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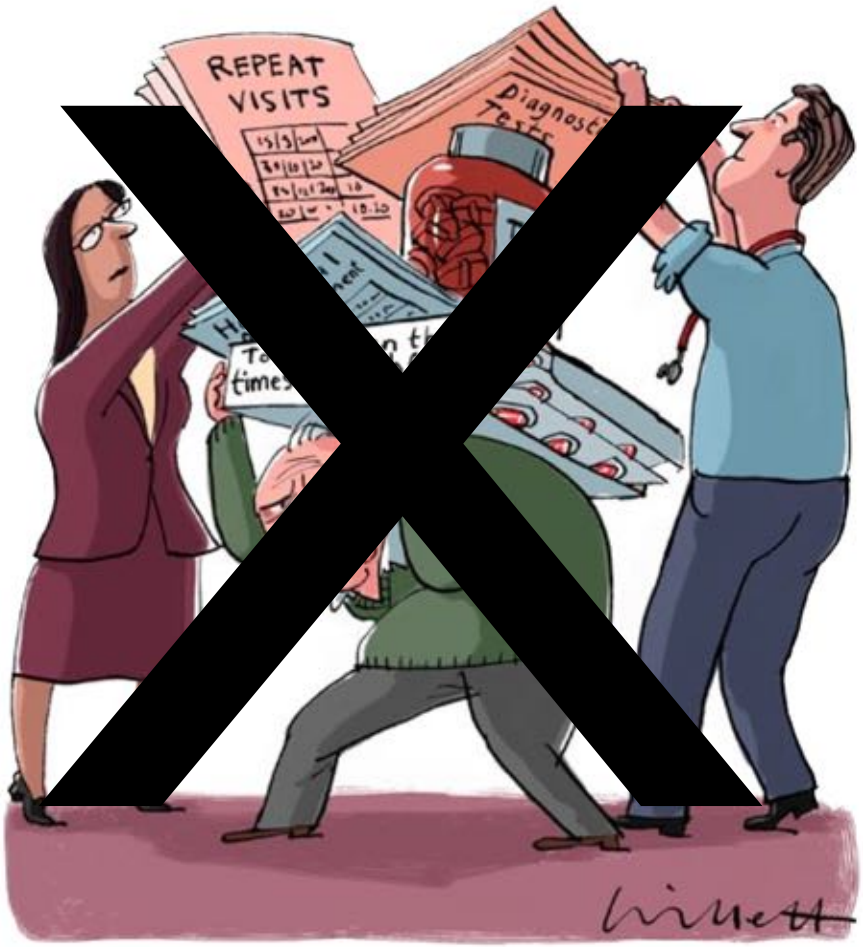
# Minimally Disruptive Medicine




