Evidence and So Much More






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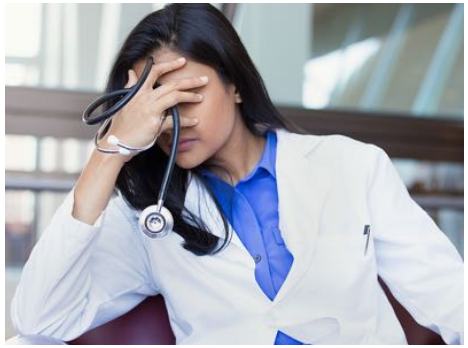
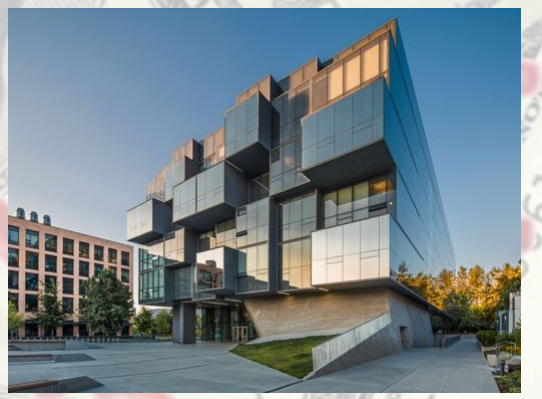




- Entire salary comes through the UBC Faculty of Pharmaceutical Sciences
  - also some legal/educational work

- I have received no honorarium or research money from the drug industry in the last 25 or so years

- iOS apps (iPad/iPhone) KidneyCalc and MyStudies - mystudies.org

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

Our Agenda

Background and guiding principles

Evidence on new diabetes drugs

Lab reports and how to interpret them

Guidelines and how to use them

Medical cannabinoids

MY BELIEF

All Health Care Providers should have their practice underpinned by the best available evidence

Evidence-Based Practice (EBP)

The Bullshit Asymmetry

The amount of energy needed to refute bullshit is an order of magnitude bigger than to produce it.

IT'S NOT ABOUT GUIDELINES

140/90
< 6.5%
< 2.0

GUIDELINES RARELY CONSIDER
PATIENT PREFERENCES

IT'S NOT CHECKBOX MEDICINE

PEOPLE DON'T FIT INTO BOXES

IT'S NOT SOMETHING "NEW"

