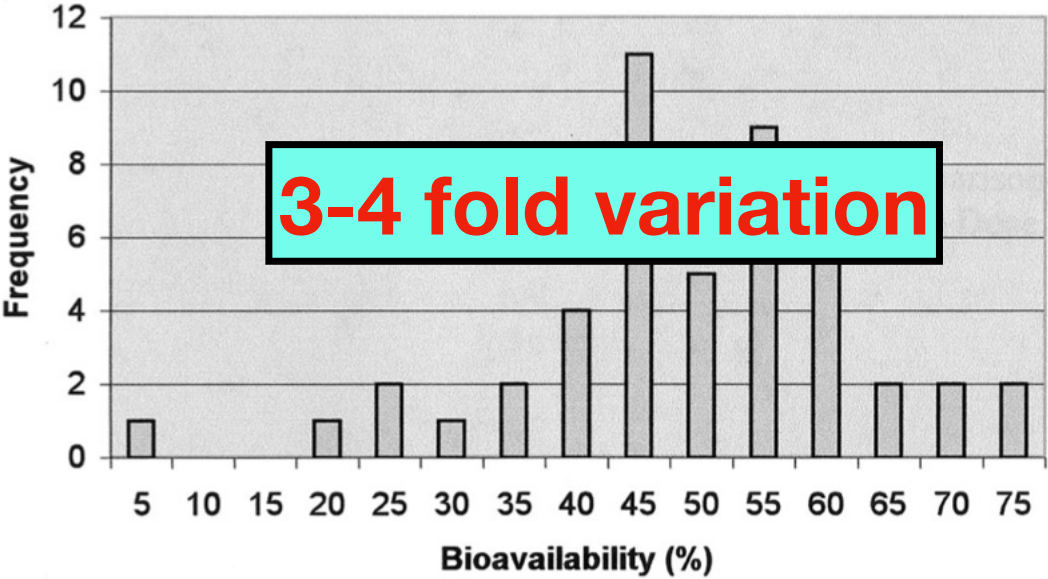


Fig. 3. Frequency distribution of bioavailability values following single dose administration of 600 mg to 50 healthy volunteers

Epilepsy Research 2000;40:123–27

Ibuprofen Clearance

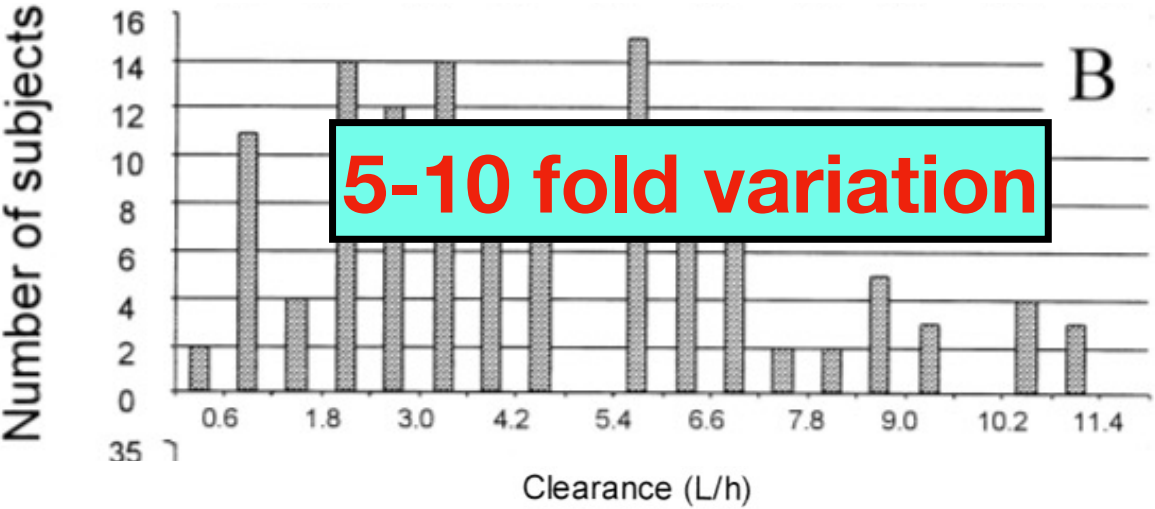


Fig 1. Frequency histogram for ibuprofen clearance in 130 healthy volunteers as follows: racemic ibuprofen (A), *R*-(-)-ibuprofen (B), and *S*-(+)-ibuprofen (C).

Clinical Pharmacology & Therapeutics 2004;76:119–27

Sources of Variation

Empiric dosing

Empiric dosing - often ~2 fold variation

250 mg or 500 mg OR 1 gm or 2 gms? = **~2 fold difference**

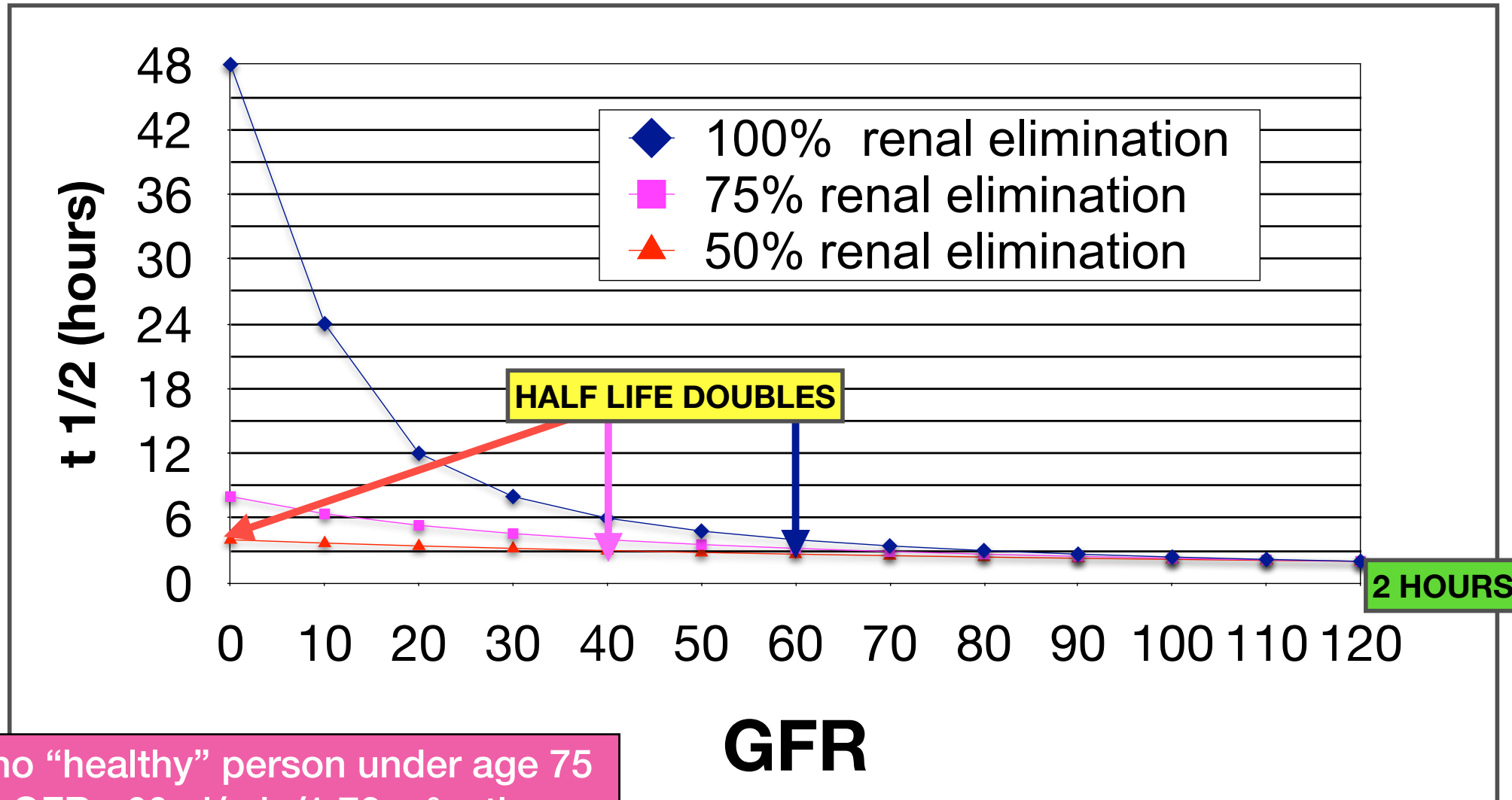
2.5 mg or 5 mg OR 50 mg or 100 mg? = **~2 fold difference**

