Polypharmacy:

A Rational Evidence-informed Approach with a Touch of Common Sense

James McCormack
B.Sc. (Pharm), Pharm.D.
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC

therapeuticseducation.org
mystudies.org
@medmyths

Get handout here - https://therapeuticseducation.org/handouts

WHY!!

We all need to do a better job when it comes to medications

POLYPHARMACY

does NOT= >5 meds

It means taking medications/supplements which

For symptoms

are not providing a complete or clinically important effect or are given at doses larger than is required to achieve that effect

For prevention

if one was fully informed by the best available evidence about benefits and harms one would not take them

BOTH COULD BE POLYPHARMACY

MY BELIEF

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

Evidence-Based Practice (EBP)

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

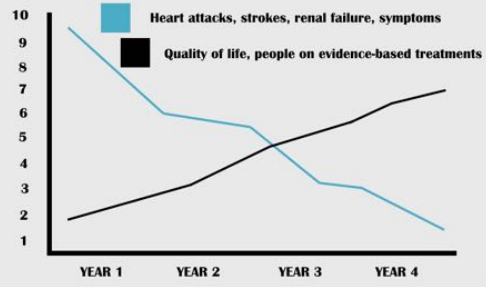
RATIONING
IS NOT THE MOTIVE

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

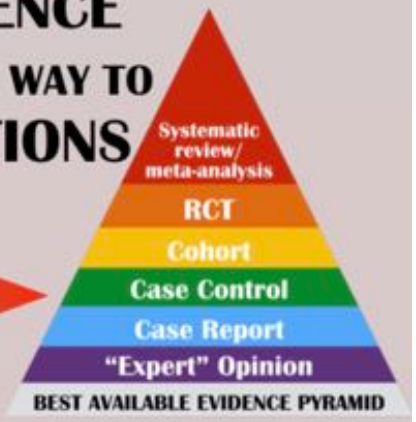
WHAT IT IS

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

Combine Evidence with Common Sense

Common Sense

"So rare that it's a superpower"

