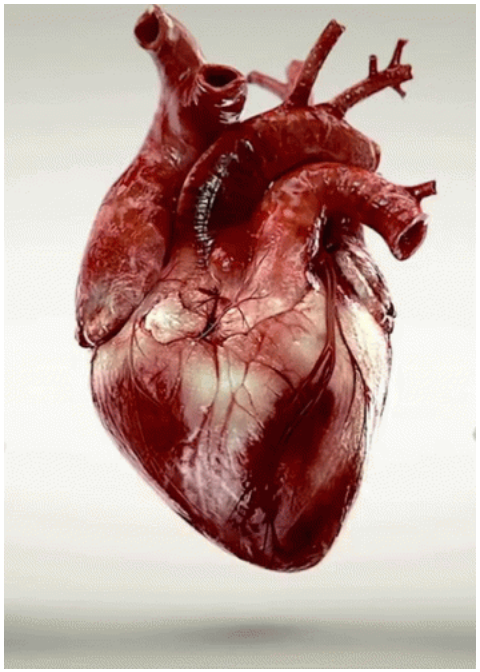
All the evidence you need when it comes to cardiovascular risk reduction

It's Just a Numbers Game And So Much More



James McCormack, BSc (Pharm), PharmD
Professor, Faculty of Pharmaceutical Sciences,
University of British Columbia, Vancouver, BC


RISK

Risk definitions…

Risk markers - associated with a bad outcome - 100s

Risk factors - potentially modifiable risk markers ~5

Risk behaviors - smoking, nutrition, activity

Risk of disease - CVD, MI, strokes, blindness, ESRD

Risk of treatment - harms, costs

Risk of overdiagnosis - inconvenience, labelling, worry

Risk Factors versus Clinical Endpoints

"a risk factor/marker is a variable associated with an increased risk of disease"

Not As Important	Very Important
blood pressure	symptoms
cholesterol	heart attacks
glucose/diabetes	strokes
bone density	heart failure
heart rate	death
CRP	dialysis
proteinuria	amputation
family history	fractures
age	blindness
gender	revascularization
race	angina
FEV1	TIAs

“Non-traditional” Risk Factors

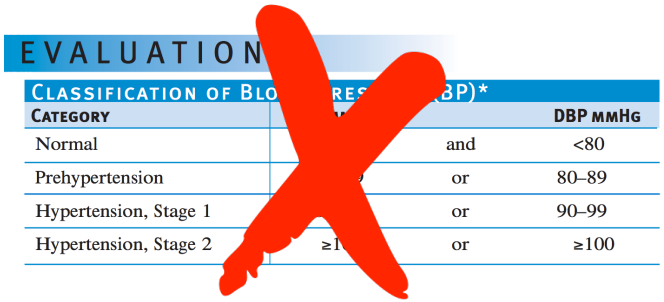
C-reactive protein
ankle–brachial index
leukocyte count
fasting blood glucose
periodontal disease
carotid intima–media thickness
homocysteine
lipoprotein(a)
coronary artery calcification score on CT

“There is at present no place for adding additional risk factors to the present risk prediction models”
Circulation 2013;127:1948–56

“There remains scant information on the incremental value of nontraditional risk factors to help with the problem of miscalibration of traditional cardiovascular risk assessment”
USPSTF Jan 2018

This one might have some use

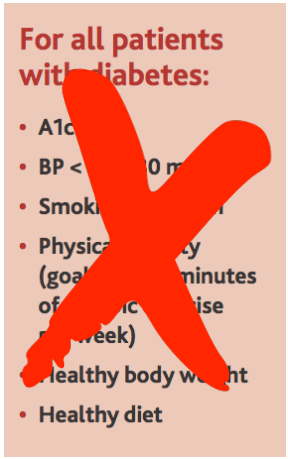
USPSTF. Ann Intern Med 2009;151:474-82



EVALUATION

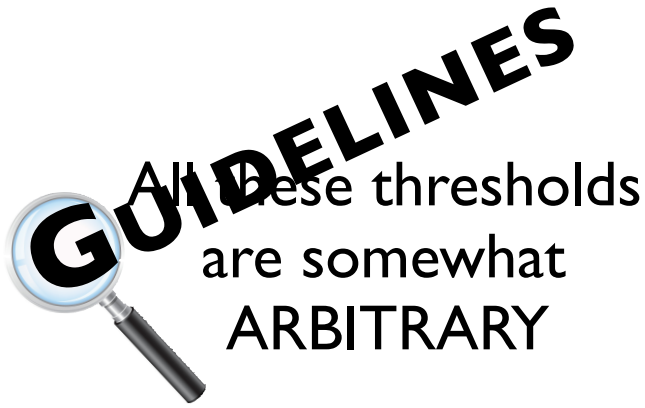
CLASSIFICATION OF BLO… RES… (BP)*

CATEGORY			DBP MMHG
Normal		and	<80
Prehypertension		or	80–89
Hypertension, Stage 1		or	90–99
Hypertension, Stage 2	≥1	or	≥100



For all patients with diabetes:

- A1c
- BP <
- Smoki
- Physica y (goa minutes of ise week)
- Healthy body w ht
- Healthy diet



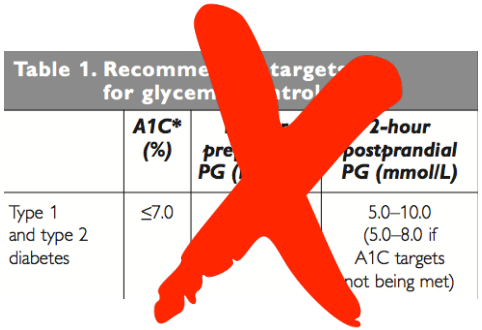
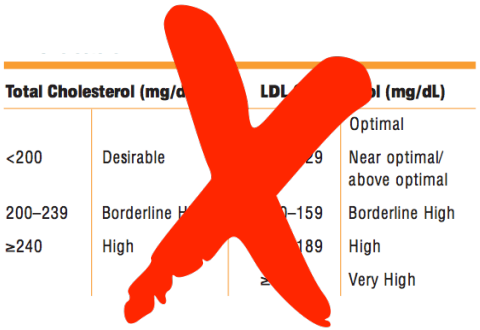


Table 1. Recomme… target… for glycem… ntrol

	A1C* (%)	pre… PG (…	2-hour postprandial PG (mmol/L)
Type 1 and type 2 diabetes	≤7.0		5.0–10.0 (5.0–8.0 if A1C targets not being met)



Total Cholesterol (mg/d…		LDL…	…l (mg/dL)
			Optimal
<200	Desirable	…29	Near optimal/ above optimal
200–239	Borderline H…	…–159	Borderline High
≥240	High	…189	High
		≥…	Very High

Major Medical Associations Feud Over Diabetes Guidelines

March 5, 2018 · 5:01 PM ET

CLINICAL GUIDELINES | 6 MARCH 2018

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

"Clinicians should aim to achieve an HbA1c level **between 7% and 8% in most patients** with type 2 diabetes"

Because of harms - primarily internists

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2018 EXECUTIVE SUMMARY*

"**An A1C level of ≤6.5% is considered optimal** if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time."