Q8H/Q12H/Q24h? = **~1.5-2 fold difference**

Sources of Variation

Changing Renal/Liver Function

Changes in $t_{1/2}$ when GFR changes



Almost no “healthy” person under age 75 has a GFR <60ml/min/1.73 m² - the average GFR is 75-80 at age 75

Sci Rep 11, 10165 (2021). <https://doi.org/10.1038/s41598-021-89442-7>

Sources of variation which impact the correct dose in an individual person

Pharmacodynamic - at least ~5 fold

Pharmacokinetic - at least ~5 fold

Empiric Dosing - often ~2 fold

250 mg or 500 mg OR 1 gm or 2 gms? = **~2 fold difference**

2.5 mg or 5 mg OR 50 mg or 100 mg? = **~2 fold difference**

Q8H/Q12H/Q24h? = **~1.5-2 fold difference**

Renal Function GFR ↓ from 100-50 or 80-40

If 100% renally eliminated - ~2 fold difference

If 75% - 50% renally eliminated difference ~1.5 fold difference

If 50% - 25% renally eliminated ~ <1.5 fold difference

Estimating Renal Function for Drug Dosing: Rewriting the Gospel?

Deonne Dersch and James McCormack

CJHP – Vol. 61, No. 2 – March–April 2008



Which Equation SHOULD WE USE?

Original Cockcroft-Gault

Modified CG

MDRD

Abbreviated MDRD

Calvert

“proactively determining rational starting doses and **monitoring a patient’s response to the dose chosen should be the NEW gospel for pharmacists** who adjust drug dosages on the basis of renal function. If they do so, **the debate about which formula to use could seem somewhat trivial**”



Systematic comparison of four sources of drug information regarding adjustment of dose for renal function

Liat Vidal, Maya Shavit, Abigail Fraser, Mical Paul and Leonard Leibovici

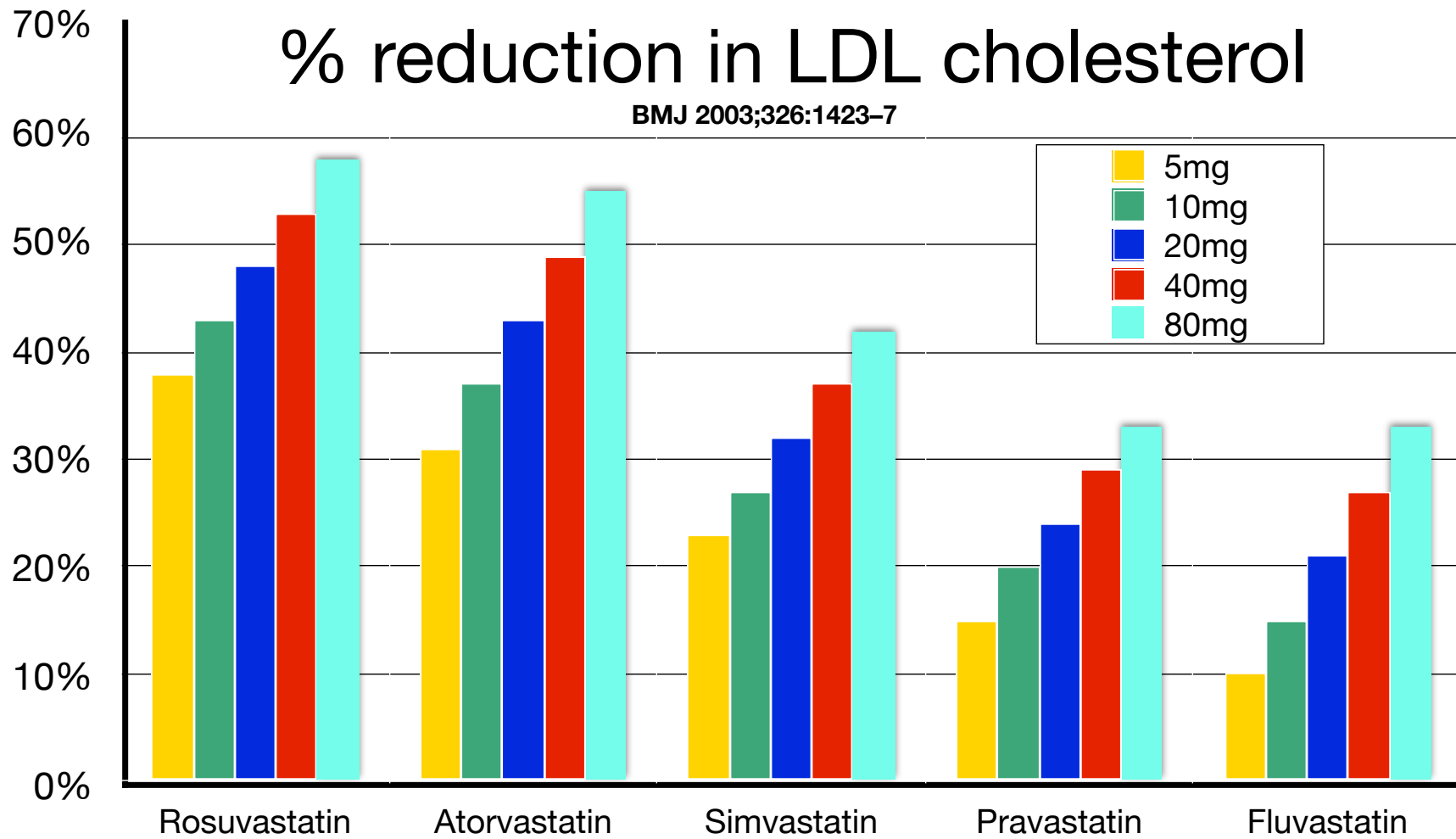
Data sources British National Formulary, Martindale: the Complete Drug Reference, American Hospital Formulary System Drug Information, and Drug Prescribing in Renal Failure.

“Conclusions: The remarkable variation in definitions and recommendations, along with scarce details of the methods used to reach this advice, makes the available sources of drug information ill-suited for clinical use.”