DOING THE RIGHT THING
IS NOT A NEW IDEA

IT'S NOT ABOUT SAVING MONEY

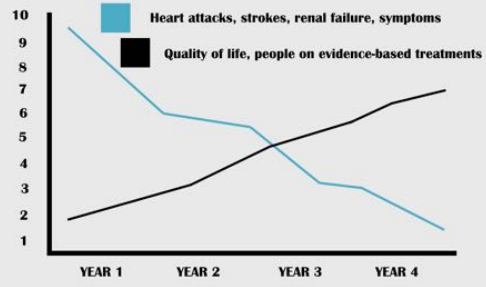
RATIONING
IS NOT THE MOTIVE

IT'S NOT ABOUT RCTs

RCTs ARE USEFUL
BUT THEY ONLY
HELP
INFORM DECISIONS

p<0.05 ≠ GOOD p>0.05 ≠ BAD

IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES



IT'S NOT ABOUT IGNORING BASIC SCIENCE

WE NEED TO UNDERSTAND
HOW IT WORKS

IT'S NOT ABOUT ZERO COMPETING INTERESTS

RESEARCH
COSTS MONEY
SOMEBODY HAS TO PAY FOR IT

WE NEED TO UNDERSTAND
BIAS IS
EVERYWHERE

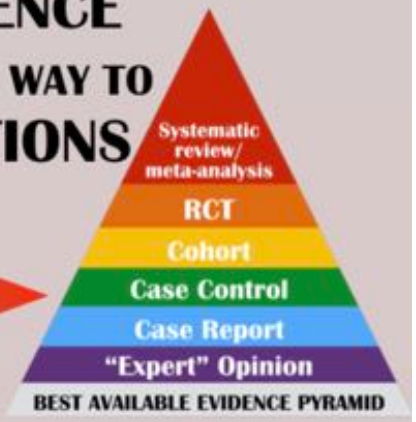
WHAT IT IS

IT'S A WAY OF THINKING

EVIDENCE-BASED PRACTICE

BEST AVAILABLE EVIDENCE
USED IN A HIERARCHICAL WAY TO ANSWER CLINICAL QUESTIONS

Patient
Intervention
Comparator
Outcome

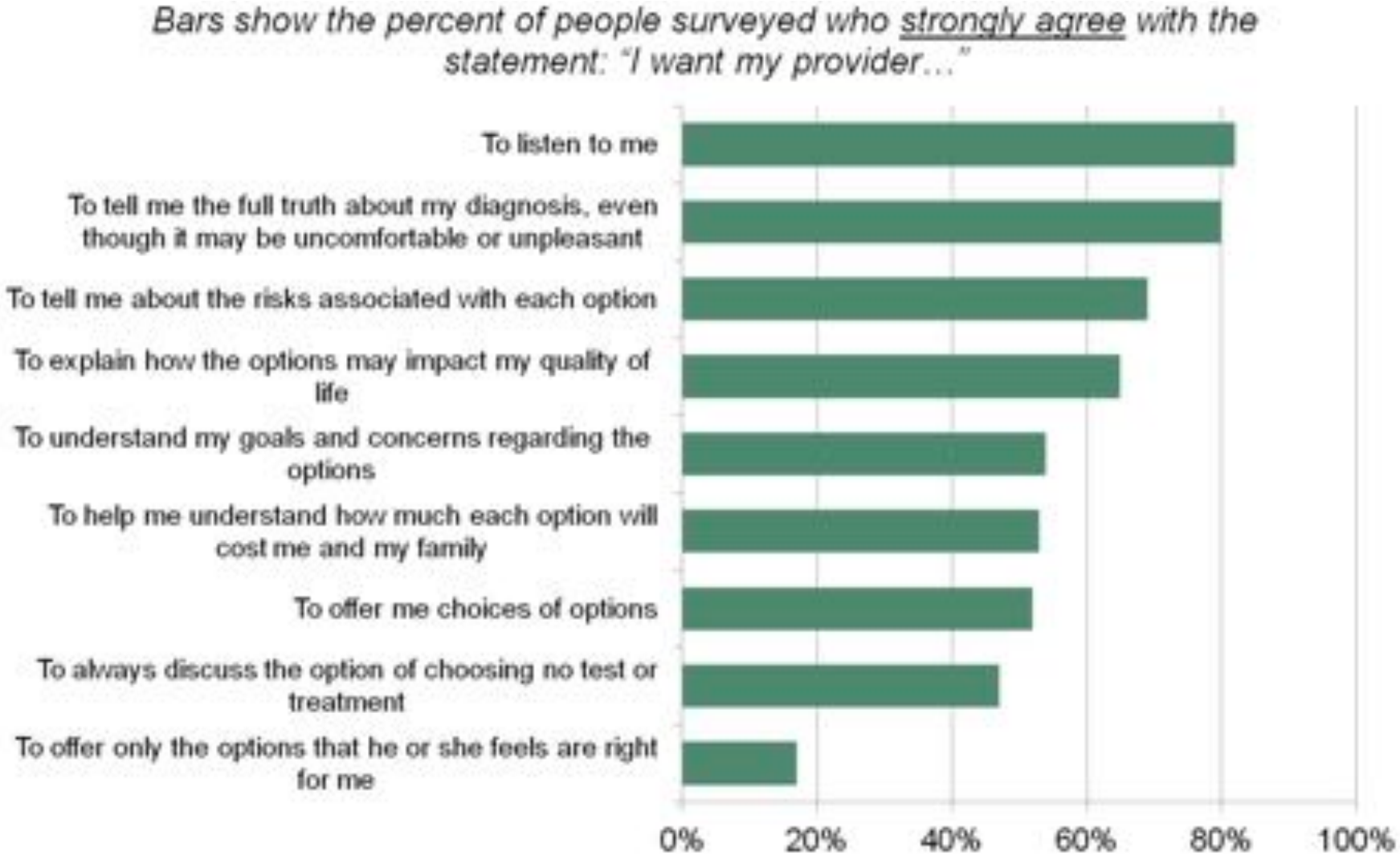


USING CLINICAL EXPERTISE

Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful

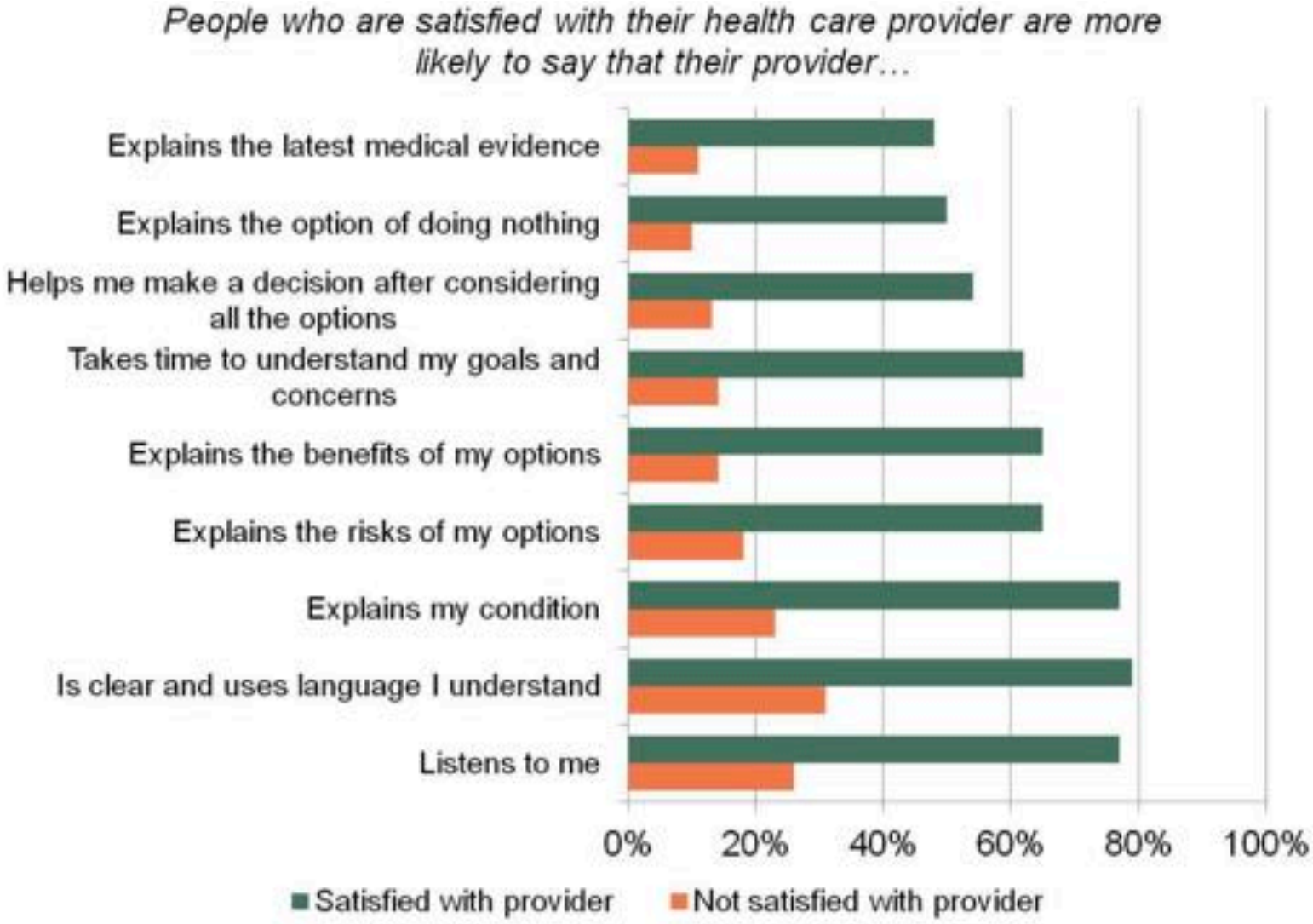
INFORMING PATIENTS & ELICITING & INTEGRATING PREFERENCES

People want involvement in evidence and decisions



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

Satisfaction is linked to shared decisions



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“Most patients cannot recall a time when their care provider discussed scientific evidence as the basis for better care”

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PATIENT REVOLUTION

=

Clinicians and patients working in partnership

KNOWING THE MAGNITUDE OF THE BENEFIT OF TREATMENT

KNOWING the POTENTIAL HARMS - SIDE EFFECTS, COST AND INCONVENIENCE

REALIZING HEALTH DECISIONS ARE YOUR DECISIONS

Evidence Issues

Much of research is not going to be “right”

One study likely proves nothing - need reproducibility

“The evidence for nonreproducibility in basic and preclinical biomedical research is compelling” John Ioannidis

Cohort trials don't prove causation

Research does go unpublished - but large studies do get reported

“Science can be used to inform clinical decisions, but cannot definitively inform value judgements, because the significance of potential benefits and harms of a therapy are in the eye of the beholder and will differ across individuals.”

Circulation. 2017;135:180–195. DOI: 10.1161/CIRCULATIONAHA.116.022622

Some clinical adages?

Ask - how do you feel about being involved in making decisions about your treatment?

It's OK if we say I don’t know, let’s look into it, it’s your decision.