Because of benefits - primarily endocrinologists

Guideline Differences	American College of Cardiology/American Heart Association (ACC/AHA)			European Society of Cardiology/European Society of Hypertension (ESC/ESH)		
Level of blood pressure (BP) defining hypertension	Systolic (mm Hg)	and/or	Diastolic (mm Hg)	Systolic (mm Hg)	and/or	Diastolic (mm Hg)
Office/Clinic BP	≥ 130		≥ 80	≥ 140		≥ 90
Daytime mean	≥ 130		≥ 80	≥ 135		≥ 85
Nighttime mean	≥ 110		≥ 65	≥ 120		≥ 70
24-hour mean	≥ 125		≥ 75	≥ 130		≥ 80
Home BP mean	≥ 130		≥ 80	≥ 135		≥ 85
BP targets for treatment	< 130/80 mm Hg			Systolic targets < 140 mm Hg and close to 130 mm Hg		
Initial Combination Therapy	Initial single-pill combination therapy in patients > 20/10 mm Hg above BP goal			Initial single-pill combination therapy in patients ≥ 140/90 mm Hg		
Hypertensive requiring intervention	> 130/80 mm Hg			≥ 140/90 mm Hg		

JACC 2019;73:3018–26

Treatment thresholds are rather arbitrary

Not based on patient preferences

Not based on cost/benefit

Seem to be primarily emotionally-based

20 "NEGATIVE" STUDIES IN A ROW

From 2008-2015

LIPIDS

AIM-HIGH, HPS2-THRIVE (niacin)

ACCORD (fibrates)

dalOUTCOMES (dalcetrapib)

STABILITY (darapladib)

DIABETES

ACCORD, ADVANCE, VADT

(aggressive A1c lowering)

ROADMAP (olmesartan)

ORIGIN (insulin)

SAVOR-TIMI 53 (saxagliptin)

EXAMINE (alogliptin)

ALECARDIO (aleglitazar)

BLOOD PRESSURE

ALTITUDE (aliskiren)

VALISH, AASK, ACCORD

(aggressive BP lowering)

GENERAL

ACTIVE (irbesartan/afib)

CRESCENDO (rimonabant)

VISTA-16 (varespladib)

182,000+ patients

FINALLY, STARTING IN 2015…

1) EMPA-REG OUTCOME (empagliflozin) ~1.5% ARR (CVD) over 3 years
2) LEADER (liraglutide) ~ 2.5% ARR over 4 years
3) SPRINT (120mmHg vs 140mmHg) ~ 1.5% ARR (CVD) over 3 years but also ~1.5% ARI (Kidney)
4) HOPE 3 (statins) YES, BUT blood pressure no benefit
5) FOURIER (evolocumab) ~1.5% ARR over 2 years BUT $15,000/year
6) DECLARE-TIMI 58 (dapagliflozin) ~1% ARR (CVD) over 4 years
7) HARMONY (albiglutide) ~ 2% ARR (CVD) over 2.5 years

BUT!!!!!

ACCELERATE (evacetrapib) - ⇧ HDL (130%), ⇩ LDL (40%) - no CVD benefit
TECOS (sitagliptin) - no benefit over 3 years - 0.5% ARI (diabetic eye diseae)
CARMELINA - (linagliptin) - no benefit over 2 years

Evidence Issues That Influence My Thoughts

Many well designed trials show that just because a treatment ⬇ a risk factor doesn't guarantee that CVD risk will by necessity be ⬇

In fact, there are a number of trials where the risk factor is ⬇ but CVD risk goes ⬆

Therefore, without well-designed trials it is very much unknown what impact these treatments will have on CVD risk

Conditions requiring risk assessment

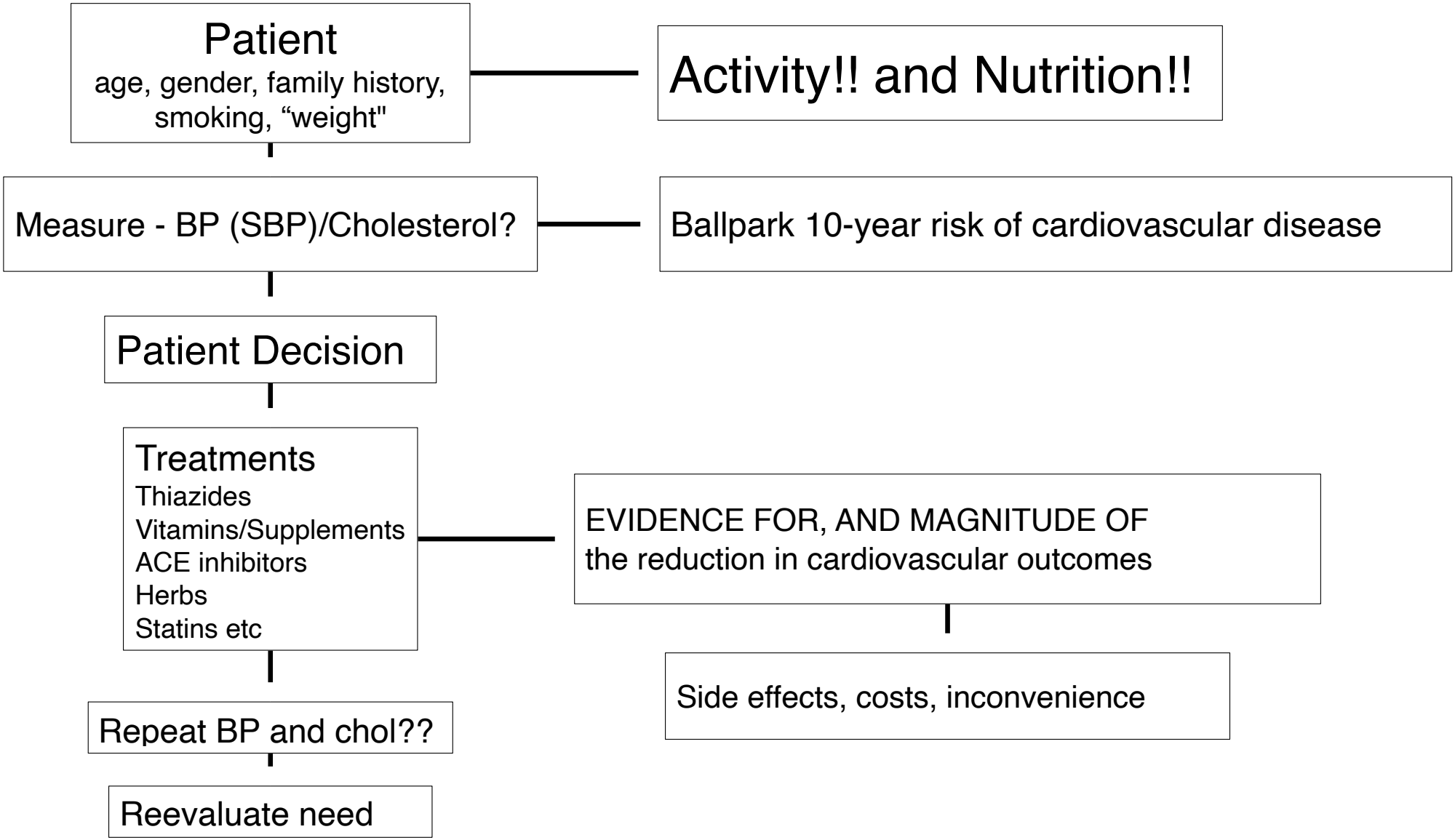
The main ones are hypertension, cholesterol, glucose/ diabetes, atrial fibrillation