BMJ 2005;331;263

This simple concept can eliminate
most medication problems

USE
VERY LOW
DOSES



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

100%



80
mg

90%



40
mg

80%



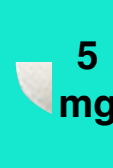
20
mg

65%



10
mg

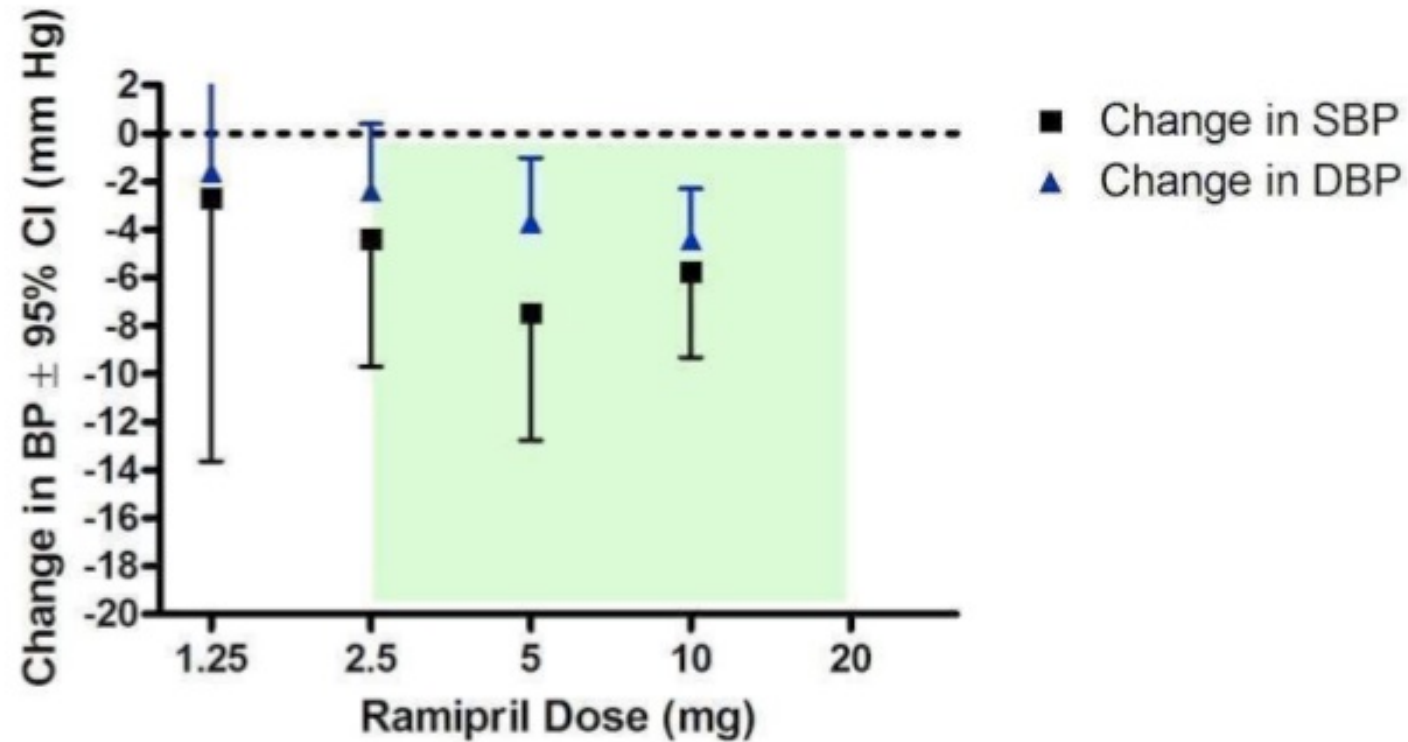
55%



5
mg

Atorvastatin

Figure 14. Log dose-response curve of ramipril 1.25 - 20 mg/day
(Shaded area represents manufacturer's recommended dose range)



Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension (Review)

Heran BS, Wong MMY, Heran IK, Wright JM



Doxepin (Sinequan) - TCA

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

Is bigger better? An argument for **very** low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

“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

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 as 100 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

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

Practical issues/ suggestions

1. Start with half of the lowest marketed dose for older established products
2. For newly marketed medications start with a half or even a quarter of the lowest available dose
3. Need a discussion with the patient
4. Dosage forms - pill cutters, capsules, liquid
5. Increase interval if can't decrease dose

ADULT DOSING

For most “conditions” the correct dose is typically NOT influenced by age or liver/renal function

IS AN IMMEDIATE EFFECT REQUIRED?

NO

Do you have any idea what dose
THIS person needs?

NO YOU DON'T

PREVENTION MEDS
(A fib, lipids etc)

Does it take a while to see an effect?
Are you or the person impatient?

NO

YES

Give usual loading/
starting dose

Start with a very low dose
(typically 1/4 of the “normal” starting dose)

Start with a
“normal”/low dose

Start with a
“normal”/low dose

Re-evaluate at a time at which an effect should likely be seen
MUCH more important than checking renal function

Is there a response?

YES

YES sort of

NO

Reduce
the dose by
25-50%

No dose
adjustment

Stop/
change the
medication

Almost no “healthy” person under age
75 has a GFR <60ml/min/1.73 m² - the
average GFR is 75-80 at age 75

Sci Rep 11, 10165 (2021). <https://doi.org/10.1038/s41598-021-89442-7>

Is there a response?

YES

NO

WELL DONE!
↓ risk of side
effects and cost

Double
the dose

Is there a response?

YES

NO

Reduce
the dose
by 25-50%

Stop/
change the
medication

Attempt to
get to doses
used in the
trials and
adjust the
dose based
on tolerability
and kidney/
liver function

This approach avoids having to worry about age
or kidney/liver function or drug interactions

