

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.

EVIDENCE-BASED PRACTICE

WHAT IT ISN'T

IT'S NOT ABOUT GUIDELINES

140/90
 $< 6.5\%$
 < 2.0
 GUIDELINES RARELY CONSIDER PATIENT PREFERENCES

IT'S NOT ABOUT RCTs

ONLY ARE USEFUL BUT THEY ONLY HELP IMPROVE OUTCOMES

IT'S NOT CHECKBOX MEDICINE

PEOPLE DON'T FIT INTO BOXES



IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES



IT'S NOT SOMETHING "NEW"



DOING THE RIGHT THING IS NOT A NEW IDEA

IT'S NOT ABOUT HANDING BASIC SCIENCE

WE NEED TO UNDERSTAND HOW IT WORKS

IT'S NOT ABOUT ZERO COMPETING INTERESTS

RESEARCH COSTS MONEY WE NEED TO PAY FOR IT

IT'S NOT ABOUT SAVING MONEY

RATIONING IS NOT THE MOTIVE

WHAT IT IS

IT'S A WAY OF THINKING

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



USING CLINICAL EXPERTISE

Diagnostician Knowledge Broker Communicator Being Kind & Careful

INFORMING PATIENTS

ELICITING INTEGRATING PREFERENCES

Evidence-based practice IS SIMPLY DOING THE RIGHT THING



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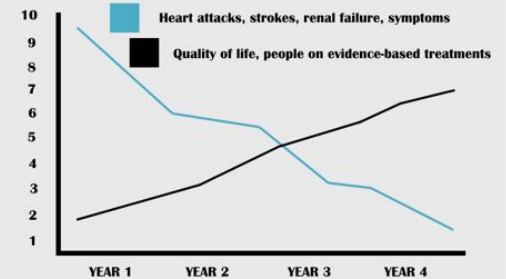
IT'S NOT ABOUT RCTs