Figure out

CVD risk

Potential CVD benefit

Potential harms, costs and inconveniences

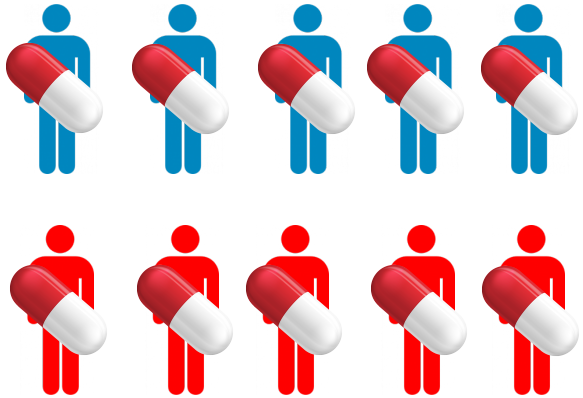

Patient
age, gender, family history, smoking, “weight"
Activity!! and Nutrition!!
Measure - BP (SBP)/Cholesterol?
Ballpark 10-year risk of cardiovascular disease
Patient Decision
Treatments
Thiazides
Vitamins/Supplements
ACE inhibitors
Herbs
Statins etc
EVIDENCE FOR, AND MAGNITUDE OF
the reduction in cardiovascular outcomes
Side effects, costs, inconvenience
Repeat BP and chol??
Reevaluate need

Based on the
best available evidence
(primarily RCTs/MAs - and sometimes cohort data)
here are the CVD numbers
you need to know


Numbers

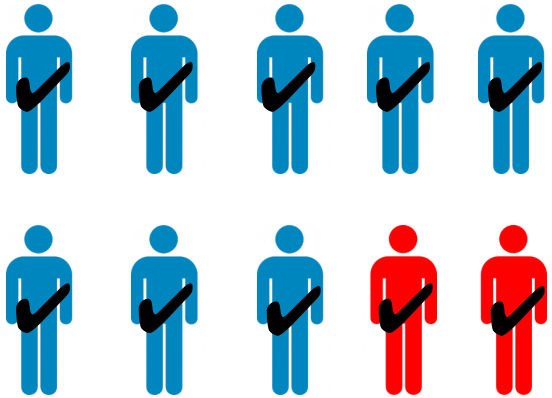
At most, 30% of people will benefit from a lifetime of
CVD risk factor modification - but you have to treat ALL of them - 100%

No CVD



60%

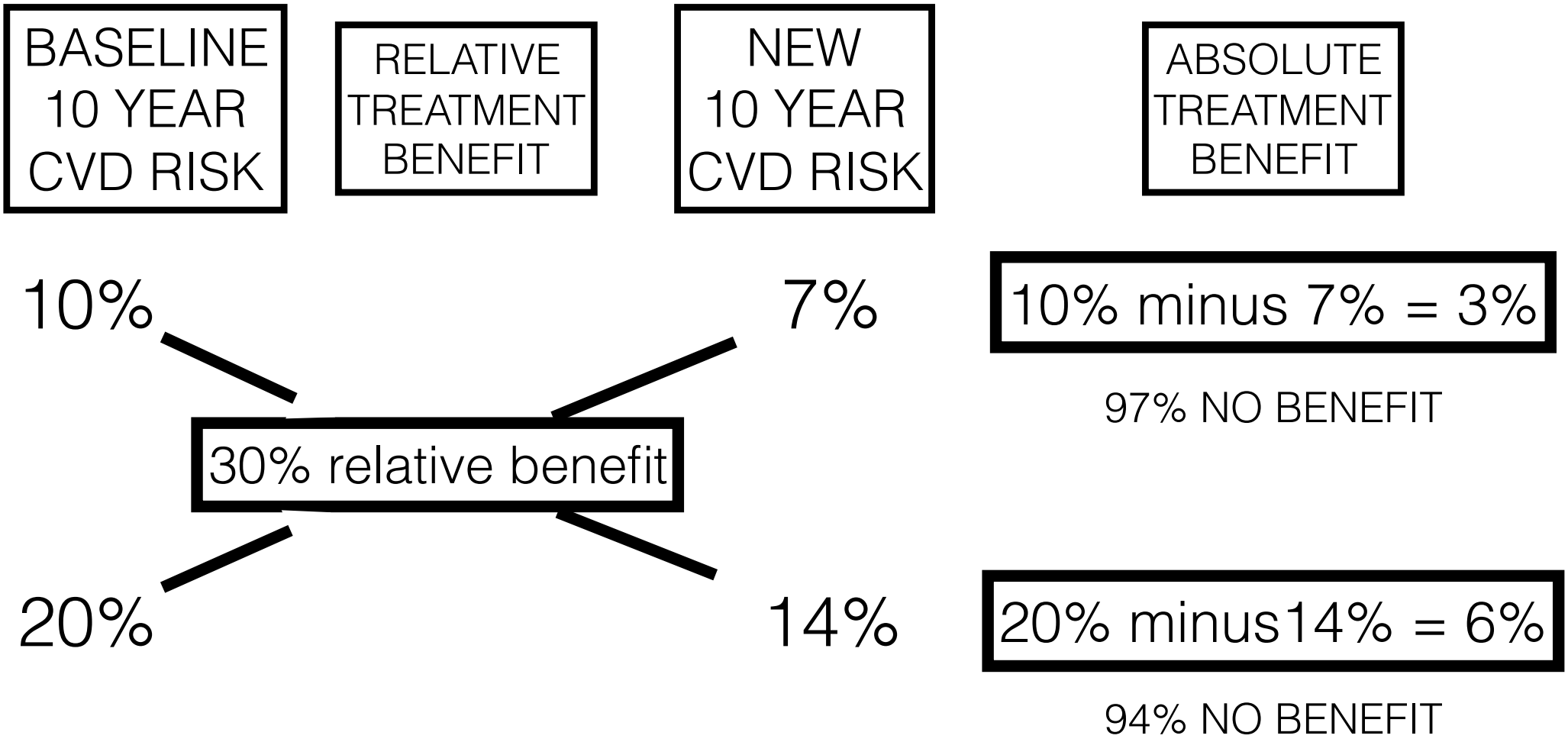
OFF



50% of males with
2 or more risk factors
will develop heart disease
over a lifetime