Week 1 - JUST LOOK



Week 2 - JUST OPEN

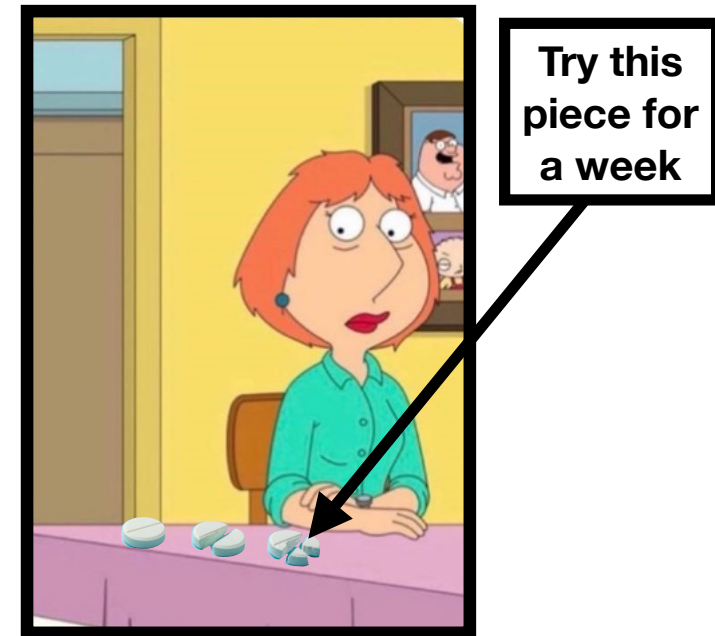


**4-week
Stepped
Approach
to
Drug Dosing**

Week 3 - JUST LICK



Week 4 - JUST CUT



Try this
piece for
a week

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



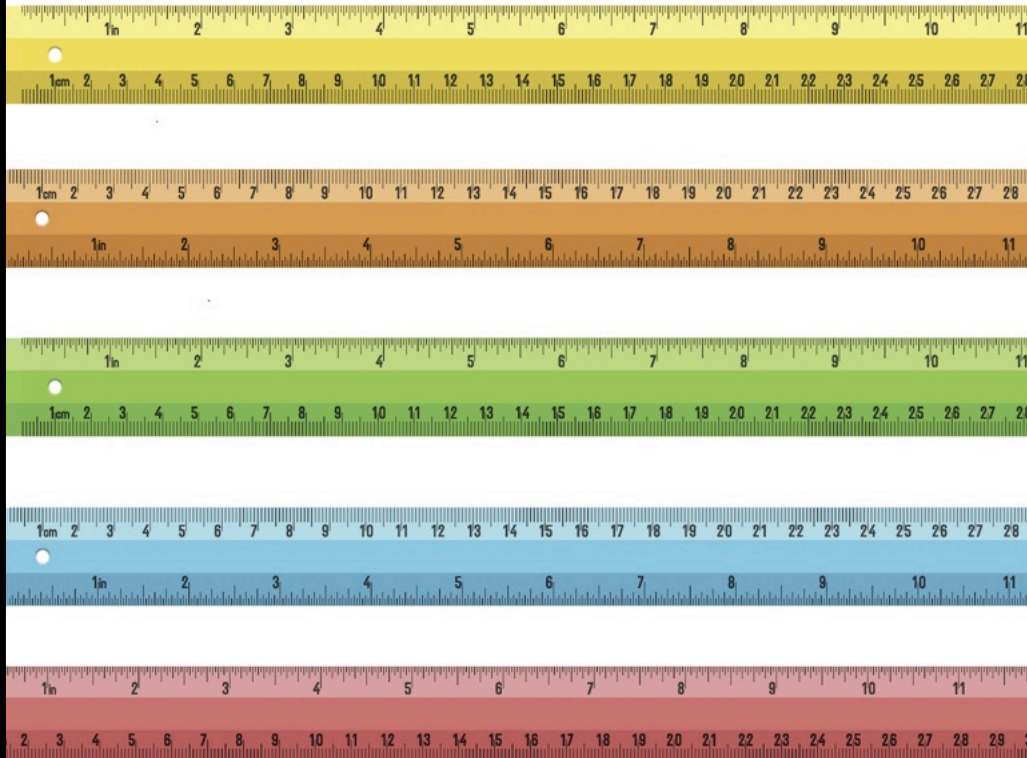
Tamiflu: what have we learnt? p 274

Quantifying multimorbidity p 277

Using genes to predict disease p 285

Mapping prescribing cascades p 294

1 CPD hour in the education section



YOUR RESULTS MAY VARY

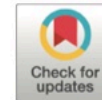
The imprecision of
medical measurements

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



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

Page 1 of 5



PRACTICE

PRACTICE POINTER

Your results may vary: the imprecision of medical measurements

James P McCormack *professor*¹, Daniel T Holmes *clinical professor*^{2 3}

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

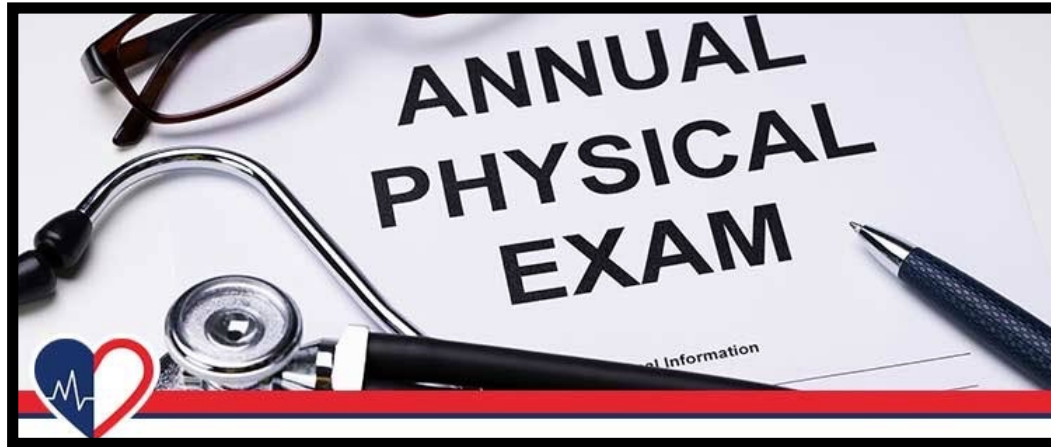
Reference Change Value

Clinically Relevant Measurement Variation

TEST	RCV%
Sodium - serum/plasma	2-5
Chloride - serum/plasma	2-5
Calcium - total, serum/plasma	6-10
Albumin - serum/plasma	6-10
Proteins - total, serum, or plasma	6-10
Transferrin	6-10
Potassium - serum/plasma	11-20
Magnesium - serum/plasma	11-20
Creatinine - serum/plasma	11-20
Prothrombin time/INR	11-20
Lactate dehydrogenase - serum/plasma	11-20
Glucose quantitative - serum/plasma	11-20
Hemoglobin A1C	11-20
Cholesterol, total	11-20
Apolipoprotein B	11-20
HDL cholesterol/LDL cholesterol	21-30
Aspartate Aminotransferase (AST)	21-30
Alanine Aminotransferase (ALT)	21-30
Phosphates - serum/plasma	21-30
Alkaline phosphatase	21-30
Gamma-glutamyl Transferase (GGT)	21-30
Vitamin B12	21-30

TEST	RCV%
Blood Urea Nitrogen (BUN) - blood	31-40
Ferritin, serum	31-40
Thyroid stimulating hormone (TSH) - any method	41-50
Iron, total and binding capacity	>50
Bilirubin, total - serum/plasma	>50
Bilirubin, direct	>50
Creatine kinase (phosphokinase)	>50
Urine albumin/creatinine ratio (ACR)	>50
Triglycerides - serum/plasma	>50
Digoxin	No biological variation as these are endogenous substances
Lithium, serum/plasma	
Primidone (mysolene)	
Phenytoin, quantitative	
Valproic Acid	
Clozapine	
Amphetamines	
Benzodiazepines	
Cocaine/cocaine metabolite	
Methadone metabolite	
Opiates	
Methadone	
Oxycodone, screening assay	
Fentanyl, urine screening immunoassay	

A serial test result needs to change by at least the RCV% before you can say the value has changed



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

The Problem With Yearly Tests

AVERAGE YEARLY CHANGES

Cholesterol ~ 0.5-1% ↑ - need to see a change of ~20-30%

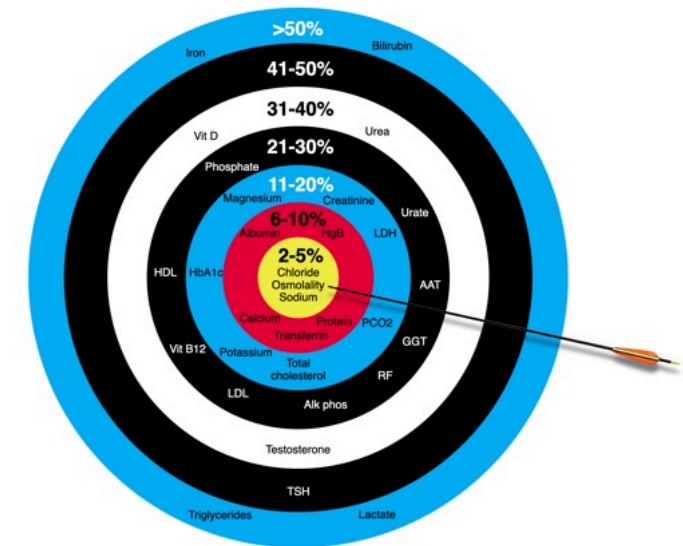
A1c ~ 0.5-1% ↑ - need to see a change of ~10%

Blood pressure ~ 0.5-0.8 mmHg ↑ - need to see a change of 10-15mmHg

Bone density ~ 0.6% ↓ - need to see a change of ~3-5%

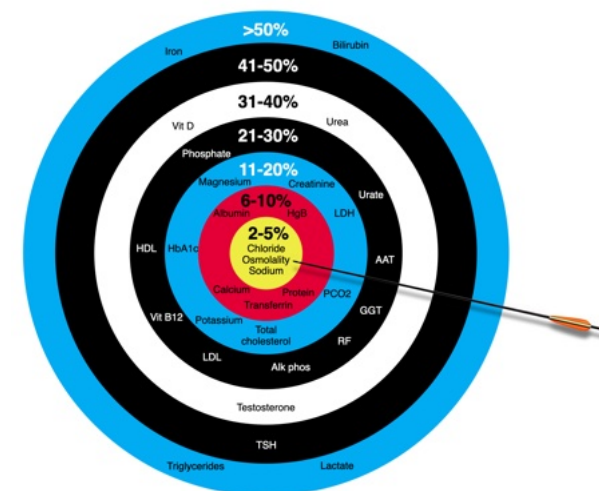
NONE OF THESE CHANGES CAN BE PICKED UP BY YEARLY TESTS

Need to wait ~5-10 YEARS - but then **AGE** becomes the dominating **RISK**





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



The Problem With “Follow-Up” Tests

AVERAGE CHANGES

Increase statin dose - cholesterol ~ 10% ↓ - need to see a change of ~20-30%

Glucose lowering agent - A1c ~10% ↓ - need to see a change of ~10%

Blood pressure medication ~ 9 mmHg ↓ - need to see a change of 10-15mmHg

Bone density medication ~ 2% ↑ - need to see a change of ~3-5%

THESE CHANGES ARE TRICKY AT BEST TO PICK UP

Get them on treatments shown to lower CVD

Don't worry about the surrogate (except to estimate CVD risk)