Establish burden of therapy

Encourage coordination in clinical practice

Acknowledge comorbidity in clinical evidence

Prioritize from the patient perspective


WE ARE
KNOWLEDGE
BROKERS

antibiotics

thiazides

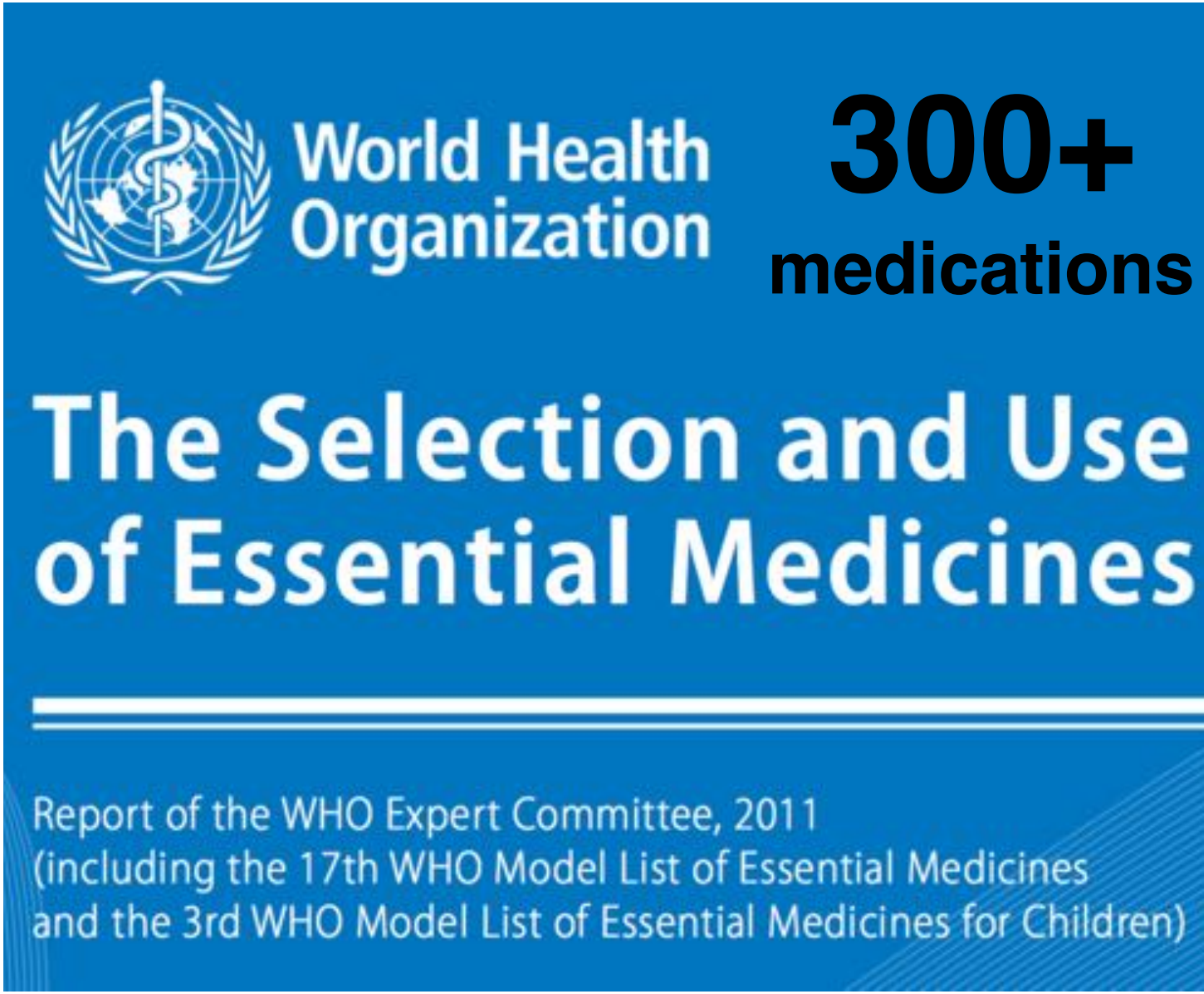
many vaccines

ACE inhibitors

proton pump inhibitors

H2 receptor antagonists

contraceptives




corticosteroids

narcotics

beta-agonists

anesthetics

warfarin

chemotherapy

insulin

adrenalin

# Drugs Removed from the Market

## 1950-70s

**Thalidomide**
Teratogenicity
**LSD (psych cure-all)**
Used recreationally
**Diethylstilbestrol**
Teratogenicity
**Phenformin/Buformin**
Lactic acidosis

## 1980s

**Ticrynafen**
Hepatitis
**Zimelidine**
Guillain-Barré syndrome
**Phenacetin**
Cancer/ kidney disease
**Methaqualone**
Addiction/overdose
**Nomifensine (Merital)**
Hemolytic anemia