CVD

3 out of 10 benefit = 30%
7 out of 10 NO benefit = 70%

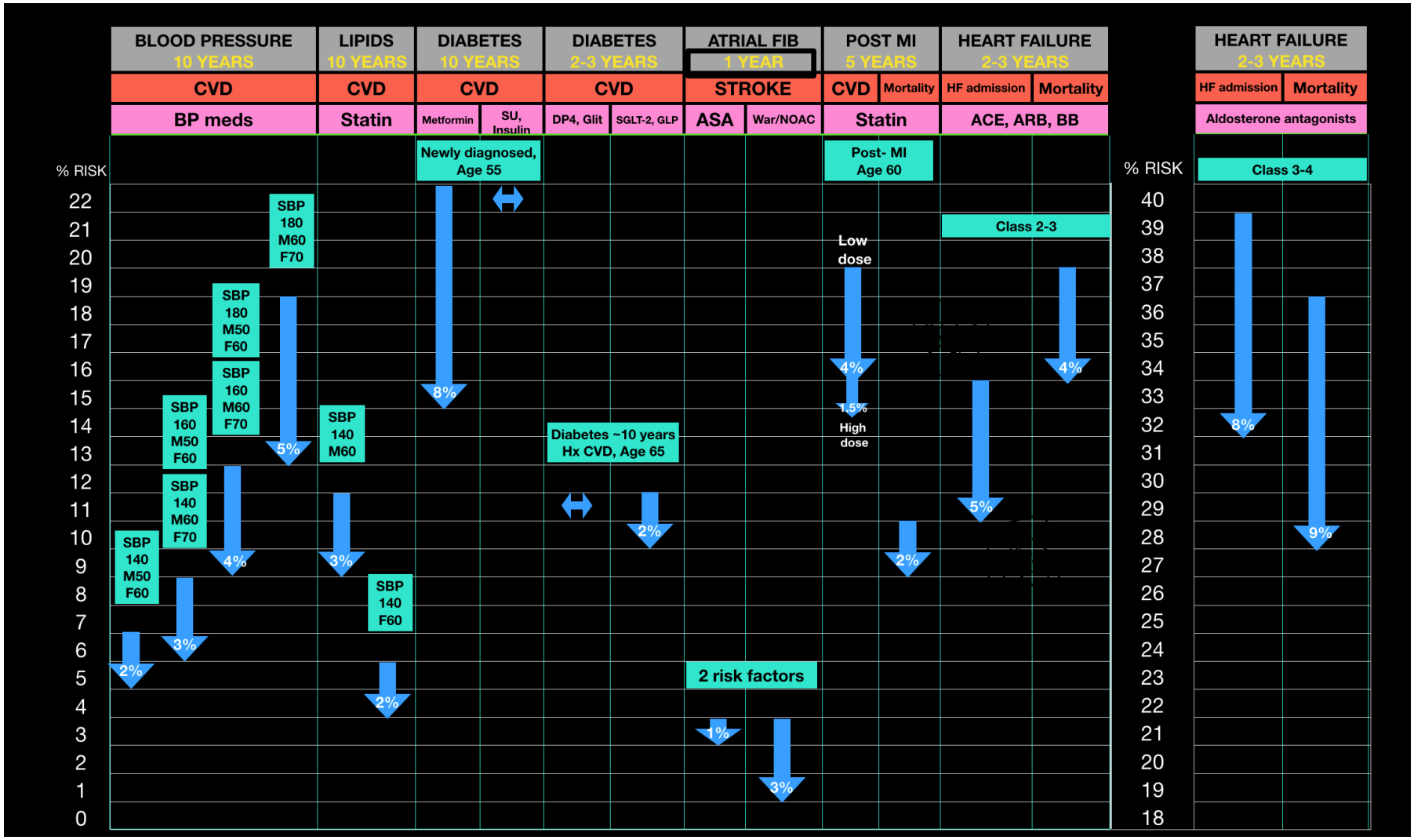

BASELINE 10 YEAR CVD RISK
RELATIVE TREATMENT BENEFIT
NEW 10 YEAR CVD RISK
ABSOLUTE TREATMENT BENEFIT
10%
7%
10% minus 7% = 3%
97% NO BENEFIT
30% relative benefit
20%
14%
20% minus14% = 6%
94% NO BENEFIT

BALLPARK RELATIVE % BENEFITS FOR CARDIOVASCULAR PREVENTATIVE TREATMENTS

	Lifestyle	**Cholesterol**	**Blood pressure**	**Glucose**	**A fib**	**Heart failure**
RRR%	Cardiovascular events				Stroke	Mortality
100	Stopping smoking (obviously no RCTs) CVD but also cancer and lung issues					
95						
90						
85						
80						
75						
70						
65					Warfarin/NOACS	
60						
55						
50			Blood pressure diabetes			
45						
40						
35		Statins		Metformin?		
30	Mediterranean diet		Blood pressure			
25	Physical Activity plus QOL				Aspirin	ACEI, BB, Aldo antag
20						
15		PCSK9 Monoclonal antibodies		SGLT2, GLP		
10		Aspirin				
5		Ezetimibe				
0		Fibrate, niacin		DPP4, SU, insulin, glitazone		

cvdcalculator.com,sparctool.com

BALLPARK ABSOLUTE % BENEFITS FOR PREVENTATIVE TREATMENTS



cvdcalculator.com,sparctool.com

It's all about figuring out

The *Ballpark* Chance
WITH NO TREATMENT

VS

The *Ballpark* Chance
WITH TREATMENT

Oswald Chesterfield Cobblepot
AKA The Penguin
60 years old
Loves birds
Lives a luxurious lifestyle
Relatively inactive
PMH - Conduct disorder
Smoker
A1c 8
BP 150/90 mm/Hg
Total cholesterol 6 (240)
HDL 1 (40)

Languages: English (EN)

The Absolute CVD Risk/Benefit Calculator

Framingham
US Data, 10 Year Risk
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK®2-2014
UK Data, 10 Year Risk
Heart attacks + strokes

ACC/AHA ASCVD
US Data, 10 Year Risk
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

PREDICT
New Zealand Data, 5 Year Risk
Heart attacks + angina + heart failure + strokes/TIAs + peripheral vascular disease

---

Age
50 years

Gender
Male ✔ Female

Smoker
Yes ✔ No
CVD risk is reversed after 5-10 years of no smoking

Diabetes
Yes ✔ No

Systolic Blood Pressure
120 mmHg
Enter present blood pressure regardless of treatment
120 mmHg is used for baseline risk

