MYTHS

FACTS

Objectives - for now

To be smarter than you are now

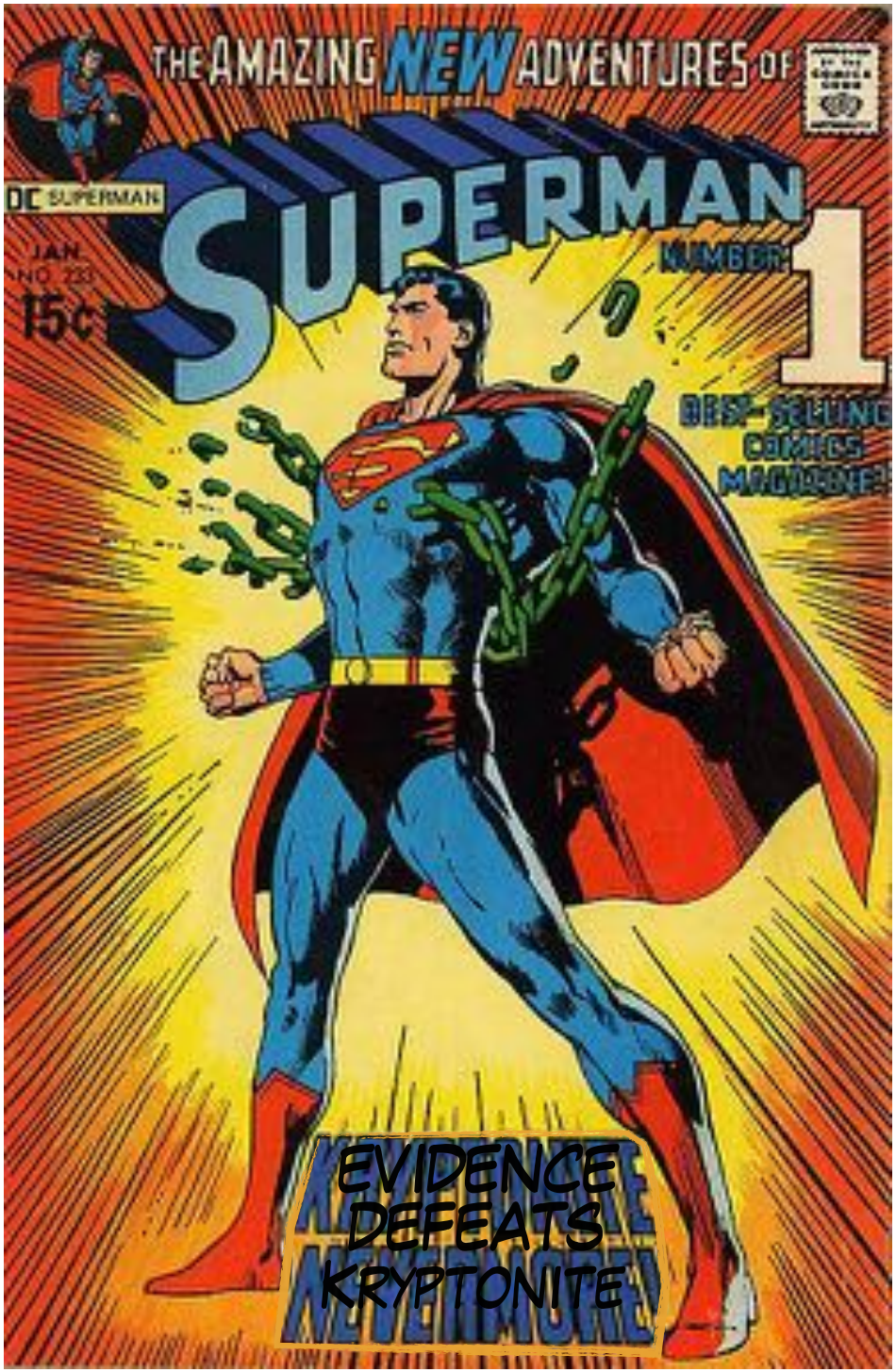
To become a healthy skeptic/enhance your degree of healthy skepticism