## 1990s

**Triazolam**
UK - psychiatric reactions
**Terodiline (Micturin)**
Prolonged QT interval
**Temafloxacin**
Allergic reactions/ hemolytic anemia
**Flosequinan (Manoplax)**
Increased hospitalization/ death
**Alpidem (Ananxyl)**
Hepatotoxicity
**Chlormezanone (Trancopal)**
Toxic epidermal necrolysis
**Dexfenfluramine/fenfluramine**
Heart valve disorder
**Tolrestat (Alredase)**
Hepatotoxicity
**Terfenadine (Seldane)**
Cardiac arrhythmias
**Mibefradil (Posicor)**
Dangerous interactions
**Etretinate**
Birth defects
**Tolcapone (Tasmar)**
Hepatotoxicity
**Temazepam (Restoril)**
Sweden and Norway - diversion, abuse, overdose
**Astemizole (Hismanal)**
Arrhythmias
**Grepafloxacin (Raxar)**
Prolonged QT interval

## 2000s

**Troglitazone (Rezulin)**
Hepatotoxicity
**Alosetron (Lotronex)**
Fatal complications of constipation
Reintroduced 2002 on a restricted basis
**Cisapride (Propulsid)**
Cardiac arrhythmias
**Amineptine (Survector)**
Hepatotoxicity
Dermatological
Abuse potential
**Phenylpropanolamine (Dexatrim)**
Stroke
**Trovafloxacin (Trovan)**
Liver failure
**Cerivastatin (Baycol)**
Rhabdomyolysis
**Rapacuronium (Raplon)**
Fatal bronchospasm
**Rofecoxib (Vioxx)**
Myocardial infarction
**Co-proxamol (Distalgesic)**
Overdose dangers
**Hydromorphone ER (Palladone)**
Overdose dangers
**Thioridazine (Mellaril)**
UK - cardiotoxicity

**Pemoline (Cylert)**
Hepatotoxicity

**Ximelagatran (Exanta)**
Hepatotoxicity
**Pergolide (Permax)**
US - heart valve damage
**Tegaserod (Zelnorm)**
Heart attack and stroke
**Aprotinin (Trasylol)**
Death
**Inhaled insulin (Exubera)**
Long-term safety and too high a cost
**Lumiracoxib (Prexige)**
Liver damage
**Rimonabant (Accomplia)**
Severe depression and suicide
**Efalizumab (Raptiva)**
Progressive multifocal leukoencephalopathy
**Sibutramine (Reductil)**
Cardiovascular risk
**Gemtuzumab (Mylotarg)**
US – no benefit and venoocclusive disease
**Rosiglitazone (Avandia)**
Europe - heart attacks and death

# Outcomes Are Not Created EQUAL Surrogate - Subjective - Objective

Ask yourself: Can a patient feel the outcome?

If No - it is a surrogate marker

# A Medical Tale (circa 1989)
# The Surrogate Heart

Once upon a time, in a Kingdom Far, Far away, a Sage noticed that abnormal beats follow Heart Attacks

More beats did ↑ risk of Sudden Death

The King declared: "Give a remedy to decrease extra beats and thou shalt live a long and prosperous life"

And so they did,…

# A Medical Tale:
# The Surrogate Heart

And all was good,… until a Jester asked: "Are we saving lives?"

After the execution, the King summoned the Fairy Godmother to solve the Jester's riddle

She gave some the magic potion and others not - 80% dec in VPDs

10 months in time did pass

# A Medical Tale:
# The Surrogate Heart

| | Magic Potion A | Magic Potion B |
|---|---|---|
| Mortality | 7.7% | 3% |
| Arrhythmia death or cardiac arrests | 4.5% | 1.2% |

NEJM 1989;321:406-12

# A Medical Tale:
# The Surrogate Heart

| | Encainide/ Flecainide | Placebo |
|---|---|---|
| Mortality | 7.7% | 3% |
| Arrhythmia death or cardiac arrests | 4.5% | 1.2% |

NEJM 1989;321:406-12

# Surrogates: The Never-ending Consistently Inconsistent Story

| The Marker | The Treatment |
| --- | --- |
| HDL | Torcetrapib<br>LDL down, HDL up<br>CVD & mortality up |
| LDL | Niacin, Ezetimibe |
| Trigly | Fibrates |
| BP | Atenolol, Aliskiren, Doxazosin |
| A1c | Rosiglitazone - Almost any diabetes medications except Metformin |
| Homocysteine | Folate |
| CRP in CVD | Vitamin E, Rosiglitazone, etc. |

N Engl J Med 2007;357:2109-22

# Typically "evidence-based" guideline recommendations are not based on "solid" evidence

JAMA®
Online article and related content current as of March 17, 2009.

**Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines**

Pierluigi Tricoci; Joseph M. Allen; Judith M. Kramer; et al.

*JAMA*. 2009;301(8):831-841 (doi:10.1001/jama.2009.205)

**Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines**

*Dong Heun Lee, MD; Ole Vielemeyer, MD* *Arch Intern Med. 2011;171(1):18-22*

| Cardiology | LEVEL | Infectious disease |
|---|---|---|
| 11% | Evidence Level (1 or A) based on RCTs | 14% |
| 48% | Evidence Level (3 or C) based on opinion | 55% |

# TREATMENT TARGETS

**2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations**

TARGETS OF THERAPY

| Risk level | Primary target: LDL-C | Class, level |
|---|---|---|
| High | <2 mmol/L | Class I, level A |
| CAD, PVD, atherosclerosis | or | |
| Most patients with diabetes | ≥50% ↓ LDL-C | |
| FRS ≥20% | apoB <0.80 g/L | |
| RRS ≥20% | | |
| Moderate | <2 mmol/L* | Class IIa, level A |
| FRS 10% to 19% | or | |
| LDL-C >3.5 mmol/L | ≥50% ↓ LDL-C | |
| Triglycerides ≥2.0 | apoB <0.80 g/L | |
| hs-CRP >2 mg/L in men >50 years and women >60 years of age | | |
| Family history and hs-CRP modulate risk | | |
| Low | ≥50% ↓ LDL-C | Class IIa, level A |
| FRS <10% | | |

"Recommended target" <2 mmo/L/80mg/dL

Level A = recommendation based on evidence from multiple randomized trials or meta-analyses

## 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

"The Expert Panel was UNABLE TO FIND RCT EVIDENCE to support titrating cholesterol-lowering drug therapy to achieve target LDL–C or non-HDL-C levels, as recommended by ATP III"

# 20 "NEGATIVE" STUDIES IN A ROW

## LIPIDS

AIM-HIGH, HPS2-THRIVE (niacin)

ACCORD (fibrates)

dalOUTCOMES (dalcetrapib)

STABILITY (darapladib)

## BLOOD PRESSURE

ALTITUDE (aliskiren)

VALISH, AASK, ACCORD

(aggressive BP lowering)