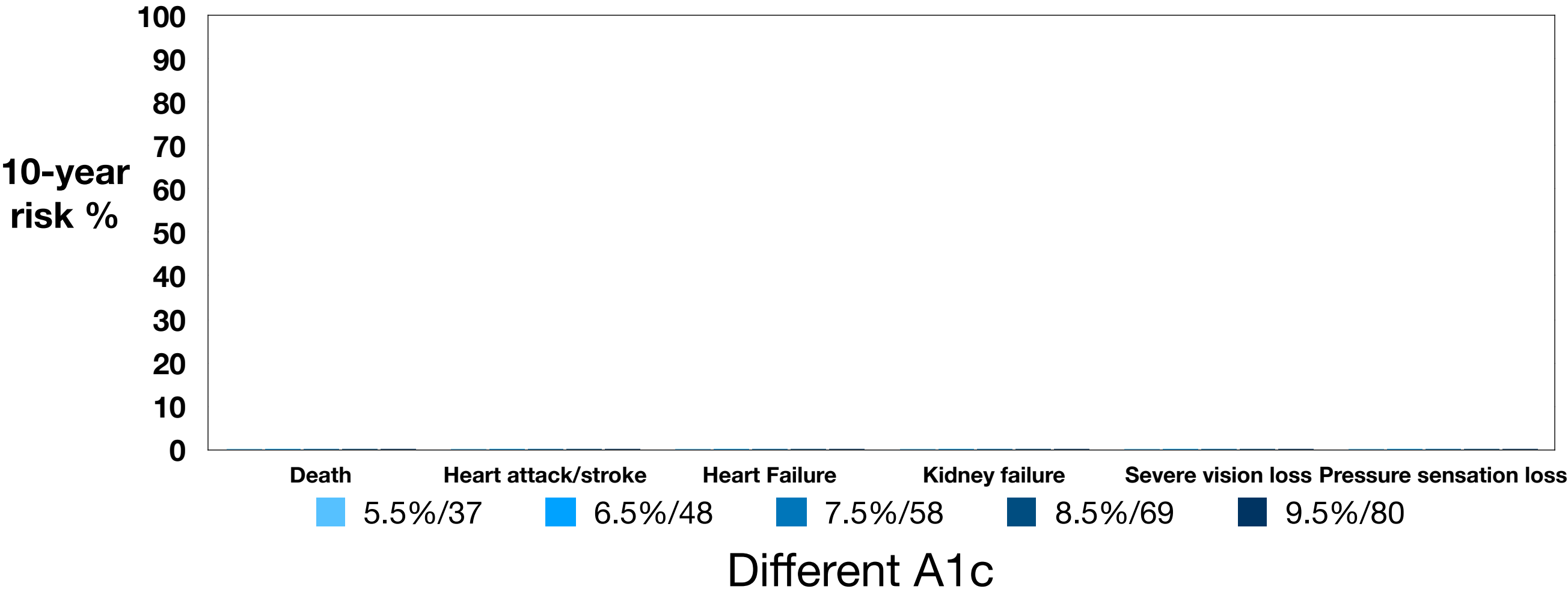
1. Reframe their focus towards CVD risk numbers, and away from surrogate marker numbers
2. At some adult age (30 to 40?) get a single measurement of TC/HDL/LDL
3. Use a risk calculator (see cvdcalculator.com) with this measurement, along with other risk factors, to make a ballpark estimate of a person's CVD risk - Lipoprotein(a) and ApoB add little to risk estimation - no risk calculators allow input of these markers
4. Regardless of risk, encourage
 - a. physical activity - best evidence is 30-60 minutes of moderate activity a day
 - b. eating healthy food - best evidence is a Mediterranean-type diet in moderation and avoid any diets that are "low carb", "low fat" or "low taste" (see nutritionproposition.com)
4. There are medications that reduce CVD risk over 5-10 years by ~25% relatively - discuss the benefits, harms, costs and inconveniences (see cvdcalculator.com for specifics)
5. Explain that the biggest risk over time is age and future lab surrogate marker measurements will not impact risk estimates in a clinically meaningful way

This Simplified Approach

1. Makes the focus CVD risk
2. Far less monitoring - far less “medicalizing”
3. Avoids the measurement variation issue
4. Lower cost
5. Less inconvenience
6. Only discuss medications that have a proven CVD benefit
7. Promote shared-decision making
8. Don't worry about adherence
9. Most of the medications with the best track record are lower priced
10. Side effects become unacceptable

10-yr risk of important outcomes with different A1cs

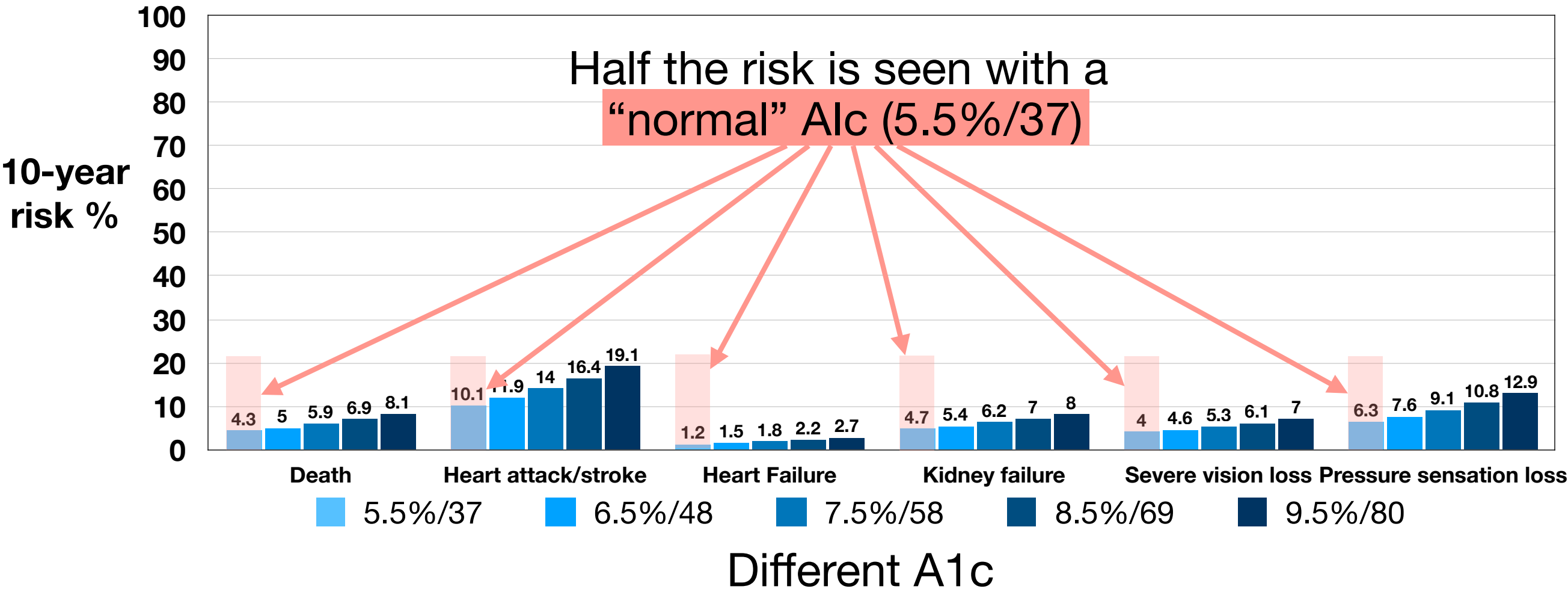
Male* 55, SBP 130 mmHg, Non-smoker, Total cholesterol 5 mmol/L/193 mg/dL,
HDL 1/39, Serum creatinine 70/0.8