Three Approaches

Dose issues

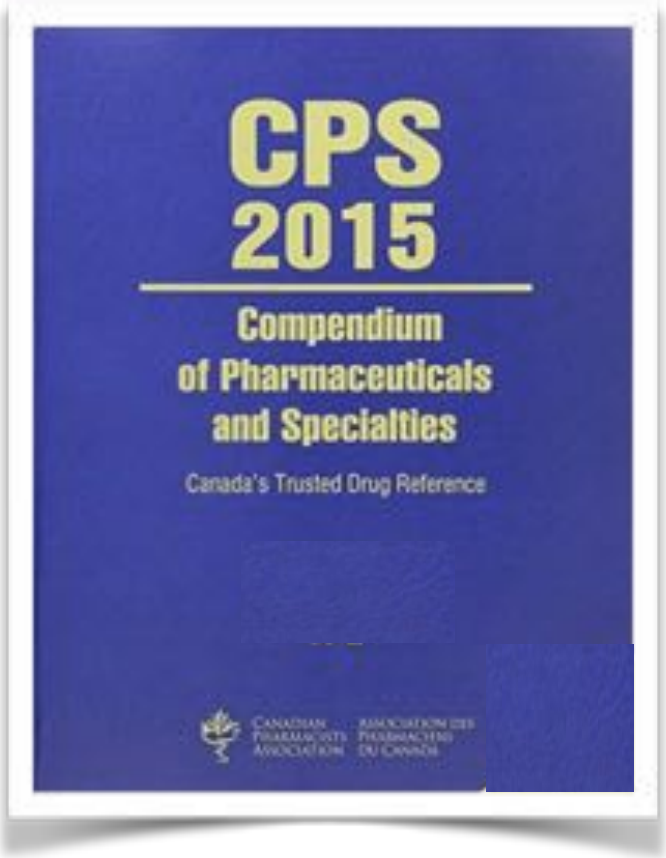
Symptom issues

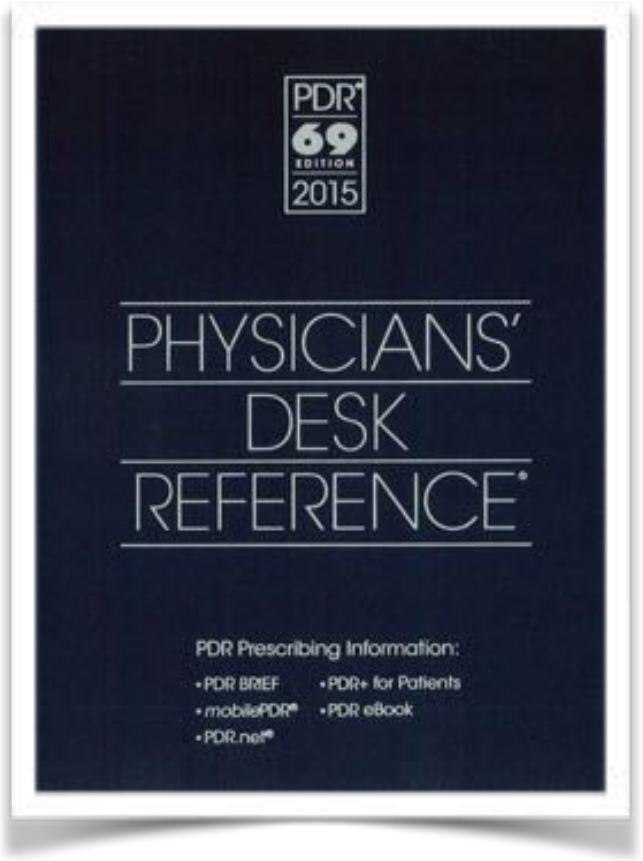
Prevention issues

This simple concept can eliminate most medication problems

USE VERY LOW DOSES

The doses in these books





are all “WRONG” for individual patients

Everyone is a genetic mongrel

It's a dose thing

"more than 80% of ADRs causing admission or occurring in hospital ... are dose related, an 'accentuation' of the known pharmacological effect of the drug, and thus predictable and potentially avoidable"

Br J Clin Pharmacol 2004; 57:121–6

CMAJ ANALYSIS

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

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 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

Doxepin (Sinequan)

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

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

J Clin Psychiatry
2001;62:453-63

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

INSOMNIA

Sleep 2007; 30: 1555–61

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

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

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

Approaches differ depending on outcome

Every patient is an experiment - dose and effect

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

PREVENTION - one will never know if it worked

Expectations

Symptoms

You primarily need to know IF it works and DID it work

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

PPIs, sildenafil - NNT ~2

NSAIDs, opioids - pain NNT ~3-5

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

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

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~7

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

	If a person has responded, what is the % chance it was the medication	
Response in the placebo group	RCT Benefit 10% - NNT 10	RCT Benefit 20% - NNT 5
0%	~100%	~100%
10%	~50%	~66%
20%	~33%	~50%
30%	~25%	~40%
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.


KEEP
CALM
AND
TAPER
ON

Cut tablets/the dose in half

It’s not as scary as you think

…or is it?

Tapering Antidepressants

Taper - approximately 25% will have a recurrence of depression over 18 months

Leave them on - approximately 10% will have a recurrence of depression

15% will be “harmed” and 85% will “benefit” because they are on medications apparently unnecessarily

“Rebound” after PPI withdrawal in healthy people

120 healthy volunteers

12 weeks of placebo or

8 weeks of esomeprazole 40 mg daily and then 4 weeks of placebo

Reporting dyspepsia, heartburn or acid regurg during weeks 9-12

Placebo ~ 5%

PPI ~ 20%

Gastroenterology 2009;137:80-7

PPI withdrawal in asymptomatic GERD patients

71 patients - tried to titrate dose down over 3-6 months
42% still on PPI - median reinstitution time 14 days
34% ended up on H2RA
7% on prokinetic agent
1% on both
16% no-drugs

Gastroenterology 2001;121:1095–1100

223 patients on lansoprazole 30mg BID
50% ended up on rabeprazole 20mg daily
10% off all drugs

56% with erosive esophagitis failed
31% of those with endoscopic-negative failed

Aliment Pharmacol Ther 2007;25:709–71

What Are the Risks and Benefits of Stopping Antipsychotics in the Elderly?