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

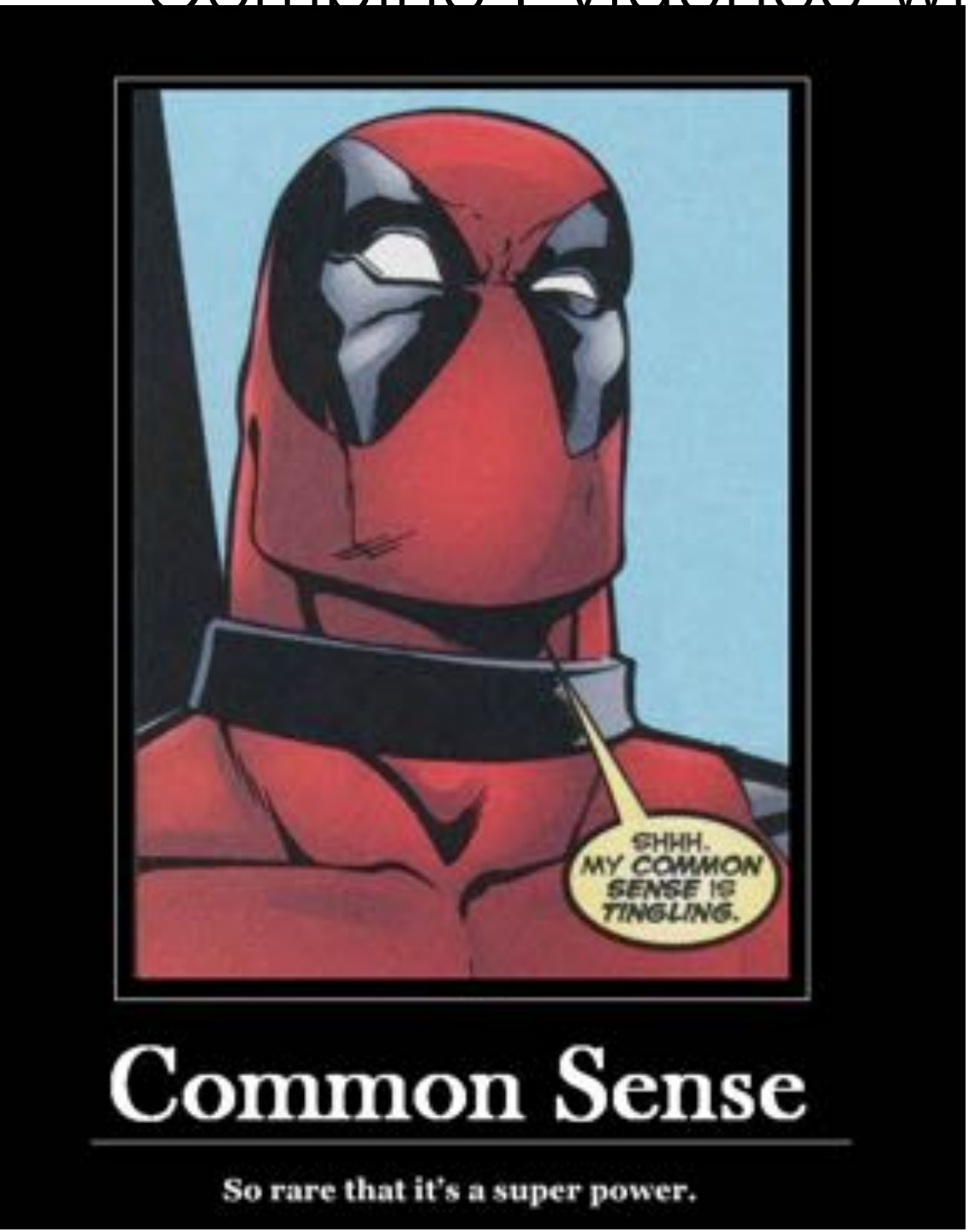
To be able to describe what ARR, RR, NNT, OR, HR and CI mean and describe why you need to understand these concepts to make clinical decisions

To be able to critically appraise an RCT in 10 minutes


EVIDENCE


THE AMAZING NEW ADVENTURES OF
SUPERMAN
NUMBER 1
DC SUPERMAN
JAN.
15¢
EVIDENCE DEFEATS KRYPTONITE!