On treatment for BP
Yes ✔ No
Click YES if taking blood pressure medication
Only applies if SBP is greater than 120 mmHg

Total Cholesterol
3 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
1.3 mmol/L
HDL should be prior to drug treatment

Relative Benefit: 0%

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)
- 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

97.9%		No event
2.1%		Total with an event
0.0%		Number who benefit from treatment
NNT	∞	Number needed to treat
2.1%		Baseline events using baseline factors alone
0.0%		Additional events "caused" by risk factors

As with all risk calculators, calculated risk numbers are +/- 5% at best. More information.

cvdcalculator.com

Bruce Banner
AKA The Hulk
Age 45
Scientist
Easily agitated,
and emotionally withdrawn
SBP 160 mm/Hg
Non-smoker
Non-diabetic
Total cholesterol 4.4 (180)
HDL 1.5 (60)
AM testosterone: 330 nmol/L (N 6.7-29)
Urine catechol: +ve (no urine found)

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 64%

ASCVD (HA, stroke) = 41%

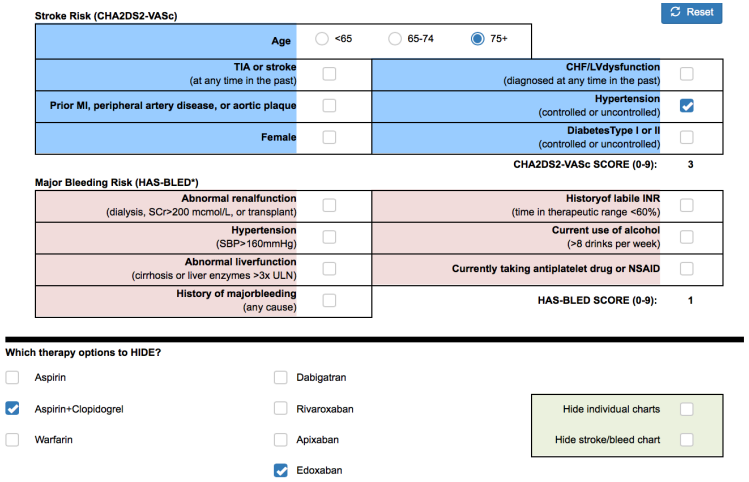
Smoker - stop ~15% absolute
A1c 8 ?
BP 150/90 mm/Hg ~ 30-50% RR
Total cholesterol 6 (240) ~ 25% RR
HDL 1 (40)

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 7%

ASCVD (HA, stroke) = 2%

SBP 160 mm/Hg ~ 30% RR
Non-smoker
Non-diabetic
Total cholesterol 4.4 (180) ~ 25% RR
HDL 1.5 (60)



	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%

http://www.sparctool.com

Type 2 Diabetes

"The disease who must not be named"

Feeling Fatigued or Irritable? There's a 1 in 4 Chance You Suffer from Diabetes...

10 Things You Should Eat If You Are Suffering From Diabetes

It is NOT a disease

It is a RISK Factor

Suffering from diabetes? Here's some good news for you

Suffering from diabetes? Fight it like your favourite B-town celebs

Medication Class	Medication
Insulin	Insulin
Biguanides	Metformin
	Phenformin
Sulfonylureas	Tolbutamide
	Chlorpropamide
	Glyburide/ glibenclamide
	Gliclazide
	Glipizide
	Glimepiride
Glitazones	Rosiglitazone
	Pioglitazone
Meglitinides	Repaglinide
	Nateglinide
Other	Acarbose
	Aleglitazar
GLP's	Exenatide
	Dulaglutide
	Albiglutide
	Lixisenatide
	Liraglutide
	Semaglutide
DPP4's	Sitagliptin
	Saxagliptin
	Linagliptin
	Alogliptin
	Omarigliptin
Gliflozins	Dapagliflozin
	Empagliflozin
	Canagliflozin
	Ertugliflozin

All the large RCTs evaluating the impact of glucose lowering medications on CVD Outcomes

RCTs evaluating the impact of medications on CVD outcomes in T2DM

YEAR	NAME		MEDICATION	RESULT	OUTCOME CHANGED	ABSOLUTE DIFFERENCE/TIME
1970	UGDP	SU	tolbutamide (Orinase)	NEGATIVE	CVD mortality	↑8%/5 years
1971		BG	phenformin (DBI)	NEGATIVE	Mortality	↑ 6%/5-8 years
1976		SU	tolbutamide (Orinase)	NEGATIVE	Fatal MI	↑ 5%/5 years
1982		IN	insulin	NEUTRAL		
1998	UKPDS 33/34	IN,SU	insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL		
1998		IN,SU,BG	metformin, insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL except POSITIVE for metformin	Mortality MI	↓7%/11 years ↓ 6%/11 years
2003	STOP-NIDDM	OTH	acarbose (Precose)	POSITIVE	MI	↓ 1.5%/3 years
2005	PROACTIVE	GLIT	pioglitazone (Actos)	POSITIVE	MI	↓ 1.5%/3 years
2007	RECORD	GLIT	rosiglitazone (Avandia)	NEGATIVE	Heart failure	↑ 1%/4 years
2012	ORIGIN	IN	insulin	NEUTRAL		
2013	EXAMINE	DPP4	alogliptin (Nesina)	NEUTRAL		
2014	SAVOR-TIMI 53	DPP4	saxagliptin (Onglyza)	NEGATIVE	Heart failure	↑ 1%/2 years
2014	ALECARDIO	OTH	aleglitizar	NEUTRAL		
2015	ELIXA	GLP	lixisenatide (Adlyxin)	NEUTRAL		
2015	TECOS	DPP4	sitagliptin (Januvia)	NEUTRAL		
2015	EMPA-REG	GLIF	empagliflozin (Jardiance)	POSITIVE	Mortality Heart failure	↓ 2.5%/3 years ↓ 1.5%/3 years
2016	SUSTAIN 6	GLP	semaglutide (Ozempic)	POSITIVE	Combined outcome	↓ 2%/2 years
2016	LEADER	GLP	liraglutide (Victoza)	POSITIVE	Mortality Combined outcome	↓ 1%/4 years ↓ 2.5%/4 years
2017	CANVAS	GLIF	canagliflozin (Invokana)	POSITIVE	Combined outcome Heart failure Amputations	↓ 2%/3.5years ↓ 1%/3.5 years ↑ 1%/3.5 years
2017	EXSCEL	GLP	exenatide (Byetta)	NEUTRAL		
2017	ACE	OTH	acarbose (Procose)	NEUTRAL		
2017	Omarigliptin	DPP4	omarigliptin	NEUTRAL		
2018	HARMONY	GLP	albiglutide (Tanzeum)	POSITIVE	Combined outcome	↓ 2%/2 years
2018	CARMELINA	DPP4	linagliptin (Tradjenta)	NEUTRAL		
2018	DECLARE-TIMI 58	GLIF	dapagliflozin (Farxiga)	POSITIVE	Combined outcome (primarily heart failure)	↓ 1%/4 years
2019	REWIND	GLP	dulaglutide (Trulicity)	POSITIVE	Combined outcome Renal outcomes	↓ 1.5%/5.4 years ↓ 2.5%/5.4 years
2019	PIONEER 6	GLP (oral)	semaglutide (Ozempic)	POSITIVE	CVD mortality Mortality	↓ 1%/1.5 years ↓ 1.5%/1.5 years
2019	CREDENCE	GLIF	canagliflozin (Invokana)	POSITIVE	Combined CVD outcome Combined renal outcome outcomes	↓ 2.5%/2.6 years ↓ 3%/2.6 years