RCTs ARE USEFUL BUT THEY ONLY HELP INFORM DECISIONS

$p < 0.05 \neq \text{GOOD}$ $p > 0.05 \neq \text{BAD}$

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

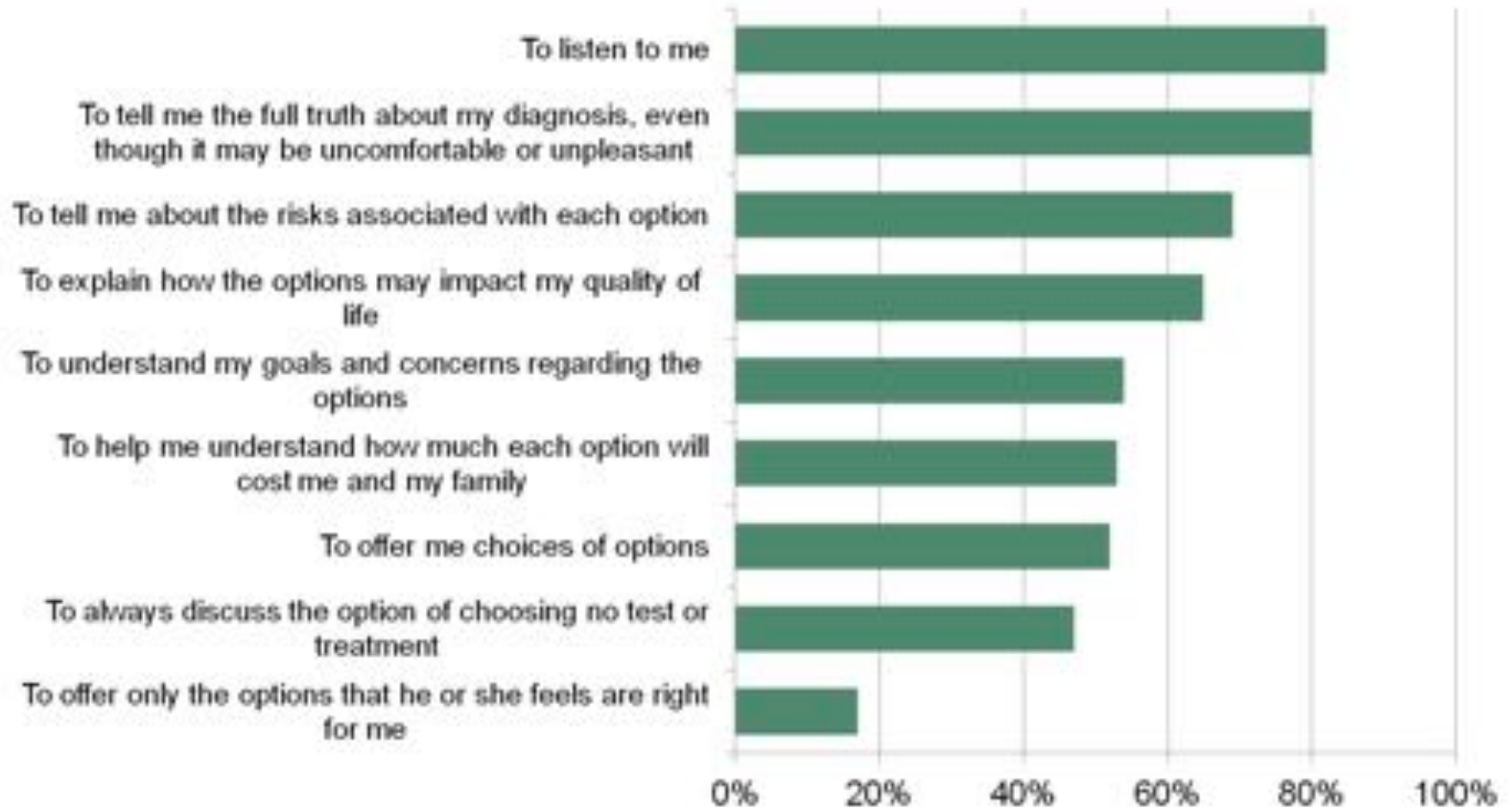
&
ELICITING
&

INTEGRATING PREFERENCES



People want involvement in evidence and decisions

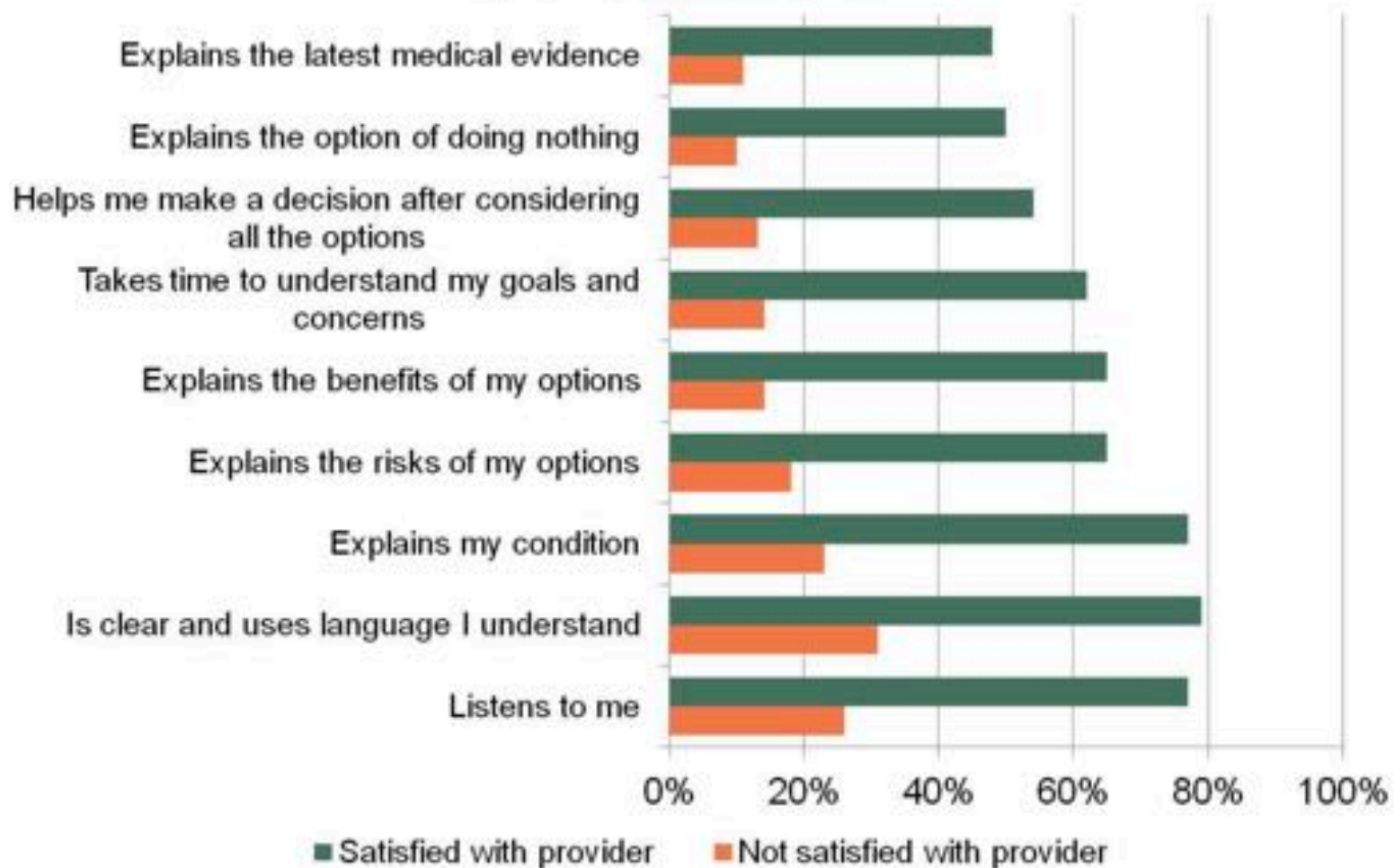
Bars show the percent of people surveyed who strongly agree with the statement: "I want my provider..."