## 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

182,000+ patients

1967

# Effects of Treatment on Morbidity in Hypertension

**Results in Patients With Diastolic Blood Pressures Averaging 115 Through 129 mm Hg**

*Veterans Administration Cooperative Study Group on Antihypertensive Agents*

Lower BP in patients with average DBP of 121 mmHg - 19 months

Placebo - 70 patients - 27 CVD events - 4 deaths

Drug - 73 patients - 2 events - 0 deaths

# EFFECT OF PROPRANOLOL IN MILD HYPERTENSION

J. W. PATERSON
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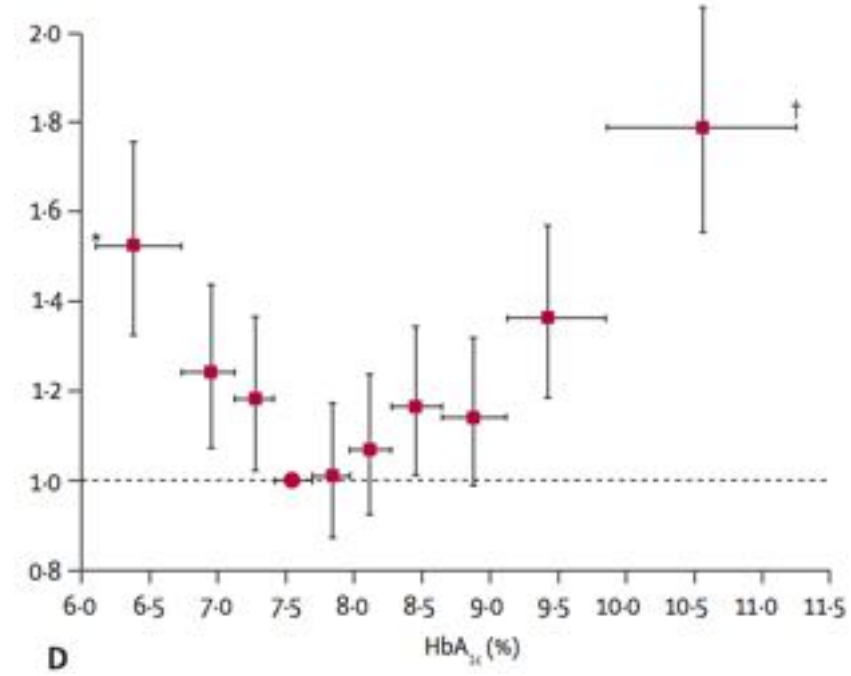
# What goes down must come up




AIC[1]

BMI[3] over 65

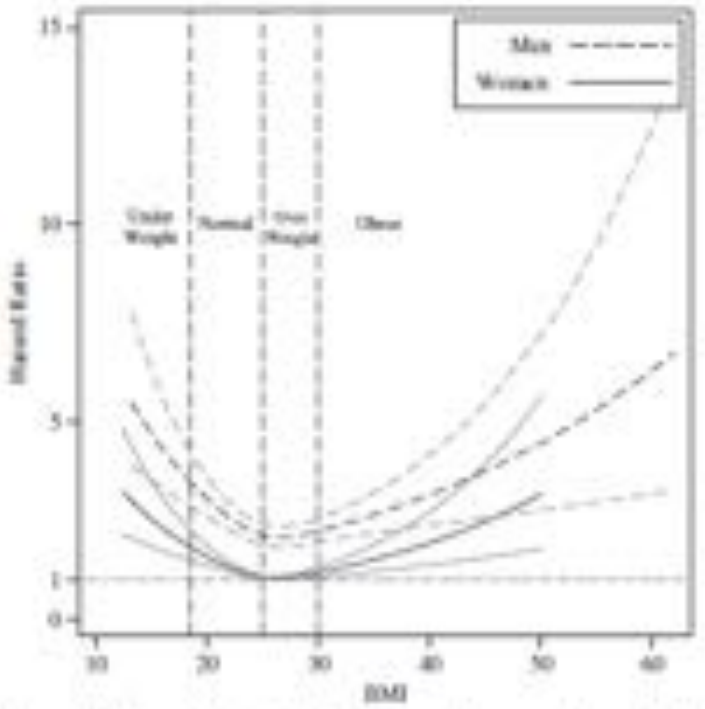
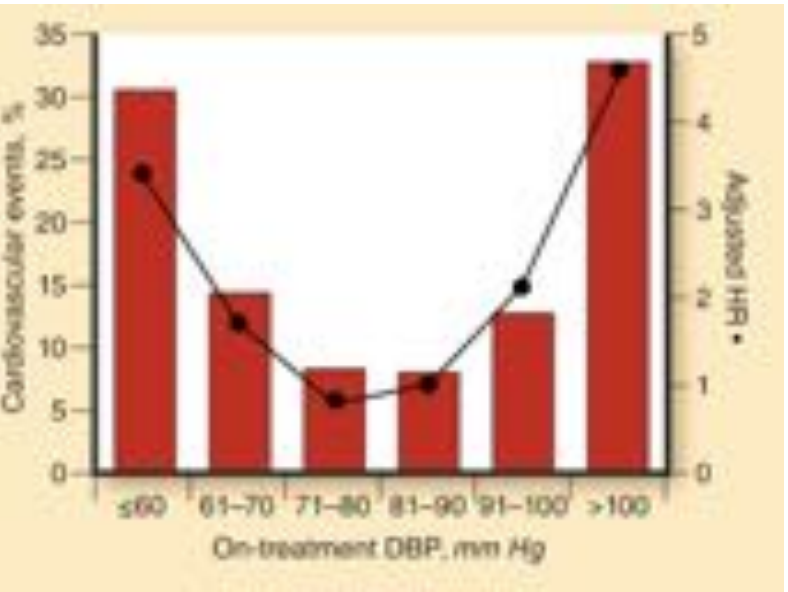



