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Objectives

To be smarter than you are now

To become a healthy skeptic/enhance your degree of healthy skepticism

To be able to describe what the term evidence-based healthcare means and why it is an essential concept for clinical practice

To be able to describe what ARR, RR, and NNT mean and describe why you need to understand these concepts to make clinical decisions

For most treatments, start off with very low doses

We are knowledge brokers

antibiotics

thiazides

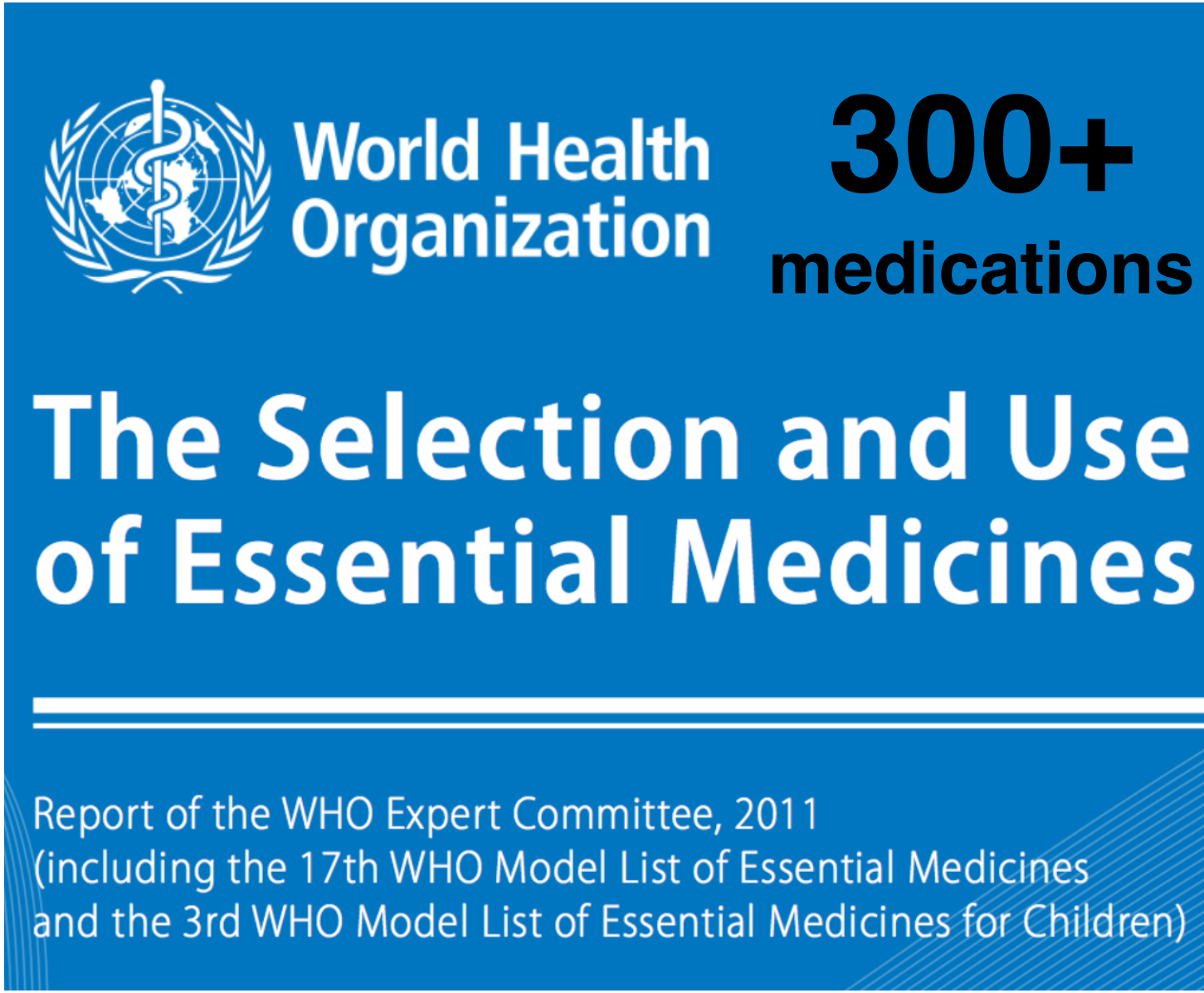
many vaccines

ACE inhibitors

proton pump inhibitors

H2 receptor antagonists

contraceptives



corticosteroids

narcotics

beta-agonists

anesthetics

warfarin

chemotherapy

insulin

adrenalin

What is (methodological) skepticism?