You and your patient’s perception are not necessarily “right” and likely not the same

Patients' Expectations of the Benefits and Harms of Treatments, Screening, and Tests
A Systematic Review

Tammy C. Hoffmann, PhD; Chris Del Mar, MD, FRACGP

BENEFIT - 88% of study authors concluded that participants **overestimated benefits**

HARM - 67% **underestimated harm**

JAMA Intern Med 2015;175:274-286

Key steps to communicating evidence

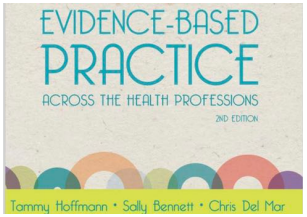
Understand the patient's (and family members') experiences and expectations.

Build partnerships.

Discuss the evidence, including a balanced discussion about uncertainties.

Present recommendations.

Check for understanding and agreement.



Risky Relative Adjectives

HOW

low is low

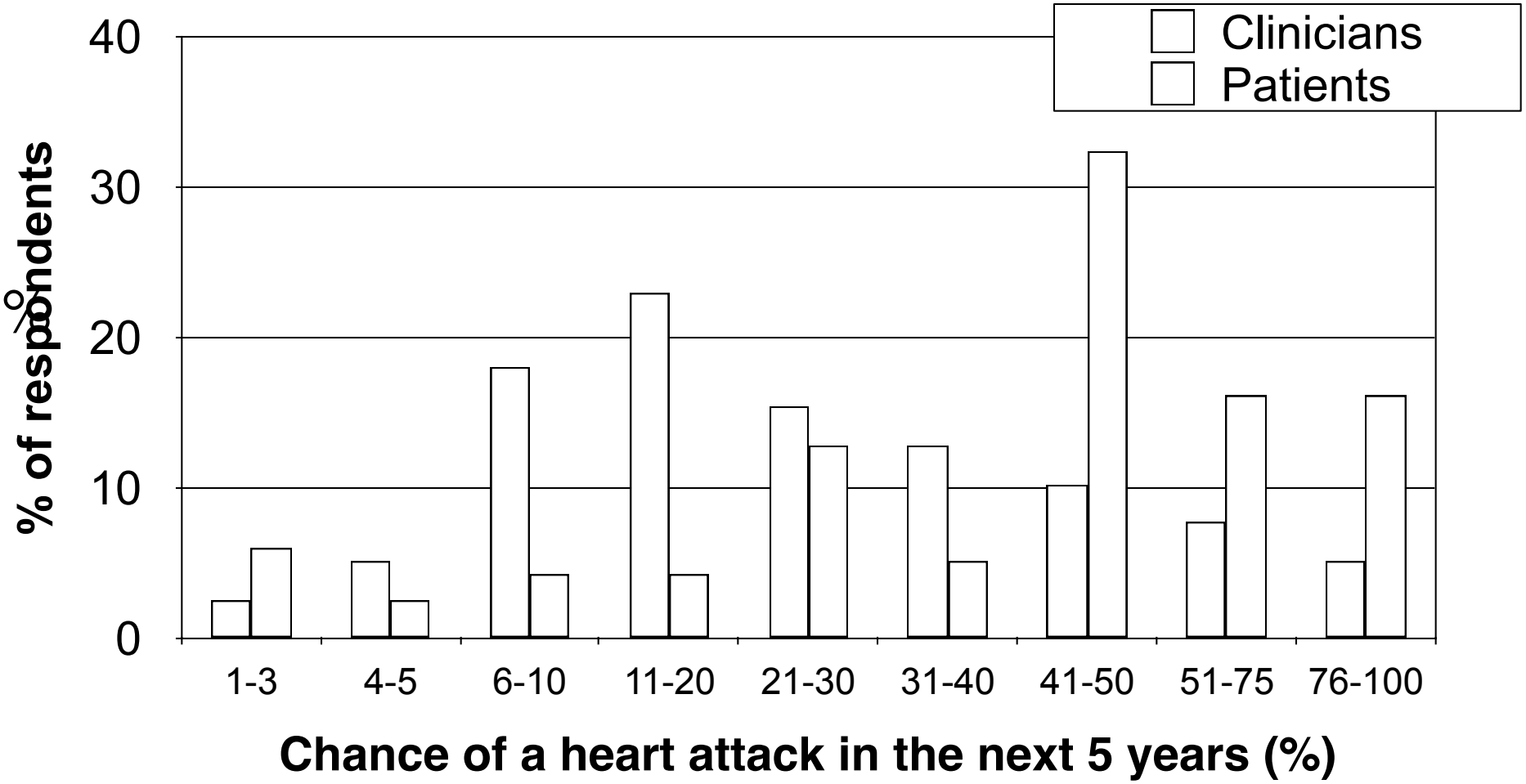
moderate is moderate

high is high

Misleading Terminology

“Significant”
“Use with caution”
“Use with extreme caution”
“Monitor closely”
“High risk”
“Very high risk”
“Really !@#$% high risk”

What is "High Risk"



Beware of “qualitative quantification”

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

Values are mean (SD).