Combine Evidence with Common Sense



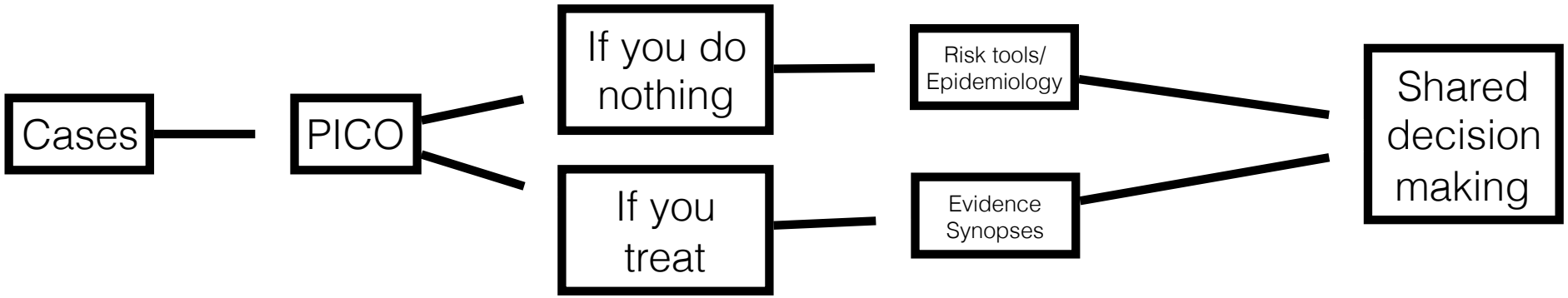
"So rare that it's a super power"

Best Available Evidence

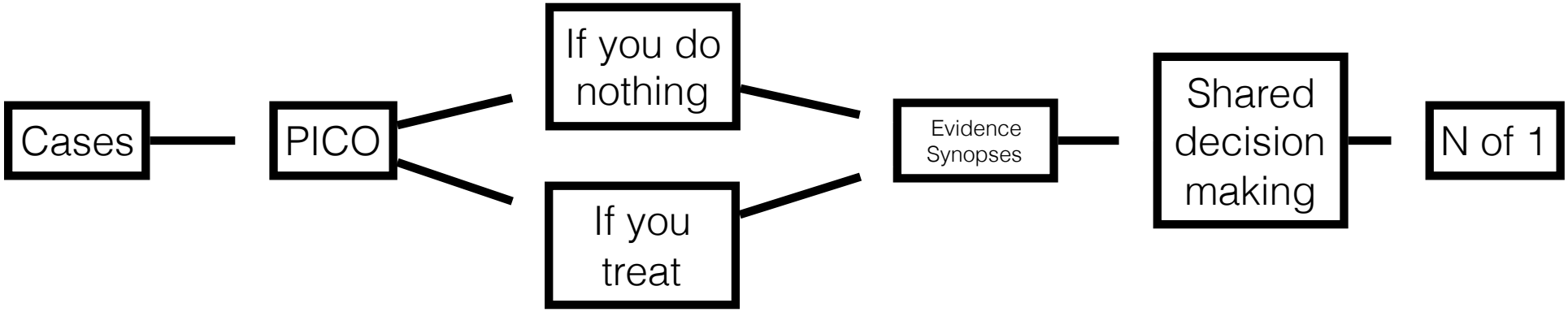
End of Term 1
4 hours

Intro to evidence/numbers/critical appraisal/PICO
how evidence will be used throughout the program

Reducing risk



Reducing symptoms



Initially “we” will provide this information

Later “you” will create this information

EBP

Evidence-Based Practice

Evidence Based Practice

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

Haynes 1995

Best Available Evidence

Knowing the best available evidence is…

rewarding

interesting

enjoyable

empowering

fun

Evidence Based Medicine/ Healthcare

“The search engine is now as essential as the stethoscope”

“Individual practitioners therefore need to be able to find and use evidence themselves—a 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system.”