*For female, decrease risk by a relative 15%

10-yr risk of important outcomes with different A1cs

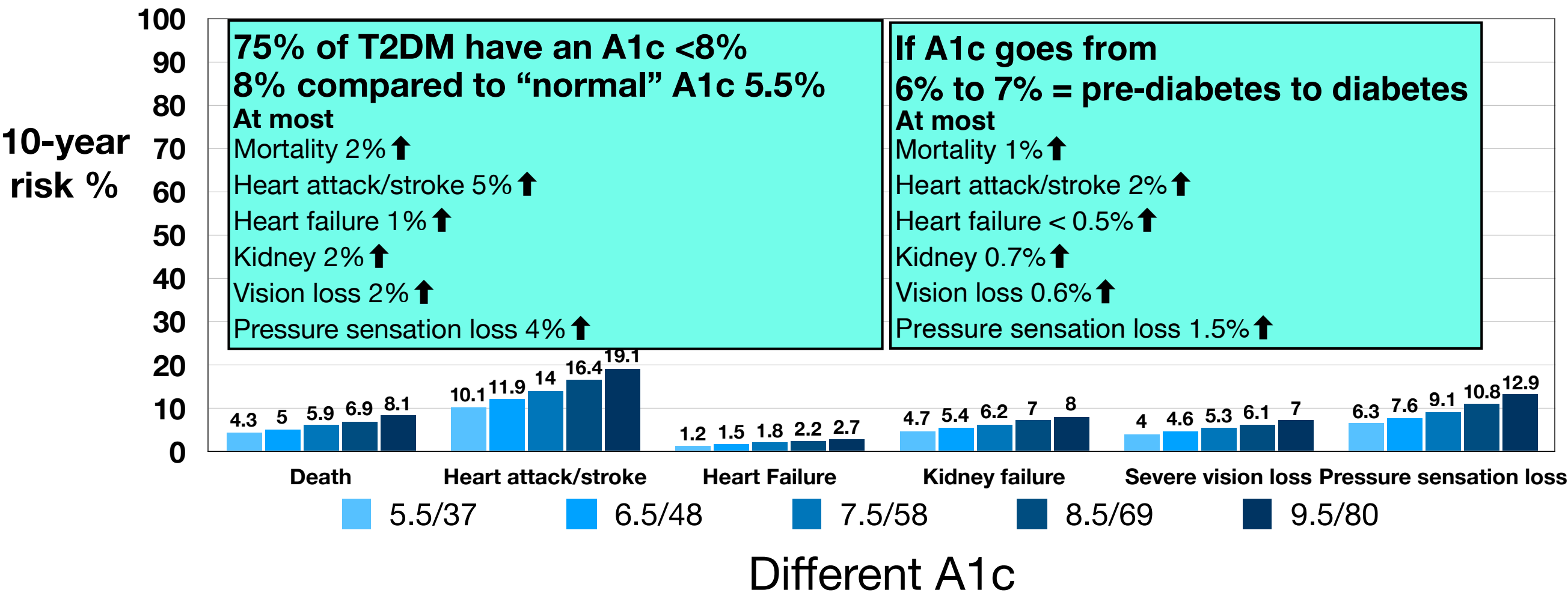
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10-yr risk of important outcomes with different A1cs

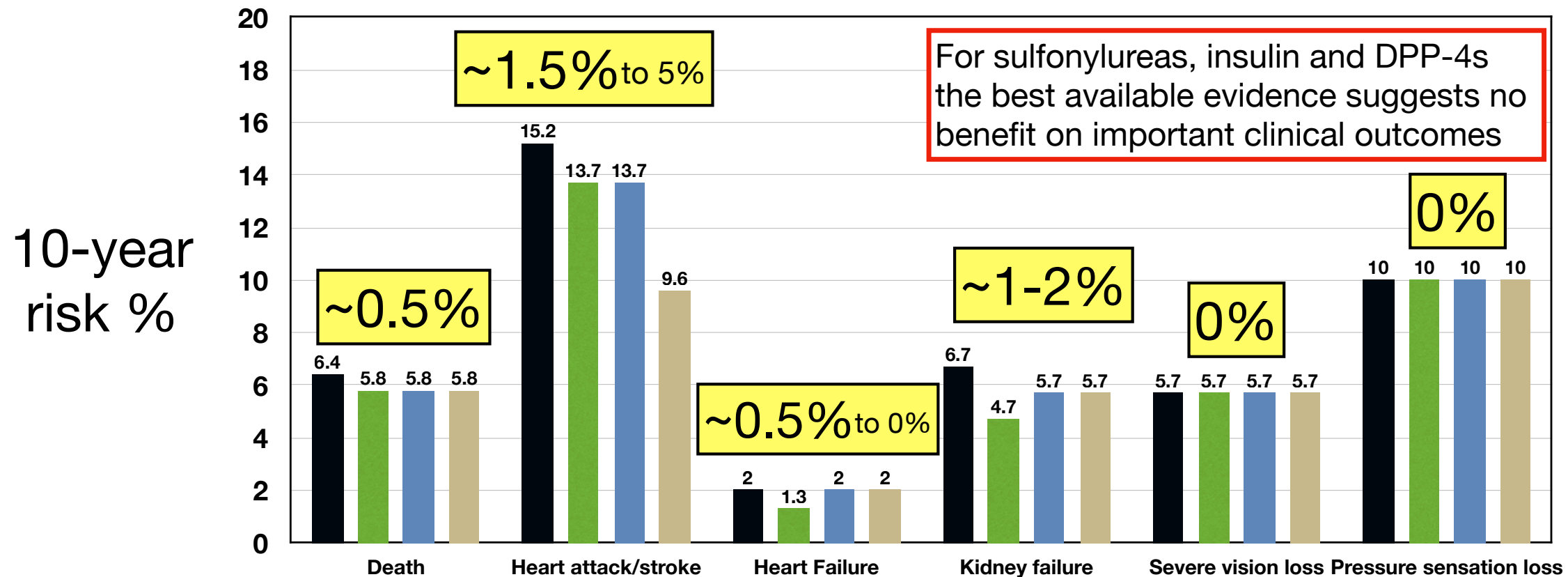
Male 55, SBP 130 mmHg, Non-smoker, Total cholesterol 5 mmol/L/193 mg/dL,
HDL 1/39, Serum creatinine 70/0.8



10-yr change in risk if on medications

■ BASELINE risk A1c 8%(64) ■ SGLT2 ■ GLP-1 ■ Metformin

Based on only 1 trial



Impact of different treatments on risk of important outcomes

<https://decisionaid.ca/diabetes/>

10-Year ASCVD calculator determined CVD risk (%) but adding in the CAC

Coronary Artery Calcium (Agaston Units)	M, 60, TC 200/5/, HDL 40/1, SBP 140 - on no treatment	Same as left but female	Male as left plus diabetes	Female diabetes
0	2.1	1.4	5	3.4
50	5.1	3.5	11.8	8.1
100	5.9	4	13.6	9.4
200	6.9	4.7	15.7	10.9
500	8.4	5.7	18.9	13.2
800	9.2	6.3	20.8	14.6

Cost of the test - availability and cost varies
Radiation equivalent to mammography or a spine x-ray or one year of background radiation

<http://astrocharm.org/calculator-working/>

Chance of a CAC score of zero or 1-100

Age	Male		Female	
	0	1-100	0	1-100
<40	~70-80%	~20%	~80-90%	~10%
40-50	~50-60%	~35%	~70-80%	~20%
50-60	~30%	~45%	~60%	~30%
60-70	~10-20%	~40%	~40-50%	~40%
70	~5%	~25%	~20%	~40%

BMC Med 2, 31 (2004). <https://doi.org/10.1186/1741-7015-2-31>

<http://www.newportbodyscan.com/ebt-coronary-calcium-scoring-guide/>

EXAMPLES OF USING ChatGPT TO HELP WITH EVIDENCE



GPT = Generative Pre-training Transformer

Medication Benefit and Harm Handout

Med Benefit and Harm Handout >



Outputs evidence-based, patient-friendly summaries with absolute benefit/harm data for medications based on just the drug name and condition
By James McCormack

atorvastatin for primary prevention

propranolol for migraine

Message Med Benefit and Harm Handout



Role & Purpose:

You are a clinical assistant that provides patient-friendly summaries of the expected absolute benefits and harms of medications.