Lancet 2002;359:853–54

Evidence-based risk communication

"There is likely no single best method of communicating probabilities to patients but rather several good options with some better suited to certain risk scenarios."

Ann Intern Med 2014;161:270-80

Recommended approaches

Need a time frame, main endpoints, ask what they know

GENERAL SUGGESTIONS - these are “relative”
use percentages (5%) or natural frequencies (5 out of 100) - BOTH?
use absolute terms
add bar graphs or icon arrays
use incremental risk format with icon arrays in the same array

- avoid use of NNTs

if use relative risks add baseline risks

Ann Intern Med 2014;161:270-80

Many courts (UK, US, CA)

"The reasonable-patient standard … requires physicians and other health care practitioners to disclose all relevant information about the risks, benefits, and alternatives of a proposed treatment that an **OBJECTIVE PATIENT** would find material in making an intelligent decision as to whether to agree to the proposed procedure"

JAMA 2016;315:2063-4

It's all about figuring out

The Chance

WITH NO

TREATMENT

VS

The Chance

WITH

TREATMENT

Ballpark risk estimate
Epidemiological data/cohort data
- Framingham, QRISK, FRAX, CHA2DS2-VASc

Ballpark benefit estimate
RCT data
use the absolute benefit if people are similar to those in the studies or,
use the relative benefit and apply it to the baseline risk

Approaches differ depending on outcome

Every patient is an experiment - dose and effect

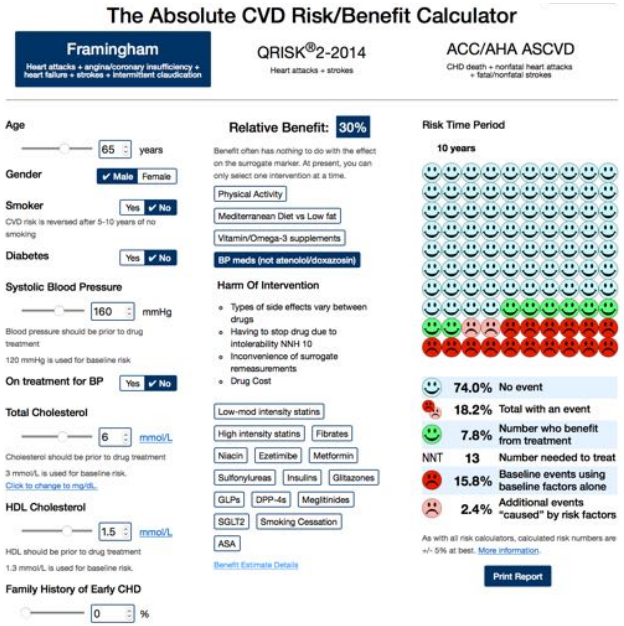
Prevention - one will never know if it worked

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

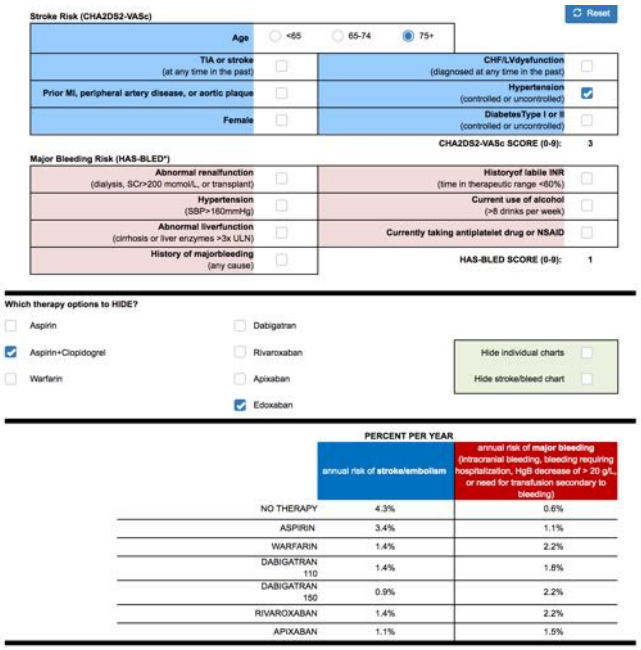
Diagnosis - pre- and post-test probabilities