A method of searching for knowledge.

Skeptics neither accept nor dismiss beliefs without evidence.

Skeptics use doubt to assess the strength of the evidence for/against a belief.

Skeptics take a (provisional) stand regarding the truth of a claim only after a fair assessment of the evidence.

Evidence Based Medicine/ Healthcare

"The judicious and conscientious use of current best evidence from research, in making decisions about the health care of individuals and populations.“

Haynes 1995

Critical Appraisal

"Critical appraisal is the process of carefully and systematically examining research to judge its trustworthiness, and its value and relevance in a particular context"

“That which can be asserted without evidence, can be dismissed without evidence.”

Christopher Hitchens

Most new things aren’t much or any better

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

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

Golden Pill Award

PRESCRIRE AWARDS

	Major therapeutic advance	Clear advantage	Modest improvement
2011	0	0	0
2012	0	0	2 **abiraterone (prostate CA)** **boceprevir (Hep C)**
2013	0	0	1 **meningococcal conjugate vaccine (infant**
2014	1 **cholic acid (hereditary bile acid deficiency)**	3 **imatinib (ALL** **artesunate (malaria)** **sofosbuvir (HepC)**	1 **sodium phenylbutyrate coated granules (urea cycle disorders)**

Many therapies "work"

Antibiotics for moderate to severe cellulitis
Beta-agonists for asthma symptoms
Steroid cream for eczema
Opioids for acute and chronic pain
Acetaminophen for osteoarthritis??????
Diuretics for heart failure symptoms
Antibiotics for pneumonia
Antivirals for HIV
Betablockers for migraine
Adrenalin for anaphylaxis