Figure 1. Hazard ratios of all-cause mortality according to body mass index (BMI) in men and women aged 70 to 75 (lines are 95% confidence intervals).




Diastolic BP[2]

Similar data for
25-59 years of age
JAMA 2007;298:2028-37


1) Lancet 2010; 375: 481–89
2) Curr Hypertens Rep (2010) 12:290–295
3) J Am Geriatr Soc 2010; 58:234–241

# Effectiveness of Estrogens for Therapy of Myocardial Infarction in Middle-Age Men

JAMA
1963;183:106-12

10 mg versus placebo - over 5 years
Cardio/renal event - first 3 months - 22% vs 5% - but mortality lower at 5 years therefore a new trial suggested
"Feminizing effect" - 40% vs 30%

# The Coronary Drug Project

## Initial Findings Leading to Modifications of Its Research Protocol

The Coronary Drug Project Research Group

Terminated early

JAMA 1970;214:1303-13

5 mg versus placebo - over 18 months
Definite non-fatal MI - 6.2% vs 3.2%
Pulmonary embolism - 1.5% vs 0.4%
Excessive shopping - 80% vs 3%



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 , G Michael Allan associate professor

# “If you say it enough it becomes the truth”

“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”

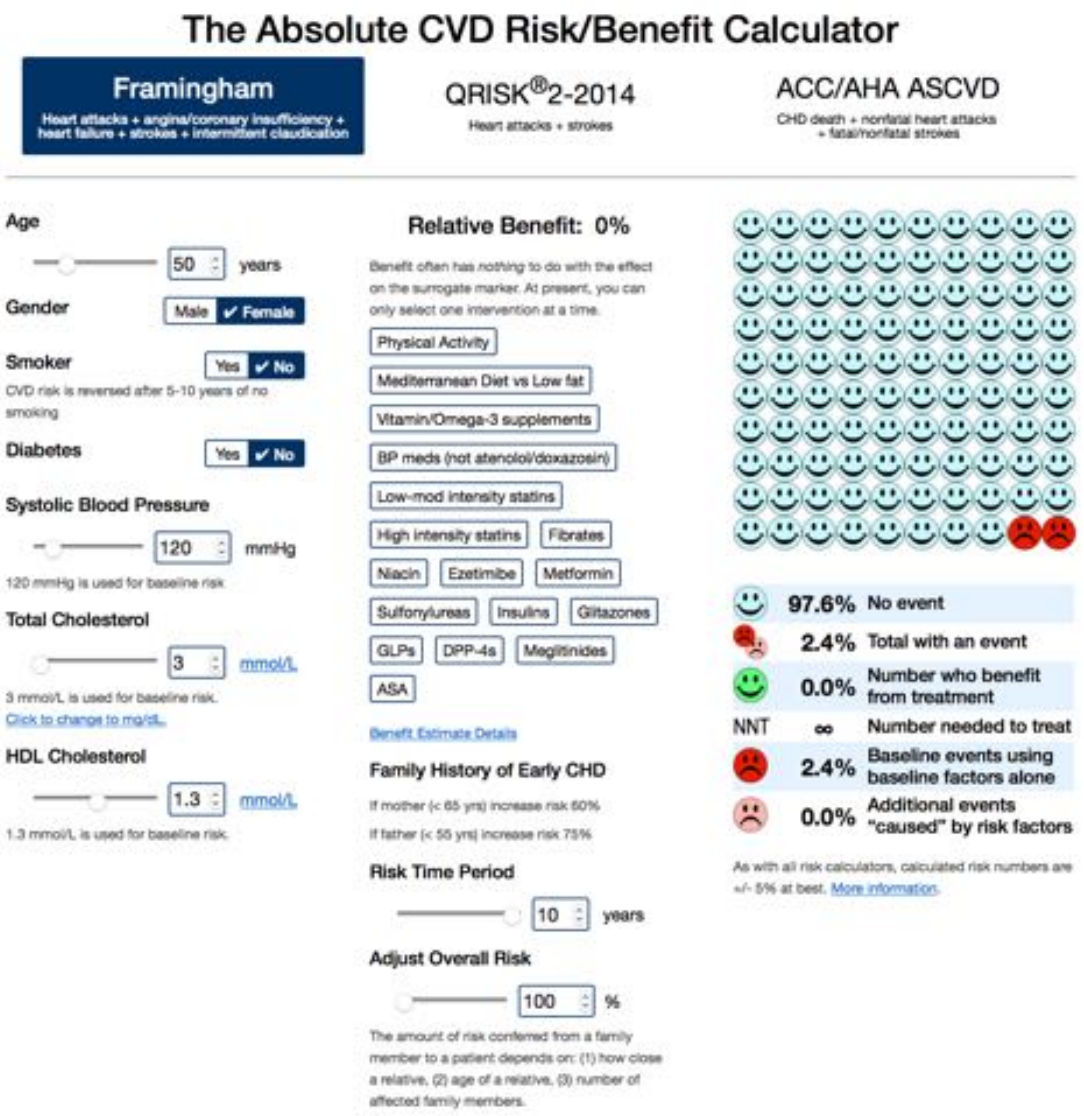
# WHERE DO SUPPOSITORIES FIT IN?