BMJ 2008;337:704–705


Evaluating Evidence Use
Evidence-based Practice
Applying Evidence to Practice
Appraising Evidence
Searching for Evidences
Formulating Your Clinical Question

Relevant and useful information

I JUST KNOW

A lot of bullshit

Systematic review/
meta-analysis

RCT

Cohort

Case Control

Case Report

“Expert” Opinion

BEST AVAILABLE EVIDENCE PYRAMID

Which is either
purposeful
based in ignorance

Need different evidence for different questions

Relevant and useful information

A lot of bullshit

Making decisions is tricky

when you are missing
a lot of the pieces

Making decisions is tricky even when you have most of the pieces

Preferences

Values

Context

antibiotics

thiazides

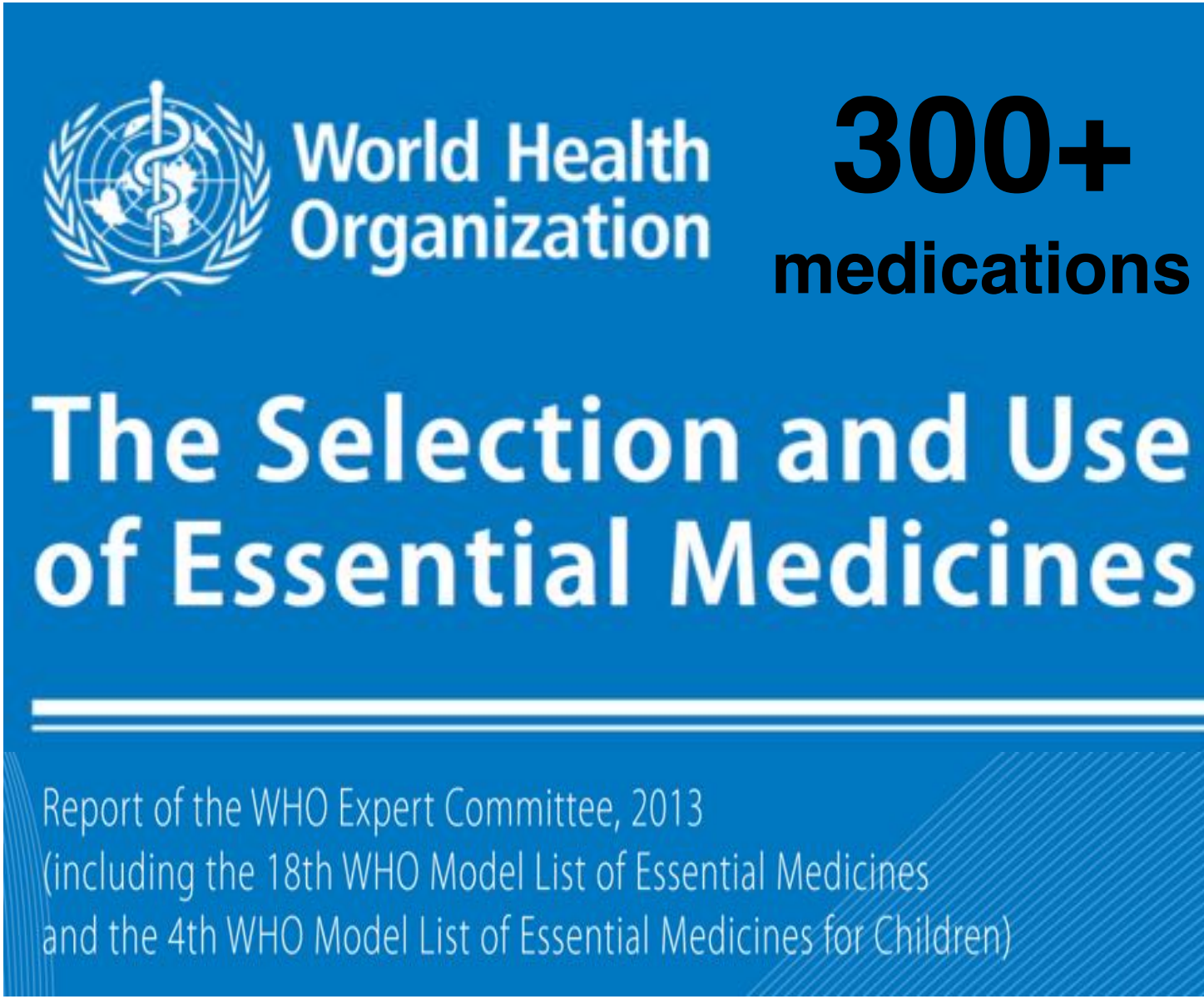
many vaccines

ACE inhibitors

proton pump inhibitors

H2 receptor antagonists

contraceptives



corticosteroids

narcotics

beta-agonists

anesthetics

warfarin

chemotherapy

insulin

adrenalin

Skepticism versus Cynicism

The core of skepticism is DOUBT

The core of cynicism is MISTRUST

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.