Overall Evidence for T2DM

THEY ALL LOWERED GLUCOSE

5 trials - increased CVD

11.5 trials - no effect on CVD

11.5 trials - decreased CVD - typically 1-3% absolute reduction in CVD over 2-5 years

Activity

150 minutes of moderate to high intensity exercise per week,
or 30-60 minutes most days of the week (includes brisk walking)

Exercise for secondary prevention (RCTs)

Death at 4 years - NNT= 32

Heart failure admissions at 2 years - NNT = 14

Similar to medications?

Tools for Practice #145

Exercise for primary prevention (Cohorts)

Going from inactivity to current recommendations

CVD - RR = 0.83 (0.77-0.89)

J Am Heart Assoc. 2016;5:e002495 doi: 10.1161/JAHA.115.002495

Exercise for patients with major depression: a systematic review with meta-analysis and trial sequential analysis

Jesper Krogh,[1] Carsten Hjorthøj,[1] Helene Speyer,[1] Christian Gluud,[2] Merete Nordentoft[1]

BMJ Open 2017;7:e014820.

"There is currently no evidence in favour of exercise for patients with depression with a view to ameliorate depressive symptoms"

Low vs high risk for bias issue

Effects of Physical Activity in Knee and Hip Osteoarthritis: A Systematic Umbrella Review

VIRGINIA B. KRAUS[1], KYLE SPROW[2], KENNETH E. POWELL[3], DAVID BUCHNER[4], BONNY BLOODGOOD[4], KATRINA PIERCY[4], STEPHANIE M. GEORGE[4], and WILLIAM E. KRAUS[5], FOR THE 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE*

Medicine & Science in Sports & Exercise 2019;51:1324-39

"Physical activity decreases pain, improves physical function and HRQoL among people with hip and/or knee OA relative to less active adults with OA"

2015 DGAC: MEETING 7 December 15, 2014

Science Base Chapter:

Food and Nutrient Intakes, and Health: Current Status and Trends

Subcommittee 1

health.gov

- Cholesterol is not considered a nutrient of concern for overconsumption.

HOWEVER, THE FINAL REPORT RELEASED IN JANUARY 2016 STATES "individuals should eat as little cholesterol as possible"

Food and Nutrient Intakes, and Health: Current Status and Trends

Annals of Internal Medicine

IDEAS AND OPINIONS

U.S. Dietary Guidelines: An Evidence-Free Zone

2016

Steven E. Nissen, MD

"a detailed review of the new guidelines confirms a disturbing reality: the nearly complete absence of high-quality randomized, controlled clinical trials (RCTs) studying meaningful clinical outcomes for dietary interventions. The report repeatedly makes recommendations based on observational studies and surrogate end points, failing to distinguish between recommendations based on expert consensus rather than high-quality RCTs. Unfortunately, the current and past U.S. dietary guidelines represent a nearly evidence-free zone"

Ann Intern Med doi:10.7326/M16-0035

Secondary prevention

EFFECTS OF CHANGES IN FAT, FISH, AND FIBRE INTAKES ON DEATH AND MYOCARDIAL REINFARCTION: DIET AND REINFARCTION TRIAL (DART)

2033 men post MI randomized to receive/not to receive advice on 3 dietary factors:
- a reduction in fat intake and an increase in the ratio of polyunsaturated to saturated fat
- an increase in fatty fish intake
- an increase in cereal fibre intake

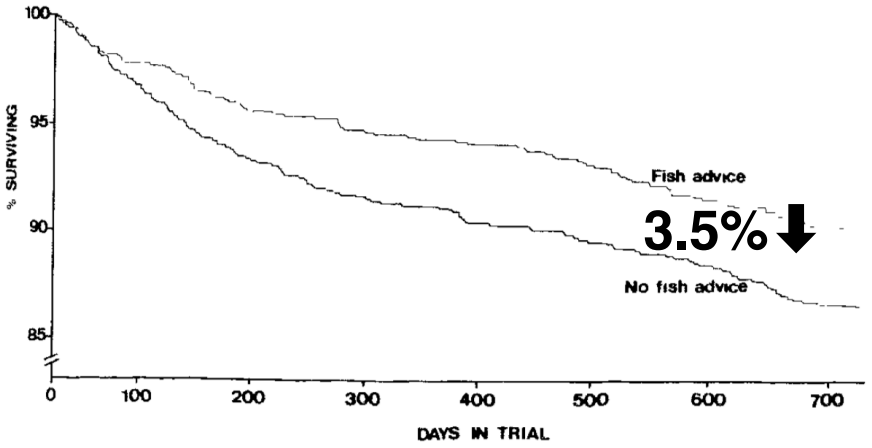


Fig 2—Survival: fish advice.

Fat - no effect

Fibre - no effect

Fish - no effect on CHD but a 29%⬇ in mortality

Lancet 1989;334;757-61

Mediterranean diet in secondary prevention of coronary heart disease - Lyon Diet Heart Study

27 months - 605 patients <age 60 with a previous MI in the last 6 months - 90% male

one group advised in a one-hour session (with a couple of follow ups) to adopt a diet of more bread, more root vegetables, more fish, less beef, lamb and pork (replaced with poultry), no day without fruit; and butter and cream replaced with margarine - also used rapeseed, and olive oils in salad

Results

Weight, cholesterol, lipoproteins and blood pressure were not statistically different between groups

Lancet 1994;343:1454-9

Mediterranean diet in secondary prevention of coronary heart disease

	Total mortality (%)	Cardiovascular deaths (%)	Non-fatal MI's (%)	Total primary endpoints (%)
Dietary intervention	3.5	1.0	1.7	2.6
No dietary intervention	6.6	5.3	5.6	10.9
Relative risk reduction	47	81	NSS	76
Absolute risk reduction	3.1	4.3		8.3
Number needed to treat	32	23		12

Lancet 1994;343:1454-9

Women's Health Initiative Randomized Controlled Dietary Modification Trial - “low fat”

48,835 postmenopausal women (62 y/o) - 4% prev CVD - 8.1 years

1) lower fat intake to 20% of their total calories, and to eat five or more fruit/vegetable servings and six or more grain servings a day

2) asked not to make any dietary changes

led to ~10% reduction in energy from fat and one more serving a day of vegetables/fruit

no statistical difference in CHD, CVD, stroke, breast cancer, colorectal cancer

JAMA 2006;295:629-642, 643-54, 655-66

What Does the PREDIMED Trial Retraction & Reboot Mean for the Mediterranean Diet?