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

Satisfaction is linked to shared decisions

People who are satisfied with their health care provider are more likely to say that their provider...



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

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

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



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.”

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**

Key steps to communicating evidence

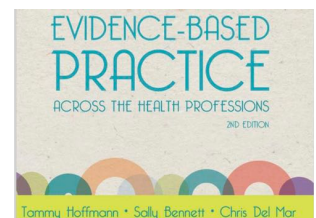
Understand the patient's (and family members') experiences and expectations.

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”

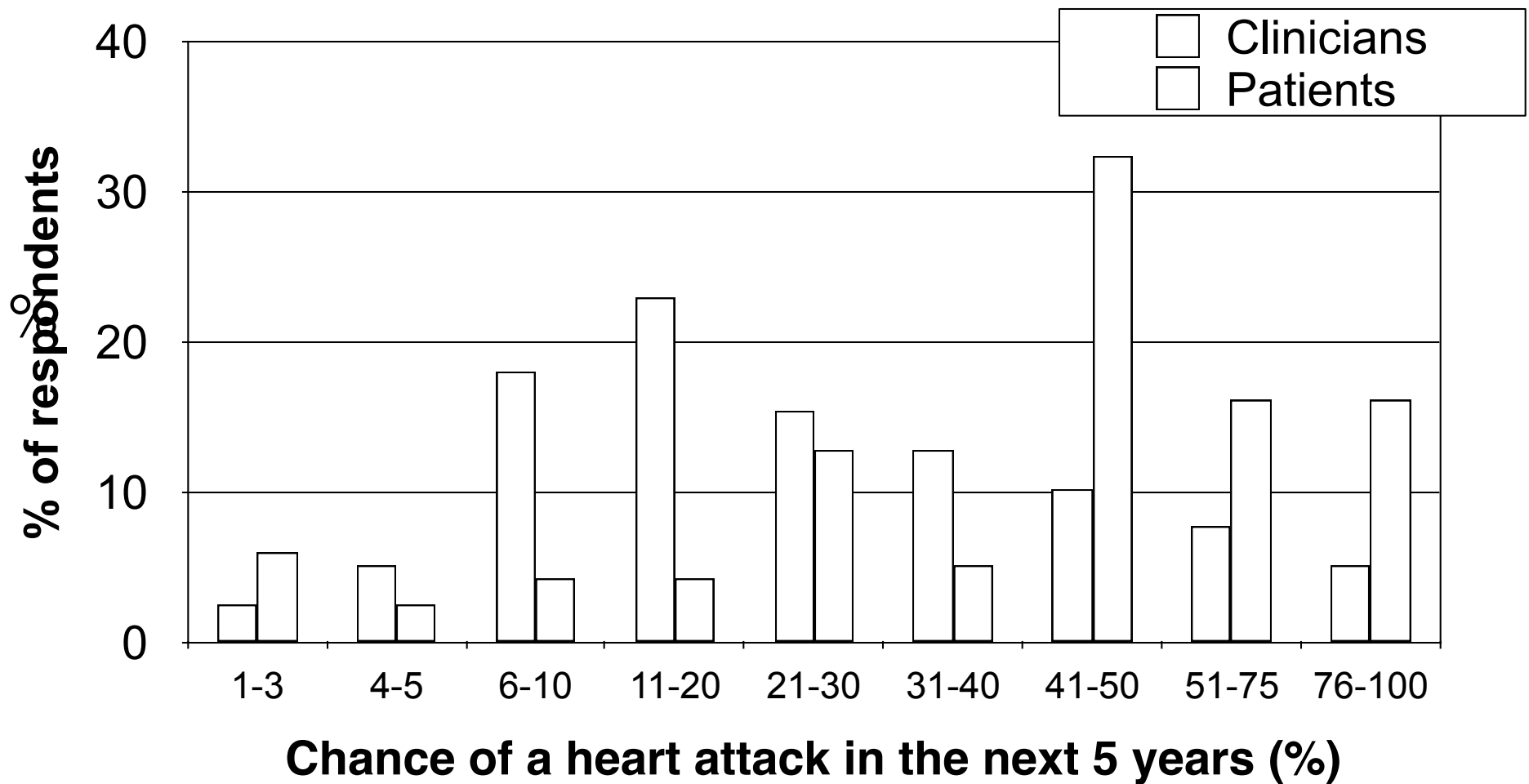
“Monitor closely”