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

Became one of these

PRESCRIRE AWARDS

Golden Pill Award

	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 immunization)**
2014	1 **cholic acid (hereditary bile acid deficiency)**	3 **imatinib (ALL** **artesunate (malaria)** **sofosbuvir (HepC) conjugate vaccine (infant immunization)**	1 **sodium phenylbutyrate coated granules (urea cycle disorders)**
2015	0	0	2 **permethrin (scabies)** **ketoconazole HRA (endogenous Cushing's syndrome)**

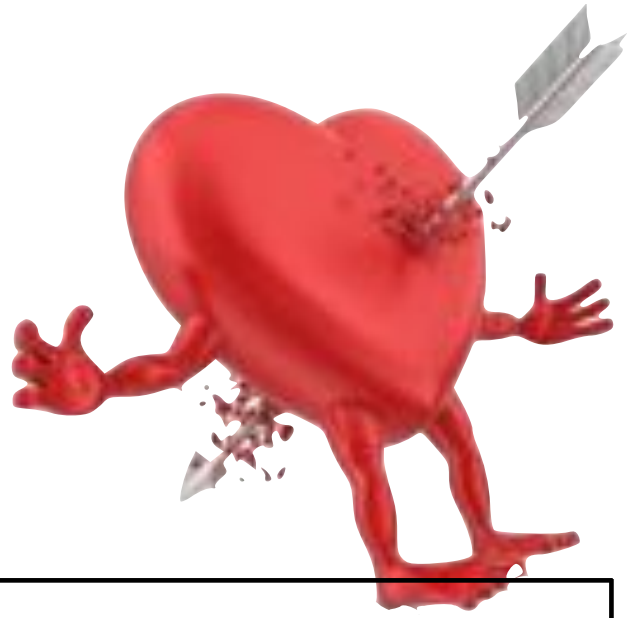
Many therapies “work”

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

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 LDL down, HDL up CVD & mortality up
LDL Trigly BP	Niacin, Ezetimibe Fibrates 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

Risk of future illness
CVD risk/benefit

(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

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)

FINALLY!!!!!!

EMPA-REG OUTCOME (empagliflozin) -1.6% ARR over 3 years

SPRINT (120mmHg vs 140mmHg) -1.6% ARR over 3 years

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

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%

Evidence ≠ Decisions

Synthesis of the Evidence
+
All other considerations

(Patient and Clinician)

=

Decision

Be Wary of the “Relatives”

Anyone who says that “an event” was reduced by a number greater than 10% is almost always talking about a relative reduction

Numbers greater than 10% are misleading unless they are put into the proper context