These are primarily symptomatic conditions

BUT WHAT ABOUT "PREVENTIVE" THERAPIES

Evidence ≠ Decisions

Synthesis of the Evidence

+

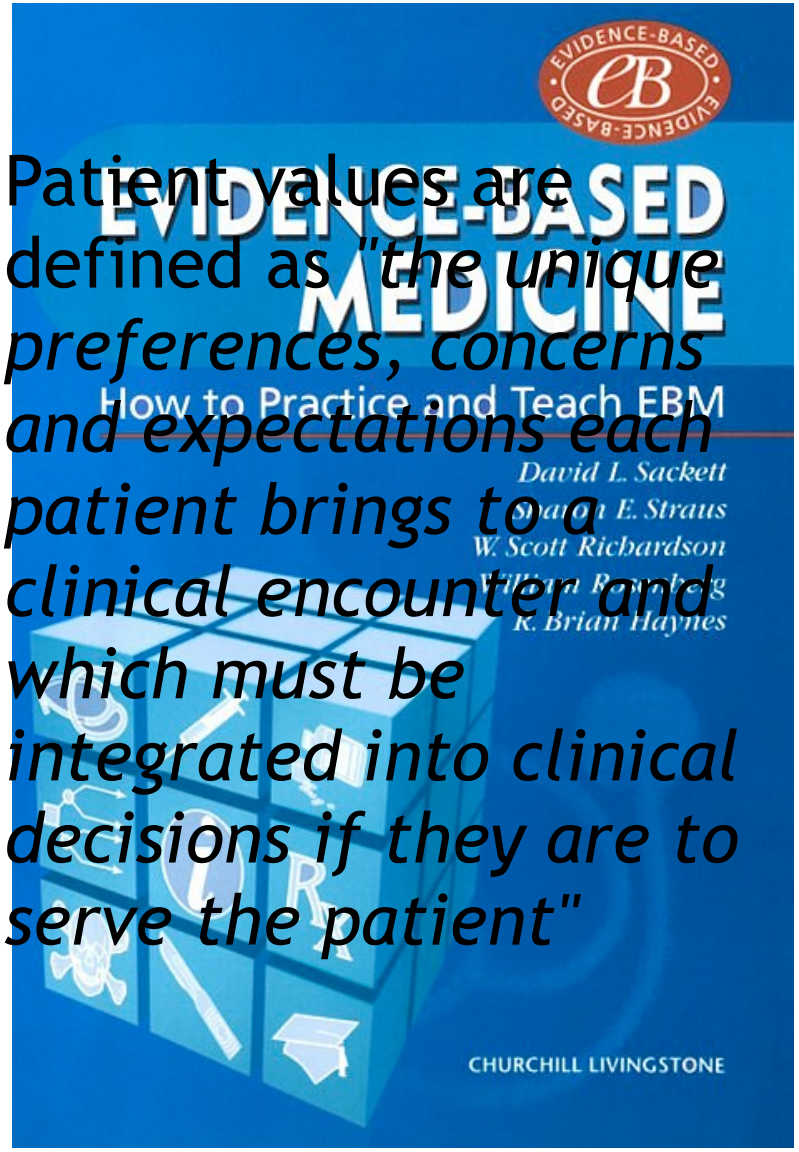
All other considerations

(Patient and Clinician)

=

Decision

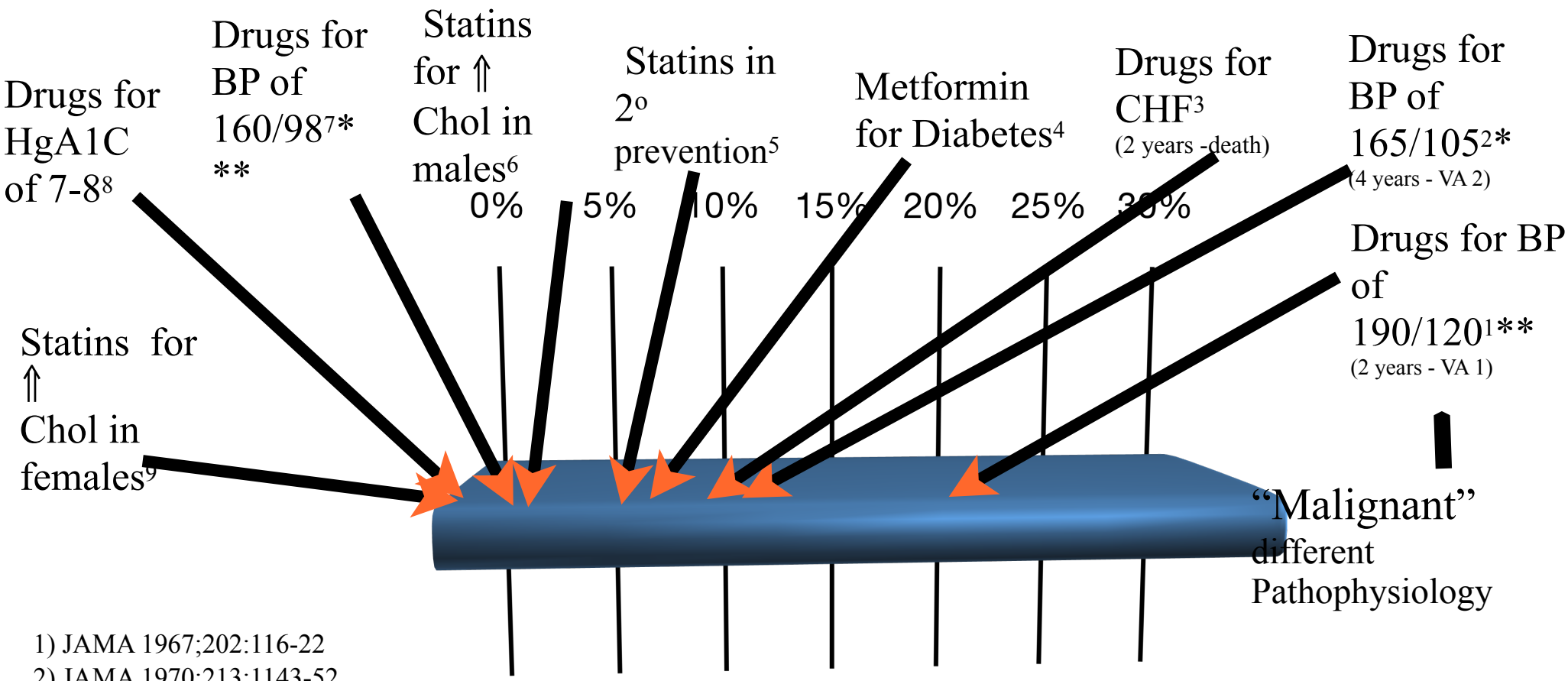
Accommodate the different values and preferences of patients