“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).

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.”

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

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”

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

The Absolute CVD Risk/Benefit Calculator

Framingham
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK®2-2014
Heart attacks + strokes

ACC/AHA ASCVD
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

Age: 65 years

Gender: Male Female

Smoker: Yes No

Diabetes: Yes No

Systolic Blood Pressure: 160 mmHg

Total Cholesterol: 6 mmol/L

HDL Cholesterol: 1.5 mmol/L

Family History of Early CHD: 0 %

Relative Benefit: 30%

Benefit often has nothing to do with the effect on the surrogate marker. At present, you can only select one intervention at a time.

Physical Activity: Mediterranean Diet vs Low fat Vitamin/Omega-3 supplements BP meds (not atenolol/doxazosin)

Harm Of Intervention:

- Types of side effects vary between drugs
- Having to stop drug due to intolerance of NNH 10
- Inconvenience of surrogate re-measurements
- Drug Cost

Low-mod intensity statins High intensity statins Fibrates Niacin Ezetimibe Metformin Sulfonylureas Insulins Glitazones GLPs DPP-4s Meglitinides SGLT2 Smoking Cessation ASA

Risk Time Period

10 years

74.0% No event
18.2% Total with an event
7.8% Number who benefit from treatment
13 Number needed to treat
15.8% Baseline events using baseline factors alone
2.4% Additional events "caused" by risk factors

As with all risk calculators, calculated risk numbers are +/- 5% at best. [More information](#)

[Benefit Estimate Details](#)

[Print Report](#)

cvdcalculator.com

Stroke Risk (CHA2DS2-VASc)

Age: <65 65-74 75+

TIA or stroke (at any time in the past) CHF/LV dysfunction (diagnosed at any time in the past)

Prior MI, peripheral artery disease, or aortic plaque Hypertension (controlled or uncontrolled)

Female Diabetes Type I or II (controlled or uncontrolled)

CHA2DS2-VASc SCORE (0-9): 3

Major Bleeding Risk (HAS-BLED*)

Abnormal renal function (dialysis, SCr > 200 micromol/L, or transplant) History of labile INR (time in therapeutic range < 60%)

Hypertension (SBP > 160 mmHg) Current use of alcohol (> 8 drinks per week)

Abnormal liver function (cirrhosis or liver enzymes > 3x ULN) Currently taking antiplatelet drug or NSAID

History of major bleeding (any cause)

HAS-BLED SCORE (0-9): 1

Which therapy options to HIDE?

Aspirin Dabigatran Rivaroxaban Apixaban Edoxaban

Aspirin+Clopidogrel Warfarin

Hide individual charts Hide stroke/bleed chart

	PERCENT PER YEAR	
	annual risk of stroke/embolism	annual risk of major bleeding (intracranial bleeding, bleeding requiring hospitalization, Hgb decrease of > 20 g/L, or need for transfusion secondary to bleeding)
NO THERAPY	4.3%	0.6%
ASPIRIN	3.4%	1.1%
WARFARIN	1.4%	2.2%
DABIGATRAN 110	1.4%	1.8%
DABIGATRAN 150	0.9%	2.2%
RIVAROXABAN	1.4%	2.2%
APIXABAN	1.1%	1.5%

<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

NOW COSTS



25% OFF SALE



Baseline risk

Relative benefit

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





Risk of future illness CVD risk/benefit

Challenging treatment thresholds

James McNamee, PhD, Anne Roberts MD, David Newman MD

Newly published data suggest that the current threshold for initiating statin therapy in primary prevention may be too high. The authors of these meta-analyses conclude that the number of people who benefit from statin therapy is much larger than previously estimated. The authors conclude that the current threshold for initiating statin therapy is too high and that a lower threshold would be more appropriate.