Relative reduction

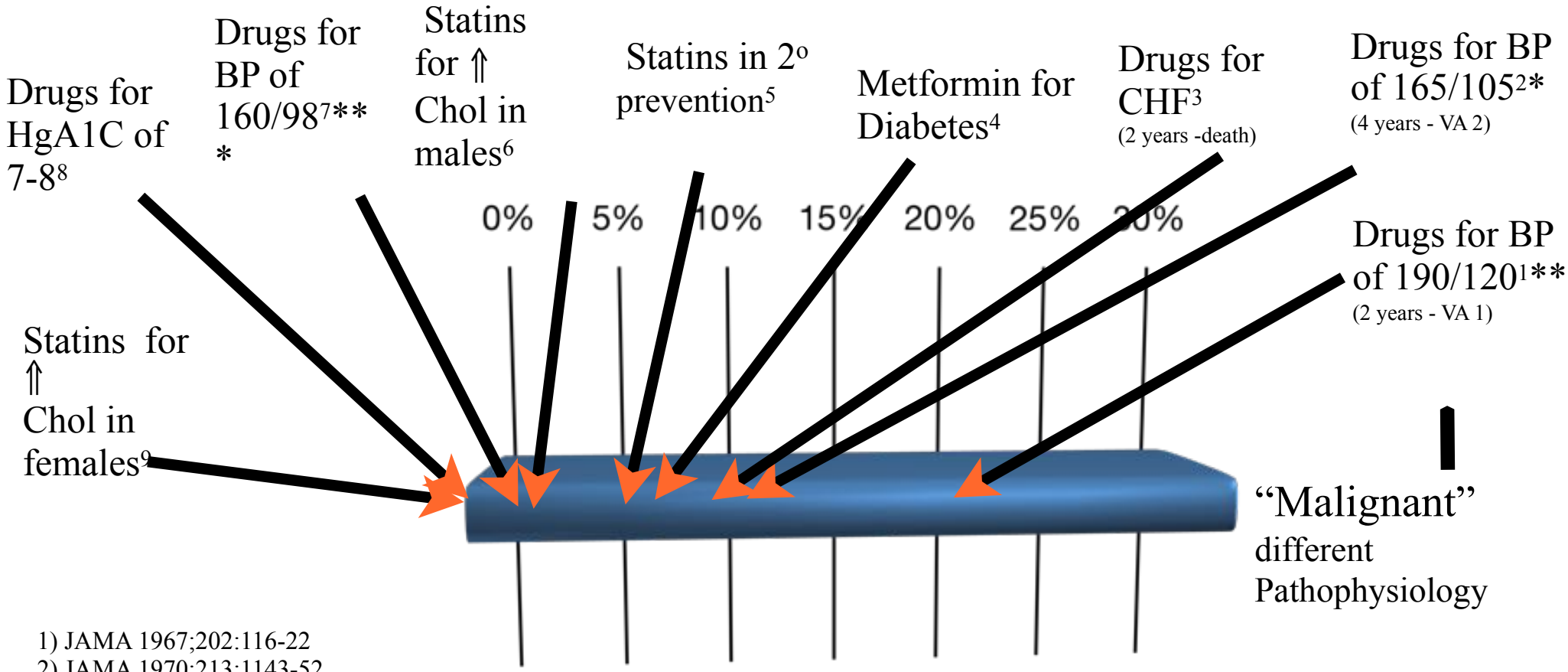
A 33% Reduction Can Mean "Events" Were Reduced From:

BASELINE	CHANGED TO	ABSOLUTE REDUCTION	NNT
3/million	2/million	1/million	1,000,000
0.3 %	0.2 %	0.1%	1000
3 %	2 %	1%	100
6 %	4 %	2%	50
30 %	20 %	10%	10
100 %	67 %	33%	3

Describing Benefits

The chance of "X"
WITH NO TREATMENT
The chance of "X"
WITH TREATMENT

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

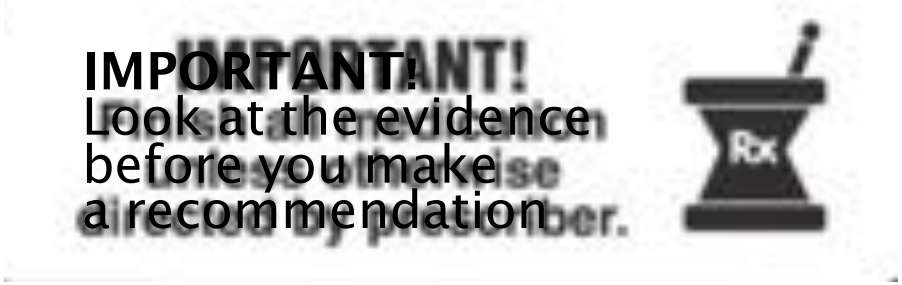
* 30/20 reduction - 3 drugs
** 40/30 reduction - 3 drugs definition of endpoint issues
***10/5 reduction - 1 drug

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



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

James McCormack professor , G Michael Allan associate professor

BMJ 2012;344:d7955 doi: 10.1136/bmj.d7955 (Published 2 February 2012)

"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"

BMJ 2012;344:d7955 doi: 10.1136/bmj.d7955 (Published 2 February 2012)

WHERE DO SUPPOSITORIES FIT IN?

NSERT 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