

Polypharmacy:

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



KEEP
CALM
BECAUSE
LESS
IS
MORE

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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)

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 LIMITED
 BUT THEY ONLY
 HELP
 INFORM DECISIONS

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 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

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



Evidence-based
 practice IS

SIMPLY
 DOING
 THE
 RIGHT
 THING



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 NEW IDEA

IT'S NOT ABOUT SAVING MONEY



RATIONING
 IS NOT THE
 MOTIVE

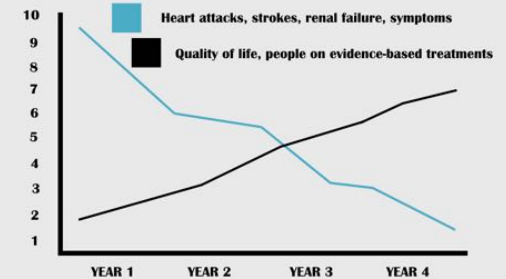
IT'S NOT ABOUT RCTs



RCTs ARE USEFUL
 BUT THEY ONLY
 HELP
 INFORM DECISIONS

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

IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES



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INFORMING PATIENTS

**&
ELICITING
&**

INTEGRATING PREFERENCES



Combine Evidence with Common Sense



Common Sense

“So rare
that it’s a
superpower”

Three Approaches

Dose issues

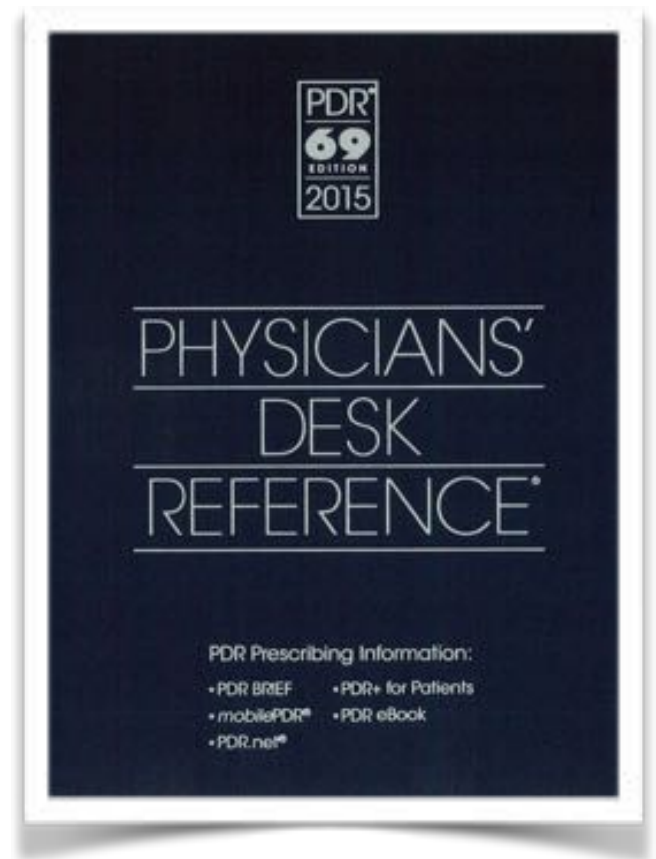
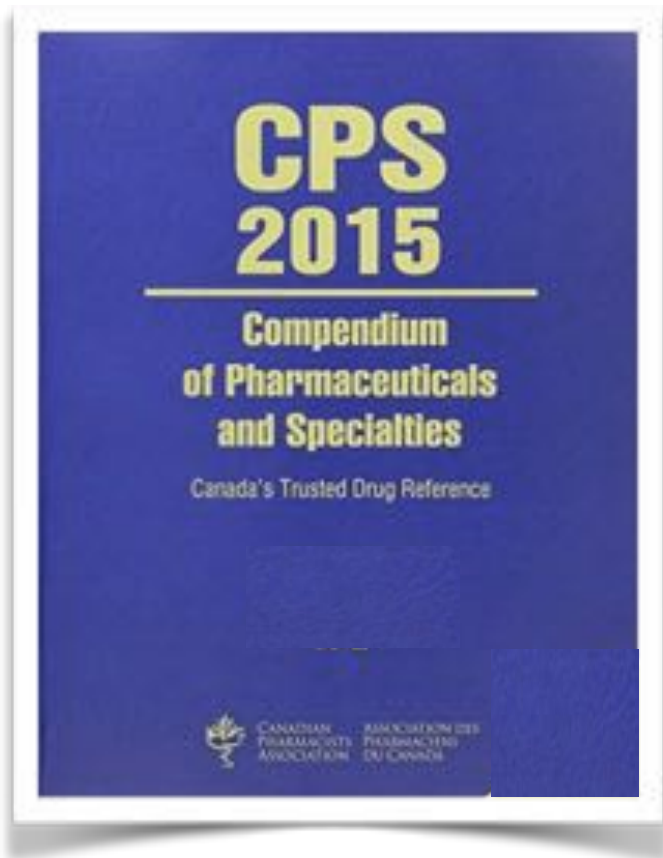
Symptom issues

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

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 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 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 4.8 mg 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%

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

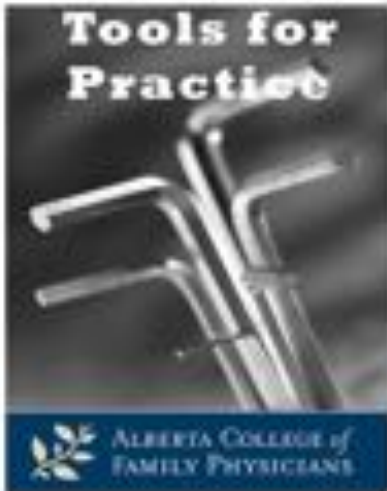
50% ended up on rabeprazole 20mg daily

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

MEDSTOPPER



MedStopper is a deprescribing resource for healthcare professionals and their patients.