June 2018

PREDIMED Study Retraction and Republication

Retraction and Republication of a Mediterranean Diet Trial

Randomization had gone wrong for ~20% of the participants - 1,588/7,447
If more than one person in a house recruited - all assigned the same diet
Randomization table hadn't been used correctly - 1 site
Clinics randomized instead of people - 1 site

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet PREDIMED - 5 years, 67 y/o, 58% male, 48% T2DM

	Total mortality (%)	Myocardial infarction, stroke, and death from cardiovascular causes (%)	MI (%)	Stroke (%)
Control "Low fat"	5.4	5.7	2.1	3.0
Mediterranean diet - EVOO - 1 liter/week**	4.4	3.6*	1.4	1.7*
Mediterranean diet - NUTS (30 gm of mixed nuts per day)**	5.4	4.0*	1.6	1.5*

**increased weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings)

* statistical different from control
N Engl J Med 2018; 368:1279-90

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Cochrane Library
Cochrane Database of Systematic Reviews

79 RCTs - 112,000 subjects

“Moderate- and high-quality evidence suggests that increasing EPA and DHA has little or no effect on mortality or cardiovascular health (evidence mainly from supplement trials)”

“Low-quality evidence suggests ALA may slightly reduce CVD event risk, CHD mortality and arrhythmia.”

eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) - supplements
alpha-linolenic acid (ALA) - from plants

Cochrane Database of Systematic Reviews 2018 CD003177

REDUCE-IT Icosapent - 5 years

highly purified eicosapentaenoic acid ethyl ester

8179 pts - Icosapent 2gm BID vs placebo

Trig 216 mg/dL, on statin, mean age 64, 71% male, 58% DM, 71% past CVD

Outcome

Trigs - 20% lower - LDL - 7% higher

All CVD: 17.2% vs 22.0%, HR 0.75 (0.68-0.83), NNT 21

Stroke, MI or CVD death: 11.2% vs 14.8%, HR 0.74, NNT 28

Death (all cause): HR 0.87 (0.74-1.02)

AFib: 5.3% vs 3.9%, NNH 72

$2500/year

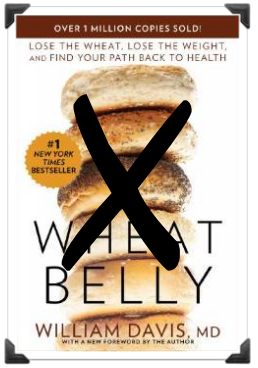
$80,000 to prevent a CVD event

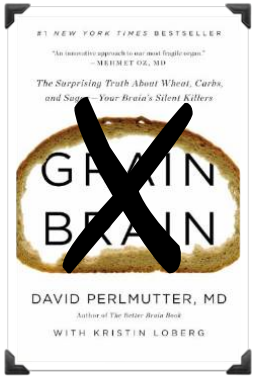
N Engl J Med 2019;380:11-22

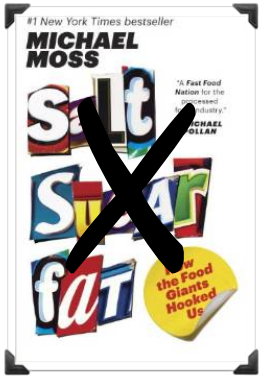
All the evidence around the debate between
Low Fat = <~30% of total energy intake
Low Carb =<~20% of total energy - ketogenic = <10%

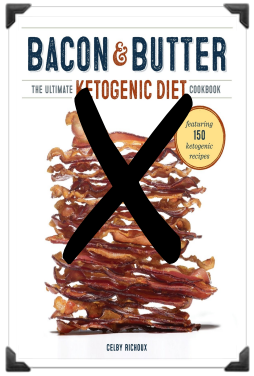
Surrogate Marker Endpoints NOT AS IMPORTANT AS				Clinically Relevant Endpoints MUCH MORE IMPORTANT				LEVELS OF EVIDENCE IN HEALTH CARE WE USE TO FIGURE OUT WHAT WORKS
LDL cholesterol	**HDL cholesterol**	**Glucose**	**Decrease weight**	**Reducing risk of heart attacks/ strokes/cancer**		**Reducing risk of dying**		
LOW FAT ⬇LDL~ 5% more than LOW CARB	LOW CARB ⬆HDL~10% more than LOW FAT	LOW CARB ⬇glucose ~3% more than LOW FAT	LOW CARB ⬇weight ~3% more than LOW FAT	NONE		NONE		**Systematic reviews/ Meta-analyses**
Many RCTs for both including head-to-head comparisons see above SR/MA for findings				LOW FAT 1 trial - 49,000 women No benefit seen over 8 years "Mediterranean"diet ⬇ CVD by 1-2% more than low fat over 5 years	LOW CARB No trials	LOW FAT 1 trial - 49,000 women No benefit seen over 8 years	LOW CARB No trials	**Randomized Controlled Trials**
Not really needed as we have lots of randomized controlled trials of surrogate markers				Only higher TRANS FAT intake consistently associated with increased CVD, other "fats" no effect	LOW CARBS associated with no effect on CVD	Only higher TRANS FAT intake consistently associated with increased mortality, others no effect	LOW CARBS associated with increased mortality	**Cohort Studies**
LOTS, IN FACT WAY TOO MUCH Just see above evidence or, in this case, lack thereof, for either side of the debate to be as definitive as they are								**Expert Opinion**

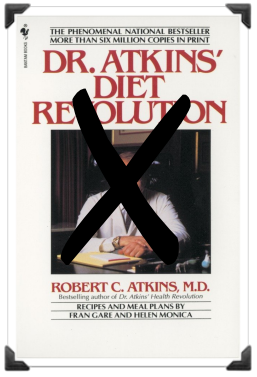
LOW ← Ability of the evidence to ascertain cause and effect → HIGH











Nutrition advice which pretty much everyone agrees with

A greater % of whole foods - food that has not been overly processed or refined as little as possible