Patient values are defined as *"the unique preferences, concerns and expectations each patient brings to a clinical encounter and which must be integrated into clinical decisions if they are to serve the patient"*

Evidence-based medicine has been defined as "*the integration of best research evidence with clinical expertise and patient values*"

Examples of Absolute risk reduction over 5 years



1) JAMA 1967;202:116-22
2) JAMA 1970;213:1143-52
3) New Engl J Med 1999;341:709-17
4) UKPDS 34
5,6) Lancet 2008;371:117-25, Br J Clin Phar 2004;57:640-51, Lancet 2004;364:685–96
7) www.ti.ubc.ca/letter62
8) N Engl J Med 2008 358:2545-59, N Engl J Med 2008 358:2560-72, N Engl J Med 2009;360:129-39
9) JAMA 2004;291:2243-52, www.ti.ubc.ca/letter48

* 30/20 reduction - 3 drugs
** 40/30 reduction - 3 drugs definition of endpoint issues
***10/5 reduction - 1 drug

Statin results in patients (45-60) without cardiac disease – 5-7 years treatment

	CHD deaths (%)	All deaths (%)	Coronary events (%)
Placebo	1.4	4.1	5
Statins	0.9	3.7	3.3
Relative risk reduction	35	NSS	35
Absolute risk reduction	0.5		1.7
Number needed to treat	200		59

(ACAPS,WOSCOPS,AFCAPS/TexCAPS) BMJ 2000;321:983-6

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: The Surrogate Heart

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

NEJM 1989;321:406-12

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%

Surrogates: The Never-ending Consistently Inconsistent Story

The Marker	The Treatment
HDL	Torcetrapib[1] LDL down, HDL up 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

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

Risk MARKERS - lots

(risk assessment)

vs

Risk FACTORS - few -

(treat)

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

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	
TC/HDL-C >5.0	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%		

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"

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%

Overdiagnosis/overtreatment

=

the diagnosis/treatment of a condition which a person fully informed by the best available evidence would not want.

Crunching the Numbers

N Engl J Med

	≥ 2 major risk factors		≥ 1major risk factors	
	Men	Wome	Men	Wome
Baseline lifetime risk of cardiovascular disease (%)	50	35	35	25
Risk % if treat 3 factors and each one provides a 25% (1 risk factor)	21 (38)	15 (26)	15 (26)	11 (19)
% who benefit = baseline risk minus treated risk	29 (12)	20 (9)	20 (9)	14 (6)
% who will **NEVER** benefit from a lifetime of treatment	71 (88)	80 (91)	80 (91)	86 (94)

Major risk factors include being a current smoker or having diabetes, having treated hypercholesterolemia, having an untreated total cholesterol level of at least 240/6.2, or having treated hypertension, untreated systolic blood pressure of at least 160 mm Hg, or untreated diastolic blood pressure of at least 100 mm Hg.

Size really does matter

CMAJ

ANALYSIS

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

CMAJ, January 11, 2011

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