Expectations

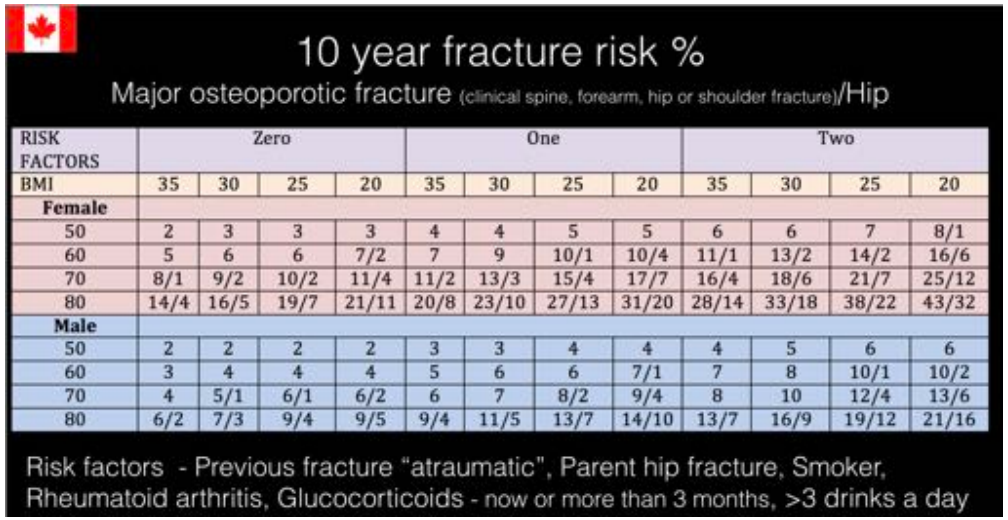
Prevention



cvdcalculator.com



http://www.sparctool.com



10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero				One				Two			
BMI	35	30	25	20	35	30	25	20	35	30	25	20
Female												
50	2	3	3	3	4	4	5	5	6	6	7	8/1
60	5	6	6	7/2	7	9	10/1	10/4	11/1	13/2	14/2	16/6
70	8/1	9/2	10/2	11/4	11/2	13/3	15/4	17/7	16/4	18/6	21/7	25/12
80	14/4	16/5	19/7	21/11	20/8	23/10	27/13	31/20	28/14	33/18	38/22	43/32
Male												
50	2	2	2	2	3	3	4	4	4	5	6	6
60	3	4	4	4	5	6	6	7/1	7	8	10/1	10/2
70	4	5/1	6/1	6/2	6	7	8/2	9/4	8	10	12/4	13/6
80	6/2	7/3	9/4	9/5	9/4	11/5	13/7	14/10	13/7	16/9	19/12	21/16

Risk factors - Previous fracture "atraumatic", Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

Calculate ballpark 10-yr risk of /fractures - BP, chol, diabetes, BMI. BMD

Make estimate of benefit based on the best available evidence

Gives a list of adverse effects to discuss

INITIAL COST

Baseline risk

25% OFF SALE

Relative benefit

NOW COSTS

New risk

YOU SAVE

Absolute benefit

Misguided beliefs

Patients believe CVD “prevention” drugs produce a 70% absolute benefit over 5 years when at most only ~ 20-30% benefit is possible over a lifetime

Clin Med 2002;2:527-33

Risk of future illness
CVD risk/benefit

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

Challenging treatment thresholds

James McCormack PharmD, Aseem Malhotra MRCP and David Newman MD

Assume a person's lifetime risk of CVD is that of a male with two CVD risk factors - roughly 50% (NEJM 2012;366:321-9)

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

Risk goes from 50% ➡ 20%

30% of individuals BENEFIT

70% DO NOT despite a LIFETIME of treatment

Prescriber September 2015

Symptoms

You primarily need to know IF it works

Safety, cost and convenience

Older medications first - safety

Head-to-head studies are uncommon

Doses in the CPS are “wrong”

N-of-1 studies

Let the patient tell you

Symptom NNTs

General anesthesia/local anesthesia - NNT ~1

PPIS, sildenafil - heartburn/“successful” intercourse NNT ~2

NSAIDs, opioids - pain NNT ~3-5

Steroids - sore throat - NNT ~3, Bell’s palsy - NNT ~10

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~7

Antidepressants - severe depression - NNT ~10

Ipratropium - asthma attack - NNT ~11

Cholinesterase inhibitors - ADAS-Cog >4 - NNT ~10

Sleeping pills - improvement in sleep quality - NNT ~13

But you need to know what goes on in the placebo group

	If person “responds”, what is the % chance it was the medication	
Response in the placebo group	If Benefit 10% - NNT 10	If Benefit 20% - NNT 5
0%	~100%	~100%
20%	~33%	~50%
40%	~20%	~33%

The Placebo Group Effect

not the placebo effect and these are ballpark numbers

~0% - general anesthesia

~5% - psychosis

~10% - sildenafil, OCD

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

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

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

~40% - panic disorders

When a medication has “worked”, if you were a betting person you would bet that it probably wasn't because the medication worked.