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Statins reduce the risk of CVD

Statins are a class of drugs that lower cholesterol. They are used to treat people with high cholesterol and to prevent heart disease. Statins have been shown to reduce the risk of heart disease and stroke. The authors of these meta-analyses conclude that the current threshold for initiating statin therapy is too high and that a lower threshold would be more appropriate.

Number of people who benefit from statin therapy

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A potential solution

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



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

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

The Lancet
Published online
February 21, 2018

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*

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

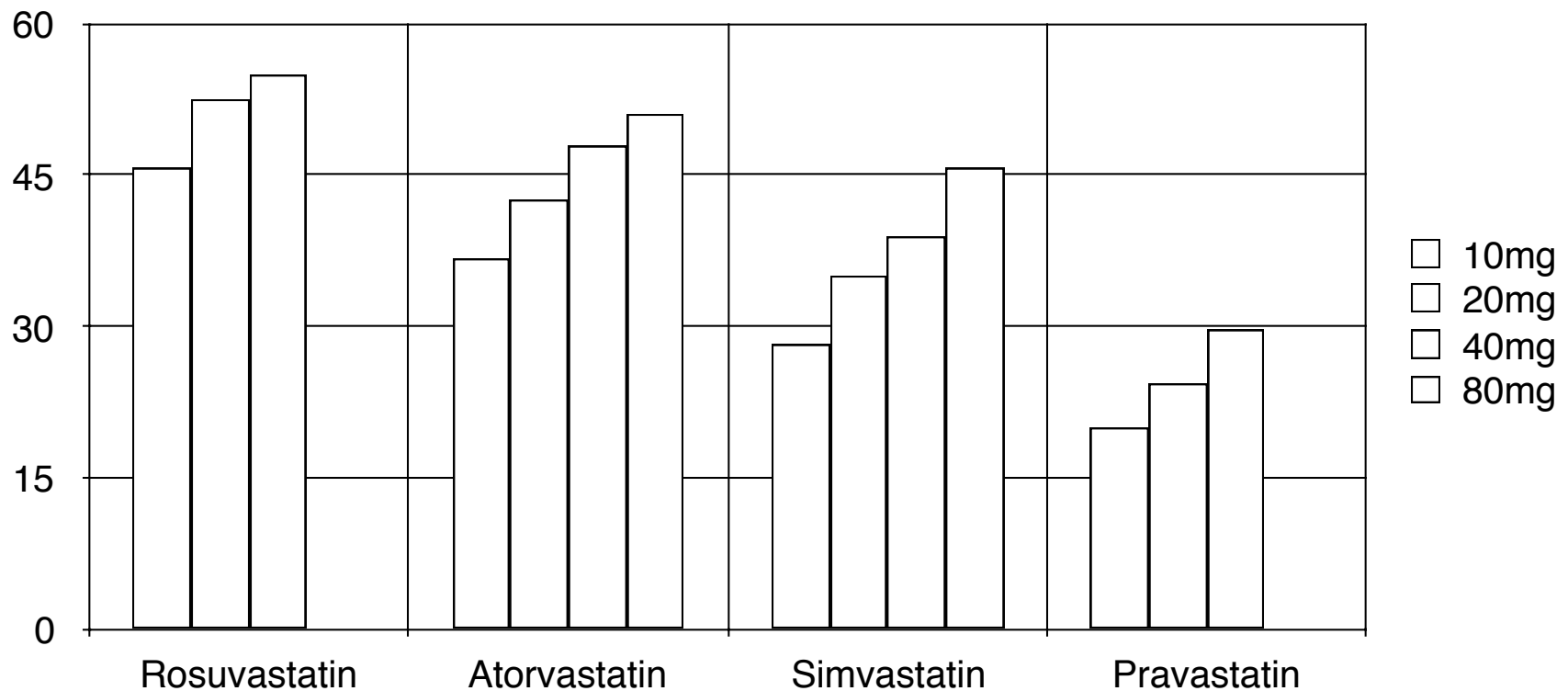
which one is likely to work best for an individual patient

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 as 100 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





**KEEP
CALM
AND
DO THE
RIGHT
THING**