July 4, 2013

Clinical Question: In elderly patients, what are the risks and benefits of stopping long-term antipsychotics (initiated for behavioral concerns)?

Bottom-line: In elderly patients on long-term antipsychotics, withdrawal of antipsychotics in four patients may prevent one death at two years. After discontinuation, neuropsychiatric symptoms appear to vary little, although one study suggests stopping after four months can cause one in four more patients to have a relapse of neuropsychiatric symptoms.

Withdrawal of antipsychotics - for every 4 people, you prevent 1 death and 1 study suggests that 1 in 4 will have a relapse of neuropsychiatric symptoms

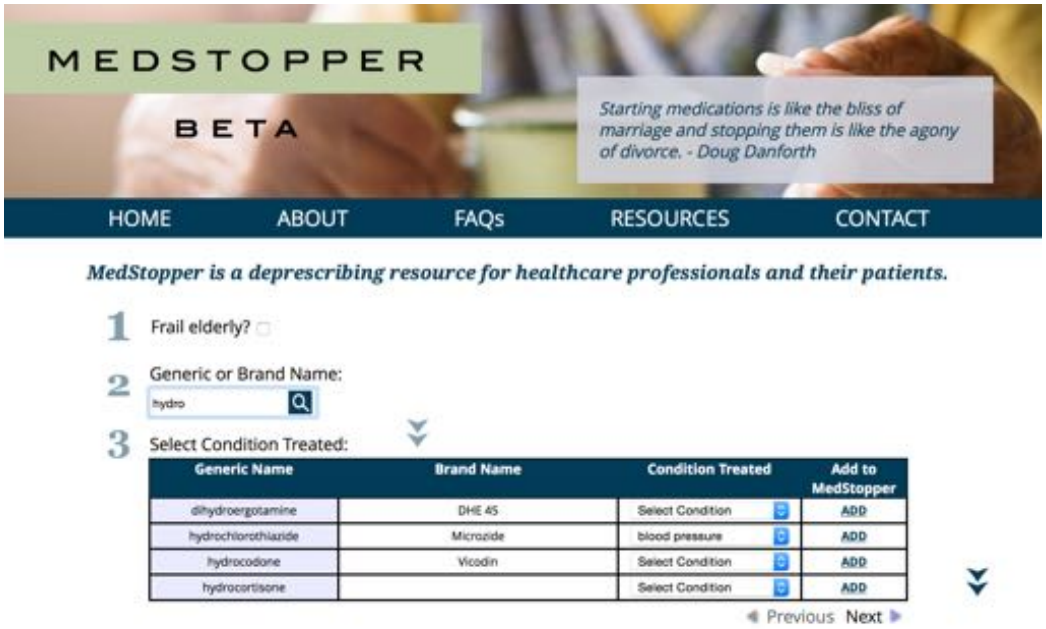
Antipsychotics also worsen cognition

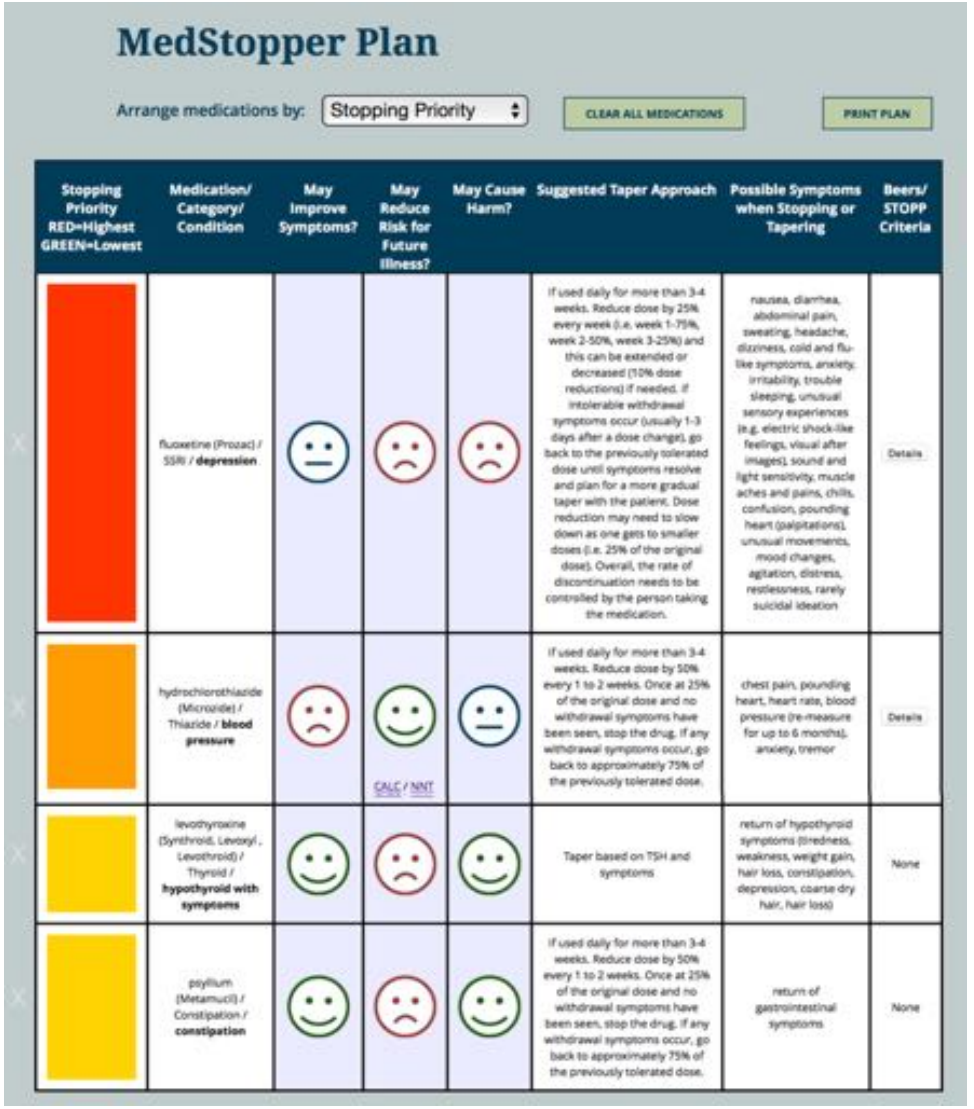
Donepezil withdrawal

- 295 Community dwelling patients on donepezil (most >2 yrs)
  - –mean age 77, mean MMSE 9, followed 1 yr.
  - –Stopping of med worsened MSE by 1.9 pts
    - Less effect (1.3) if severe dementia (<9 MSE)
    - Don't give number attaining MCID (1.4)
  - –Withdrawal from study more if stopped!
  - –Death: no difference

N Engl J Med 2012;366:893-903

MEDSTOPPER





medstopper.com

Symptom meds

PPIs, NSAIDs etc

Typically one should reduce the dose “slowly” - cut the dose in half or do something similar - change interval