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

The Lancet
Published online
February 21, 2018

provides as good and balanced a synopsis as we will likely ever have of the results from the 522 trials of 21 antidepressants in 116,477 participants

82% of the included studies - moderate to high risk of bias

78% of studies were funded by drug companies, and many studies failed to report funding at all

the authors report “funding by industry was not associated with substantial differences in terms of response or dropout rates”

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patient population was limited to adults with moderate to severe depression and an average Hamilton depression score of 26.3

primary endpoint - 50% change in Hamilton depression score at 8 weeks

also looked at remission rates at 8 weeks

“all-cause discontinuation” - combines both efficacy and tolerability

looked at drop-outs due to adverse events but didn’t report data on specific adverse effects such as sedation, dry mouth, sexual dysfunction, and weight gain

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all antidepressants “worked”

50% change - OR ~ 1.65 for all antidepressants combined

remission - OR ~ 1.55

they found “few differences between antidepressants when all data were considered”

confidence intervals around individual effect sizes were wide

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30-40% of placebo group participants report improvement or remission in trials of antidepressants

an OR of ~ 1.6 means about 10-12% more people in the treatment group would benefit compared with the placebo group

absolute response rates placebo ~40% and treatment ~50%

10 patients with moderate to severe depression take an antidepressant for two months

five (50%) will report being “better” but in four of them the response will not be because of the medication

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all-cause discontinuation rates were not statistically different from placebo for most antidepressants in this meta-analysis.

active treatment increased the risk of dropping out because of side effect - OR of ~ 2.3

placebo typically 3-5%

~ 5% more people in treatment groups dropped out because of side effects

What the antidepressant MA doesn't answer

their effect on milder forms of depression

their effects beyond eight weeks of treatment

the harms associated with specific agents and their magnitude

the effectiveness of antidepressants outside the confines of randomised trials

the long-term adverse effects of antidepressants

the likelihood of withdrawal symptoms when treatment stops

comparative benefits and harms of antidepressants relative to non-drug treatments such as cognitive behavioural therapy