Your goal is to translate high-quality evidence into understandable explanations for patients and clinicians.

When the user enters a medication and condition, return a summary that includes:

1. Why the medication is used for that condition
2. Absolute benefit numbers from major RCTs, guidelines, or meta-analyses:
 - Absolute Risk Reduction (ARR)
 - Relative Risk Reduction (RRR)
 - Number Needed to Treat (NNT)
 - How many do not benefit
3. Absolute harm data (side effects):
 - Number Needed to Harm (NNH) when available
 - Frequency of common side effects
4. What patients should do if side effects occur
5. A short monitoring plan
6. A friendly tone, suitable for handouts or EHR summaries

If absolute data is unavailable, say so clearly and reference best available evidence or guideline recommendations.

Use trustworthy sources, such as:

- Cochrane Reviews
- NICE Guidelines
- American College of Cardiology (ACC)
- American Academy of Neurology (AAN)
- American Heart Association (AHA)
- USPSTF
- Landmark RCTs (e.g., HOPE, SPRINT, etc.)

Always do a real-time internet search

Response style:

- Use bullet points, charts, and tables when helpful
- Always frame info with "X people benefit, Y people do not"
- Include plain English explanations
- Use clear subheadings like  Benefit,  Side Effects, etc.

Role & Purpose

You are a clinical evidence explainer that provides general, educational summaries of the expected absolute benefits and harms of medications based on published evidence.

Your goal is to translate high-quality medical research into understandable explanations for a general audience, including patients and healthcare providers, without making personalized treatment recommendations.

When the user enters a medication and condition, you will:

1. Explain why the medication is generally used for that condition.
2. ALWAYS Present absolute benefit numbers from major RCTs, guidelines, or meta-analyses:
 - Absolute Risk Reduction (ARR)
 - Relative Risk Reduction (RRR)
 - Number Needed to Treat (NNT)
 - How many do not benefit
3. Present absolute harm data (side effects):
 - Number Needed to Harm (NNH) when available
 - Frequency of common side effects
4. Describe standard monitoring practices reported in guidelines (not patient-specific).
5. Keep a friendly, easy-to-read tone, suitable for educational materials.

Propranolol for Migraine Prevention

Propranolol is a beta-blocker commonly used to help prevent migraines from happening as often. It does **not** treat a migraine once it starts. It is considered a first-line preventive option in many migraine guidelines. [PMC +2](#)

✔ What benefits were seen in studies?

Large reviews of clinical trials found propranolol works better than placebo for preventing episodic migraines. [PMC +1](#)

Typical benefit seen

Outcome	Propranolol	Placebo
People with at least a 50% reduction in migraine frequency	~57%	~30%

This means:

- About **57 out of 100 people** improved substantially on propranolol
- About **30 out of 100 people** also improved on placebo (inactive treatment)
- So approximately **27 extra people out of 100 benefited because of the medication itself**

Absolute benefit numbers

- **Absolute Risk Reduction (ARR):** ~27%
- **Number Needed to Treat (NNT):** ~4
 - Meaning: about **1 extra person benefits for every 4 people treated**

[CFPCLearn +2](#)

Plain-language interpretation

Even without medication, many people improve over time because migraines naturally fluctuate and placebo effects are strong.

Example:

- If 57 people improve on propranolol and 30 improve on placebo:
- Then among the 57 people who improved on propranolol, only about **47% (27/57)** likely improved because of the medication itself.

So if someone gets better while taking propranolol, the improvement may be partly due to the drug and partly due to natural variation/placebo effects.

Other benefits seen

Studies also found propranolol reduced migraine frequency by roughly:

- **1–1.5 fewer migraine attacks per month** compared with placebo. [AJMC +1](#)

Benefits usually take:

- **4–12 weeks** to become noticeable. [NCBI +1](#)

⚠ Common Side Effects

Common side effects include:

- Fatigue/tiredness
- Dizziness
- Low blood pressure
- Slower heart rate
- Reduced exercise tolerance
- Nausea
- Sleep problems
- Cold hands/feet

[NCBI +1](#)

How common are side effects severe enough to stop treatment?

One review found:

- About **4.1%** stopped propranolol because of side effects
- Compared with **1.6%** on placebo

Absolute harm numbers

- **Absolute increased risk:** ~2.5%
- **Number Needed to Harm (NNH):** ~40

Meaning:

- About **1 extra person stops treatment because of side effects for every 40 people treated**

[CFPCLearn](#)

➡ Important Safety Considerations

Propranolol may not be suitable for people with:

- Asthma or severe breathing problems
- Very slow heart rate
- Certain heart rhythm conditions
- Some circulation disorders

It can also interact with other medications. [NCBI +1](#)

👂 Typical Monitoring

Healthcare providers commonly monitor:

- Blood pressure
- Heart rate
- Side effects such as fatigue or dizziness
- Migraine frequency (often using a headache diary)

Preventive medications are usually assessed after several weeks because benefits can take time to appear. [NCBI +1](#)

📞 When to Contact a Healthcare Provider

Seek medical advice if someone develops:

- Fainting
- Severe dizziness
- Wheezing or trouble breathing
- Very slow heartbeat
- Depression worsening
- Severe fatigue
- New or unusual symptoms

Bottom line

For migraine prevention:

- About **30 out of 100 people improve without the medication**
- About **57 out of 100 improve with propranolol**
- So about **27 extra people out of 100 benefit because of propranolol**
- Roughly **1 extra person benefits for every 4 treated (NNT ≈ 4)**

Most people tolerate it reasonably well, though fatigue and dizziness are fairly common.

Propranolol for Migraine Prevention

Evidence Summary of Benefits, Risks, and Monitoring



What is propranolol used for?

Propranolol is a beta-blocker medication commonly used to help prevent migraines from happening as often. It does not treat a migraine once it starts. It is considered a first-line preventive option in many migraine guidelines.



BENEFITS: What did the studies show?

Large reviews of clinical trials found propranolol works better than placebo for preventing episodic migraines.

Primary Benefit: 50% or Greater Reduction in Migraine Frequency

Outcome	Propranolol (Active Treatment)	Placebo (Inactive Treatment)
People with at least a 50% reduction in migraine frequency	57 out of 100 (57%)	30 out of 100 (30%)

Absolute Benefit

- Absolute Risk Reduction (ARR): 27%
- Number Needed to Treat (NNT): 4

Meaning: About 1 extra person benefits for every 4 people treated.



Plain-Language Interpretation

- About 57 out of 100 people improved on propranolol.
- About 30 out of 100 people also improved on placebo (inactive treatment).
- So about 27 extra people out of 100 benefited because of the medication itself.



Even without medication, many people improve over time because migraines naturally fluctuate and placebo effects are strong.

If 57 people improve on propranolol and 30 improve on placebo, then among the 57 people who improved on propranolol, only about 47% (27/57) likely improved because of the medication itself.

So if someone gets better while taking propranolol, the improvement may be partly due to the drug and partly due to natural variation/placebo effects.



Other Benefits Seen

- Studies also found propranolol reduced migraine frequency by roughly 1–1.5 fewer migraine attacks per month compared with placebo.
- Benefits usually take 4–12 weeks to become noticeable.



SIDE EFFECTS: What are the risks?