The dose likely wasn’t right in the first place

Put the onus on, and give the power to, the patient to find the right dose

Prevention

Wrong guidelines: why and how often they occur

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

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

EBM 2017;22:1-3

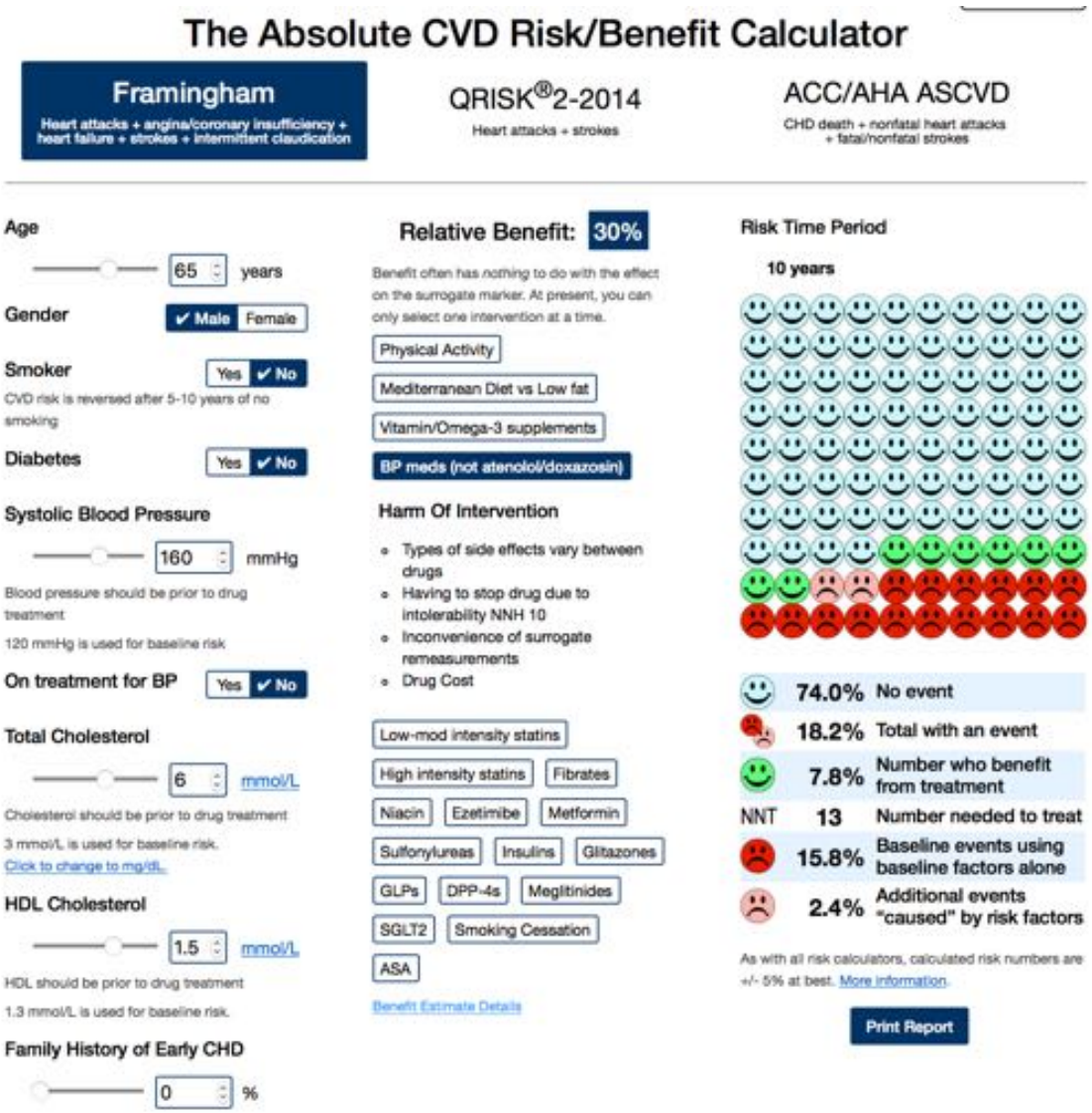
Factors involved in deciding to start preventive treatment: qualitative study of clinicians' and lay people's attitudes

David K Lewis, Jude Robinson, Ewan Wilkinson

Qualitative study using semi-structured interviews

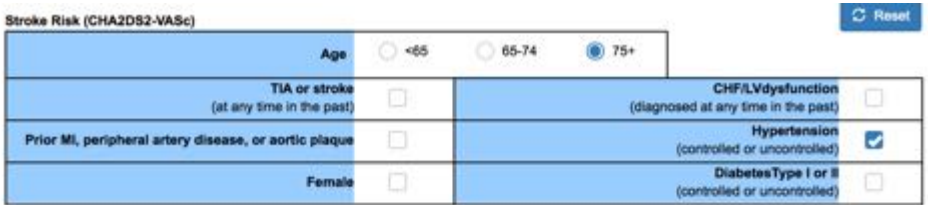
"Many of the preferences expressed by the clinicians and lay people in this study are at odds with recommendations in guidelines"

BMJ 2003;327:841



cvdcalculator.com

Calculate ballpark 10-yr risk of CVD - BP, chol, diabetes
Make estimate of benefit based on the best available evidence
Gives a list of adverse effects to discuss



http://www.sparctool.com

	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%

Calculate ballpark annual risk of stroke - based on risk factors- BP, chol, diabetes
Make estimate of benefit based on the best available evidence - all agents
Make estimate of a GI bleed

Optimal management of elderly pts with vascular disease (DEBATE)

RCT, f/u 3.4 years 400 patients - avg age 80, all CVD

Usual care (primary care) or specialized care

“Evidence-Based” European CPG for chronic CVD

“it was possible and safe to institute evidence-based cardiovascular treatments and improve risk factors in patients 75 years or older in a pragmatic setting.”