INSERT THE A OR B END FIRST?

A = 83% needed to introduce finger - 3% expulsion

B = 1% needed to introduce finger - 0% expulsion - 98% found this method easier

Lancet 1991;338:798-800




cvdcalculator.com

# Risk: Relative, Absolute & NNT

If you don't know where you start, it's hard to know where you finish

- If you don't know where you start, it's hard to know where you finish.
- Zoster Vaccine reduces shingles up to 70%

Zoster Vaccine reduces shingles up to 70%

| Study | Placebo | Zoster Vac | Benefit | NNT (3 yrs) |
|---|---|---|---|---|
| Age 50-59 (3 yrs) | 2.03% | 0.62% | 1.41% | 71 |
| Age ≥60 (3 yrs) | 3.42% | 1.67% | 1.75% | 58 |

Bottom-Line: Over 3 years, one in 60-70 patients will avoid shingles due to the vaccine

- One in 350 for post-herpetic neuralgia

Tools for Practice Nov 12, 2012

# New and improved

vs

# Unsafe/withdrawn

# The last decade (2000s)

Drugs considered to provide substantial improvements (PMPRB)

**19**

Drugs removed from the market (FDA etc)

Xigris - for severe sepsis

**23**

Just became one of these

# 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*

# 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

NEWER IS RARELY BETTER - WAIT 5 YEARS

SURROGATES CAN BREAK YOUR HEART

VERY HIGH IS BAD BUT AGGRESSIVE LOWERING RARELY SEEMS TO DO MUCH

COLLATERAL DAMAGE CAN COME FROM SHOOTING AT TARGETS

LEAVE PHYSIOLOGICAL MECHANISMS TO PHYSIOLOGISTS

START WITH VERY LOW DOSES

MEASUREMENT OBSESSION

RECONSIDER HOW YOU USE "RISKY" WORDS

9. HEALTHY SKEPTICISM AND BASIC CRITICAL APPRAISAL SKILLS ARE ESSENTIAL FOR STUDENTS/PRACTITIONERS