1 Frail elderly? ☐

2 Generic or Brand Name:

hydro

3 Select Condition Treated:

Generic Name	Brand Name	Condition Treated	Add to MedStopper
dihydroergotamine	DHE 45	Select Condition	ADD
hydrochlorothiazide	Microzide	blood pressure	ADD
hydrocodone	Vicodin	Select Condition	ADD
hydrocortisone		Select Condition	ADD

◀ Previous Next ▶

MedStopper Plan

Arrange medications by:

Stopping Priority

CLEAR ALL MEDICATIONS

PRINT PLAN

Stopping Priority RED=Highest GREEN=Lowest	Medication/ Category/ Condition	May Improve Symptoms?	May Reduce Risk for Future Illness?	May Cause Harm?	Suggested Taper Approach	Possible Symptoms when Stopping or Tapering	Beers/ STOPP Criteria
	fluoxetine (Prozac) / SSRI / depression				If used daily for more than 3-4 weeks. Reduce dose by 25% every week (i.e. week 1-75%, week 2-50%, week 3-25%) and this can be extended or decreased (10% dose reductions) if needed. If intolerable withdrawal symptoms occur (usually 1-3 days after a dose change), go back to the previously tolerated dose until symptoms resolve and plan for a more gradual taper with the patient. Dose reduction may need to slow down as one gets to smaller doses (i.e. 25% of the original dose). Overall, the rate of discontinuation needs to be controlled by the person taking the medication.	nausea, diarrhea, abdominal pain, sweating, headache, dizziness, cold and flu-like symptoms, anxiety, irritability, trouble sleeping, unusual sensory experiences (e.g. electric shock-like feelings, visual after images), sound and light sensitivity, muscle aches and pains, chills, confusion, pounding heart (palpitations), unusual movements, mood changes, agitation, distress, restlessness, rarely suicidal ideation	Details
	hydrochlorothiazide (Microzide) / Thiazide / Blood pressure		<small>CALC / NNT</small>		If used daily for more than 3-4 weeks. Reduce dose by 50% every 1 to 2 weeks. Once at 25% of the original dose and no withdrawal symptoms have been seen, stop the drug. If any withdrawal symptoms occur, go back to approximately 75% of the previously tolerated dose.	chest pain, pounding heart, heart rate, blood pressure (re-measure for up to 6 months), anxiety, tremor	Details
	levothyroxine (Synthroid, Levoxyl, Levothroid) / Thyroid / hypothyroid with symptoms				Taper based on TSH and symptoms	return of hypothyroid symptoms (iredness, weakness, weight gain, hair loss, constipation, depression, coarse dry hair, hair loss)	None
	psyllium (Metamucil) / Constipation / constipation				If used daily for more than 3-4 weeks. Reduce dose by 50% every 1 to 2 weeks. Once at 25% of the original dose and no withdrawal symptoms have been seen, stop the drug. If any withdrawal symptoms occur, go back to approximately 75% of the previously tolerated dose.	return of gastrointestinal symptoms	None

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 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.”

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”

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

years

Gender

☒ Male ☐ Female

Smoker

☐ Yes ☒ No

CVD risk is reversed after 5-10 years of no smoking

Diabetes

☐ Yes ☒ No

Systolic Blood Pressure

mmHg

Blood pressure should be prior to drug treatment

120 mmHg is used for baseline risk

On treatment for BP

☐ Yes ☒ No

Total Cholesterol

mmol/L

Cholesterol should be prior to drug treatment

3 mmol/L is used for baseline risk

[Click to change to mg/dL](#)

HDL Cholesterol

mmol/L

HDL should be prior to drug treatment

1.3 mmol/L is used for baseline risk

Family History of Early CHD

%

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 intolerability NNH 10
- Inconvenience of surrogate remeasurements
- Drug Cost

Low-mod intensity statins

High intensity statins

Fibrates

Niacin

Ezetimibe

Metformin

Sulfonylureas

Insulins

Glitazones

GLPs

DPP-4s

Meglitinides

SGLT2

Smoking Cessation

ASA

[Benefit Estimate Details](#)

Risk Time Period

10 years



	74.0%	No event
	18.2%	Total with an event
	7.8%	Number who benefit from treatment
NNT	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](#)

[Print Report](#)

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

cvdcalculator.com

Age	<input type="radio"/> <65	<input type="radio"/> 65-74	<input checked="" type="radio"/> 75+
TIA or stroke (at any time in the past)	<input type="checkbox"/>	CHF/LV dysfunction (diagnosed at any time in the past)	<input type="checkbox"/>
Prior MI, peripheral artery disease, or aortic plaque	<input type="checkbox"/>	Hypertension (controlled or uncontrolled)	<input checked="" type="checkbox"/>
Female	<input type="checkbox"/>	Diabetes Type I or II (controlled or uncontrolled)	<input type="checkbox"/>

<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%)

ACTUAL BENEFIT - NONE
IN BOTH GROUPS

Mortality 18%

Stroke 6%

MI/coronary death 16%

NNT = infinite

**PREDICTED
BENEFIT**

**UKPDS risk engine
18% CVD risk
reduced to 14%
NNT = 25**



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%

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
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**KEEP
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AND
USE VERY
LOW DOSES**



**KEEP
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**KEEP
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