Am Heart J 2006;152:585-92

Outcome

Systolic BP: 7.8 mmHg lower
Diastolic BP: 3.9 mmHg lower
Glucose: 0.55 mmol/L lower
Cholesterol: 0.78 mmol/L lower
LDL: 0.73 mmol/L lower (45% to target)
MEDS: ACE (+30%) & statin (+50%)

PREDICTED BENEFIT
UKPDS risk engine
18% CVD risk
reduced to14%
NNT = 25

ACTUAL BENEFIT - NONE

IN BOTH GROUPS

Mortality 18%

Stroke 6%

MI/coronary death 16%

NNT = infinite

Treatment of Hypertension in Patients 80 Years of Age or Older

Patients

3,845 patients with a SBP > 160 mm Hg, TC 5.3 mmol/L, 12% history of CVD, 60% were female, average age was 83, BMI 25

Treatment

Indapamide (1.25 mg) - then indapamide plus perindopril (2 or 4mg) or placebo daily

Duration

Followed for 1.8 years

Results

BP differences at the end (15/6 mm Hg lower) - 74% on both drugs

N Engl J Med 2008:358

BP elderly results

	Fatal or non-fatal stroke (%)	Serious adverse event (%)	Overall mortality (%)	MI (%)	Any cardiovascular event (%)
Placebo	3.6	23.4	12.3	0.5	10
Inda/perin	2.9	18.5	10.1	0.6	7.1
Relative risk reduction	P=0.06	21	18	NSS	29
Absolute risk reduction		4.9	2.2		2.9
Number needed to treat		20	45		35

No mention of adverse effects

All the TARGET dose evidence

Drug	High/low dose	Duration (years)	Absolute Benefits	Absolute Harms
Enalapril	4x	0.5	None	8%
Lisinopril	7-15x	4	4/6%	3/7%
Carvedilol	4x	0.5	None	10%
Carvedilol	8x	4	None	20%
Losartan	3x	5	3%	3/7%

Benefits - primarily hospitalizations
Harms - hypotension, withdrawal, dose reduction

Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial

883 heart failure patients - age - 73

66% class II, 29% class III

Randomised to bisoprolol (10 mg daily) or carvedilol (25 mg BID) and slowly up-titrated patients to the “RECOMMENDED” doses

Fraction of dose	0	1/8	1/4	1/2	FULL
Patients on dose at end/12 weeks	10%	10%	25%	25%	30%

Eur J Heart Fail 2011;13:670-80

Prevention medications do NOT make you feel better

primary prevention

1-2% benefit over 5 years - 98-99% do not

secondary prevention

5-10% benefit over 5 years - 90-95% do not

lab tests

false positives

witch hunt

evidence plus patient values - 1/3 not adherent

Risk reduction meds

ASA, statins - you can just stop them

Fibrates - please just stop them

Blood pressure and diabetes drugs?

- dosage should be reduced by 50%, with reassessment of blood pressure at 2 weeks
- if the patient is still normotensive, reduce the dosage by another 50% (i.e., to 25% of the initial dose) and recheck the blood pressure in another 2 weeks

Use ‘tricks’ to get patient interest

THEIR ARGUMENTS

I’ve taken these for years and now you are telling me I don’t need them

But these are for my heart!!

It’s OK, I don’t pay for my medications

But my “specialist” says I need these

“If it isn’t broken then don’t fix it”

YOUR ARGUMENTS

Well your renal function/hepatic function are decreased

Look what you've been able to do for yourself

You take control and figure out the dose - you teach me what works

Your specialist doesn't know you like I do

We can always restart if we need to


KEEP
CALM
BECAUSE
LESS
IS
MORE


KEEP
CALM
AND
USE VERY
LOW DOSES


KEEP
CALM
AND
TAPER
ON


KEEP
CALM
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