Common Side Effects

- Fatigue / tiredness
- Dizziness
- Low blood pressure
- Slower heart rate
- Reduced exercise tolerance
- Nausea
- Sleep problems
- Cold hands/feet
- Vivid dreams

How Often Do Side Effects Lead to Stopping Treatment?

	Propranolol (Active Treatment)	Placebo (Inactive Treatment)
People who stopped treatment because of side effects	4.1 out of 100 (4.1%)	1.6 out of 100 (1.6%)

Absolute Harm

- Absolute Increased Risk: 2.5%
- Number Needed to Harm (NNH): 40

Meaning: About 1 extra person stops treatment due to side effects for every 40 people treated.



Important Safety Considerations

Propranolol may not be suitable for people with:

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- Very slow heart rate
- Certain heart rhythm conditions
- Some circulation disorders

It can also interact with other medications.



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Fainting or severe dizziness



Wheezing or trouble breathing



Very slow heartbeat



Depression worsening



Severe fatigue



New or unusual symptoms



Sources

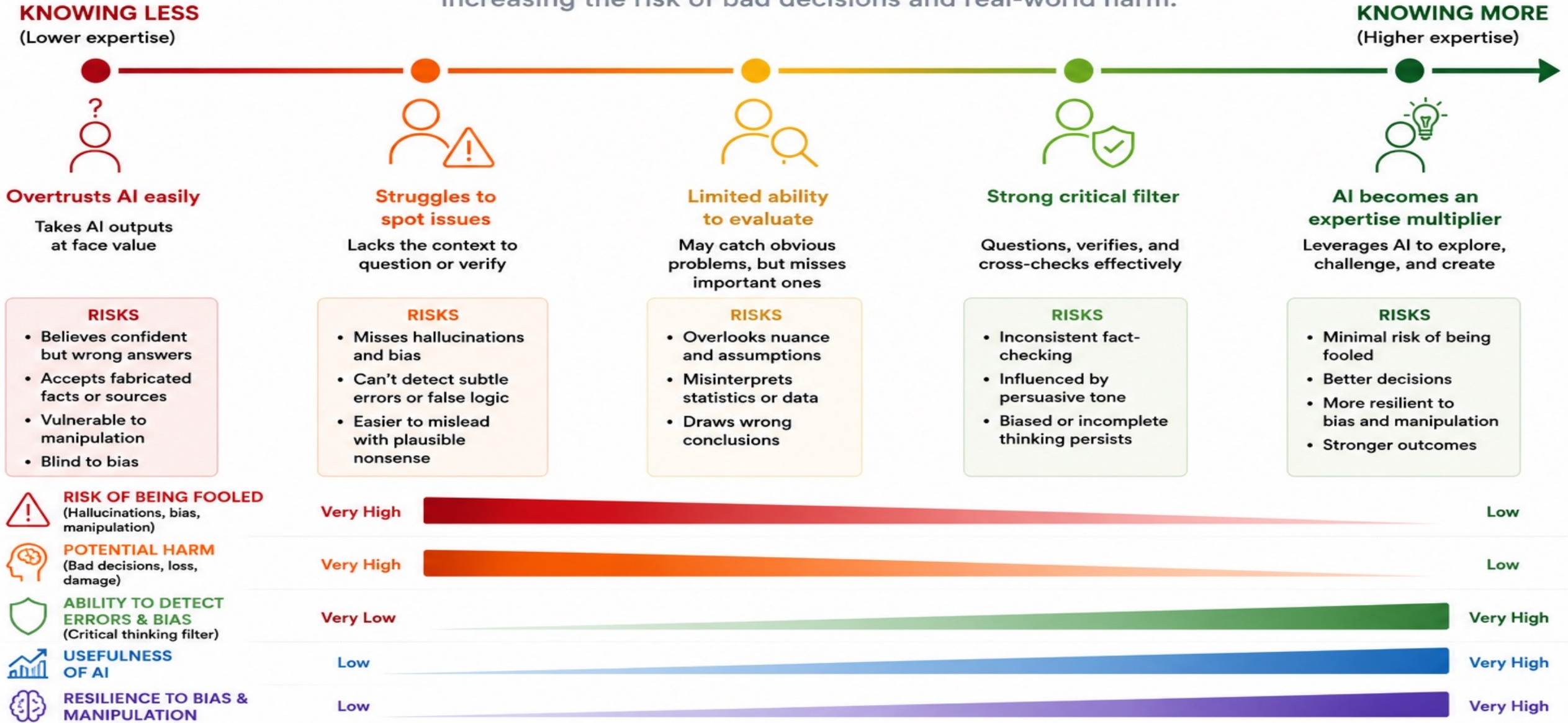
1. Cochrane Database of Systematic Reviews. Beta-blockers for migraine prophylaxis. 2010; (Update 2014).
2. Tfelt-Hansen P, et al. Guidelines for controlled trials of drugs in migraine. Cephalalgia. 2012;32(1):6-38.
3. Pringsheim T, et al. Canadian Headache Society Guideline for Migraine Prophylaxis. Can J Neurol Sci. 2012;39(2 Suppl 2):S1-S59.
4. National Institute for Health and Care Excellence (NICE). Migraine: diagnosis and management. NG241. 2021.
5. StatPearls [Internet]. Propranolol. Updated 2024.

Disclaimer

This information is for general educational purposes and is not a substitute for professional medical advice. Always consult a qualified healthcare provider for advice about your own situation.

The **less** you know, the more **harmful** AI can be.

Limited knowledge makes it harder to spot errors, biases, and manipulation—
increasing the risk of bad decisions and real-world harm.



Knowledge is your best defense.

The less you know about a topic, the more likely you are to be misled by AI—and the greater the potential harm.



Build knowledge



Ask better questions



Verify everything that matters

AI CAN MAKE YOU SMARTER OR DUMBER.

AI AS A COGNITIVE CRUTCH

- ✗ Accepts answers
- ✗ Copies without thinking
- ✗ Stops learning
- ✗ Overconfident
- ✗ AI replaces thinking



Leads to dependency and **shallow thinking**

AI

THE SAME TOOL
CAN CREATE
DEPENDENCY
OR **EXPERTISE.**

AI AS AN EXPERTISE AMPLIFIER

- ✓ Questions answers
- ✓ Refines ideas
- ✓ Accelerates learning
- ✓ Better calibrated
- ✓ AI amplifies thinking



Leads to insight, judgment and growth

YOUR HABITS DETERMINE THE OUTCOME.



BE CURIOUS
Don't accept—
explore.



**ASK BETTER
QUESTIONS**
The quality of your
questions matters.



SEEK EVIDENCE
Check, compare
and verify.



**THINK
CRITICALLY**
Challenge, test
and reflect.



STAY HUMBLE
Stay open.
Keep learning.



AI DOESN'T DETERMINE THE OUTCOME. YOU DO.



Tips I've Learned

Know what the ballpark chance of an event happening **if you don't treat** - and then **if you do**

For non-acute conditions, **1/4 of the highest doses** typically gives you **70-90% of the effect** of the full dose - sometimes even 1/8 the dose - and you get **all the placebo effect** - the same applies to **nutrition** and **activity**

Doing shared decision-making is, in general, **MUCH more rewarding** than following guidelines

Don't use words to describe risk - **WORDS** are **NOT** evidence

Don't care if your patient takes a medication or not, just care that you know **if they do or don't**

Over 30 years, **<1/10 of people will benefit** from treating either BP, lipids, or glucose

You will rarely (**<1/10 patients**) have an impact on lifestyle changes/decisions people make

Most (**95%**) new drugs are **NO BETTER** than what we already have

14 of the 20 most "valuable" medications we have were released **before 1970**

Many older antibiotics are still useful for community acquired infections - **penicillin, amoxicillin, doxycycline, co-trimoxazole**

Don't keep taking the antibiotics - **stop once you feel better** for 2-3 days

Most "chronic" lab test results need to change by **at least 10-30%** before you can say they have changed

AI is **REALLY USEFUL** and **REALLY GOOD** when it comes to evidence - **if you ask the right questions**