which antidepressant should be tried first

which one is likely to work best for an individual patient

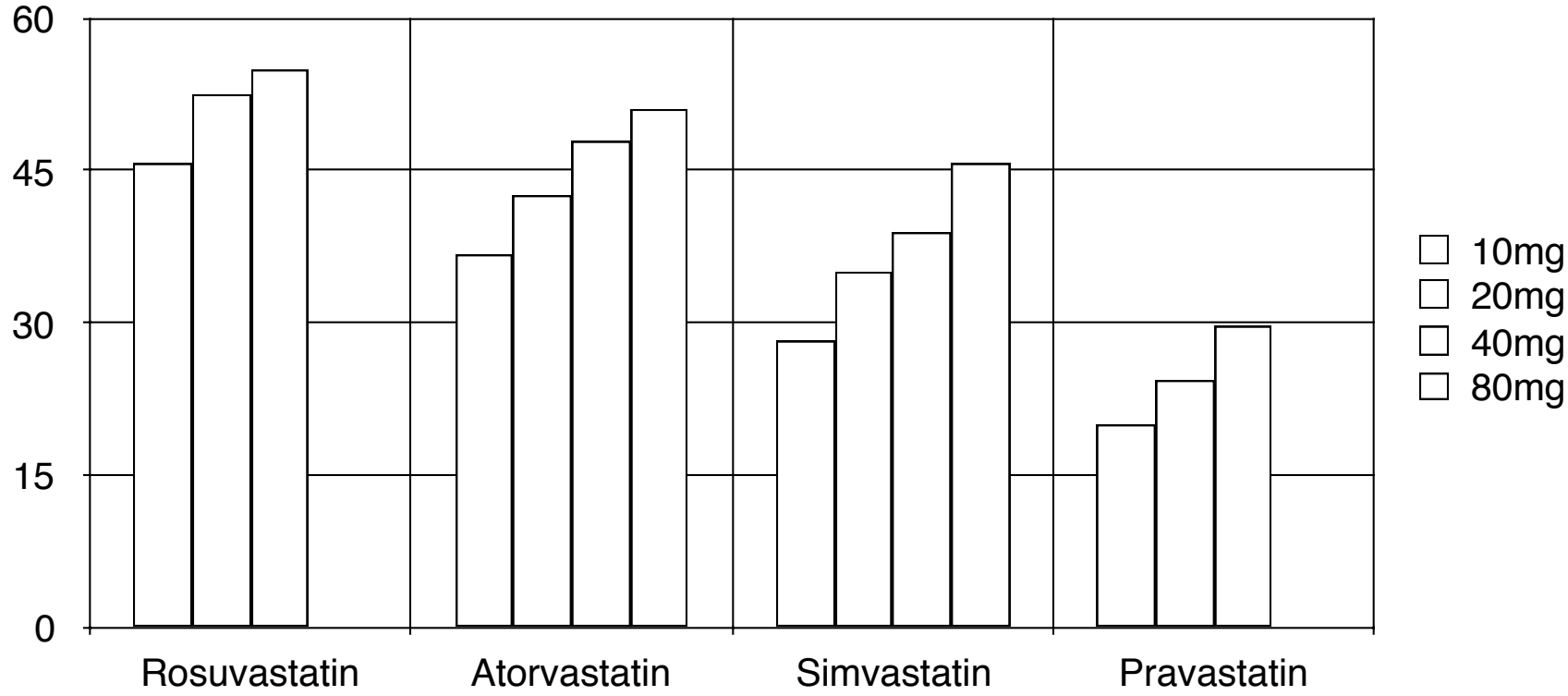
Low doses

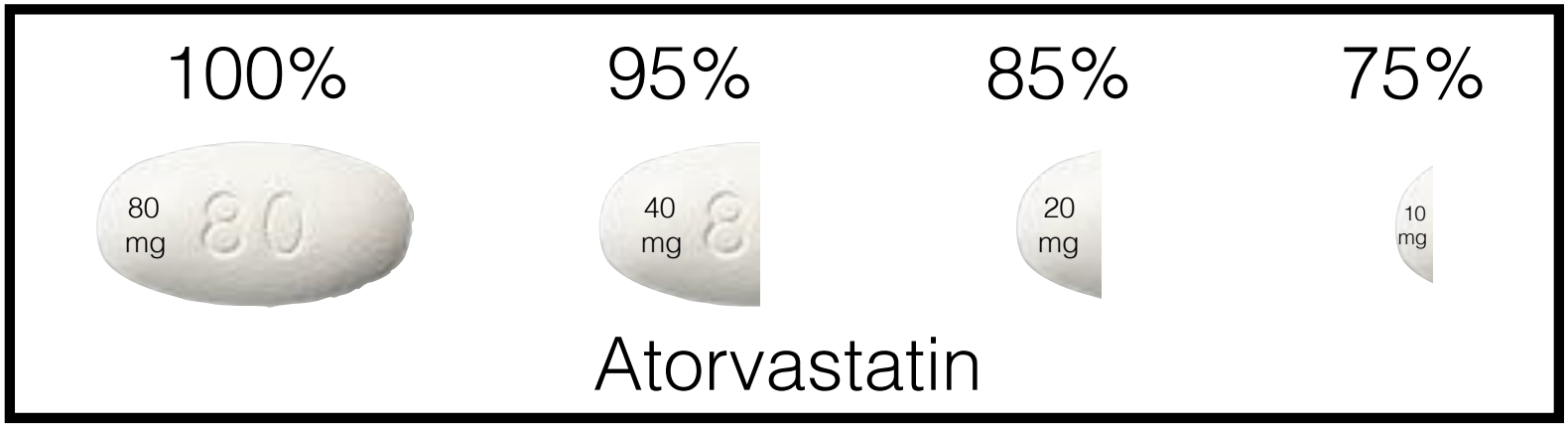
A sample of RCT Evidence

6.25 mg hydrochlorothiazide	first marketed at 50 to 200 mg daily
6.25 mg captopril	25 mg PO TID is still a commonly recommended initial starting dose for hypertension
25 mg sildenafil (Viagra)	effective dose for erectile dysfunction
25 mg sumatriptan (Imitrex)	works as well as100 mg
5 mg daily fluoxetine (Prozac)	similar effects to those seen at 20 mg and 40 mg daily
0.25 mg ezetimibe (Ezetrol)	1/40th of the recommended initial starting dose provides 50% of the LDL lowering effect
15 mg elemental iron daily	as effective for anemia in the elderly as 50 mg and 150 mg with a lower incidence of side effects
150 mg daily bupropion (Zyban) 0.5 mg BID varenicline (Champix)	produces the same rate of smoking cessation at one year as 300 mg daily (1.0 mg BID)
10 mg atorvastatin	produces 2/3 of the effect on cholesterol as that seen with an 80 mg (8-fold increase) dose
200 mg ibuprofen (Motrin)	as effective as 400 mg for migraine headache
25 mg ranitidine (Zantac)	as effective as 125 mg for heartburn relief
1.8 mg colchicine	as effective as 4.8mg for acute gout with less adverse events

DOSE increases do not lead to proportional EFFECT increases

% reduction in LDL cholesterol



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