More vegetables specifically

Less added sugar

Less refined grains

Choose an eating style that fits your food preferences, health goals, lifestyle

Most importantly, choose an eating style you can sustain

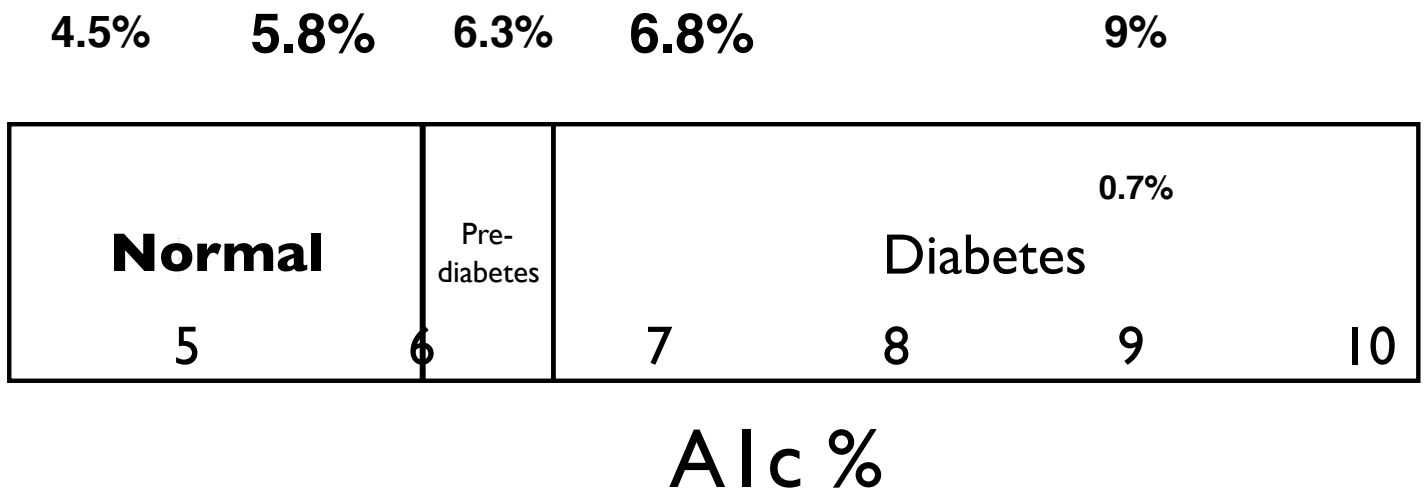
Make ballpark estimates of CVD risk

Make treatment recommendations based on the best available evidence

Allow the patient to participate in the decision - shared-decision!!

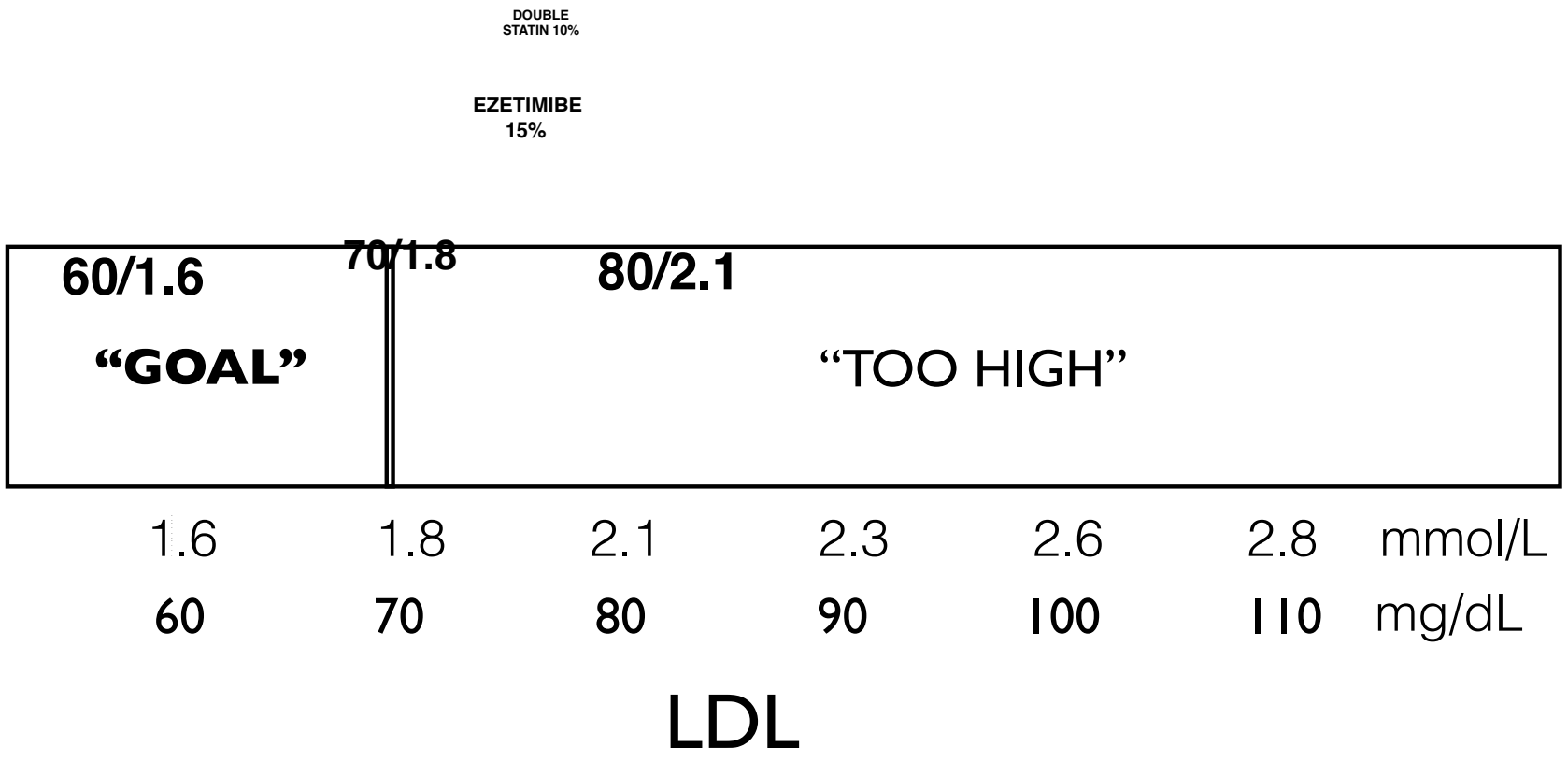
Precisely Imprecise

What an A1c result really means ~ +/- 10%



Precisely Imprecise

What an LDL result really means ~ +/- 15%



~Relative Benefits of Individual treatments

30-60 minutes a day
most days of the week

Mediterranean

1) chlorthalidone
2) ACEI - least expensive
3) ARB - least expensive

Least expensive

Expensive

1) metformin
2) SGLT2

Activity ~25% - secondary prevention

"Nutrition" ~30% - secondary prevention

Blood pressure medications ~30%

Statins ~25-35%

PCSKP ~15% - secondary prevention

Glucose medications ~0-30%

1 or more interventions ~additive???

The absolute benefit
depends
on baseline risk -
but remember that
even with the
best case example
only 30% will
benefit from
a lifetime of treatment

Treatments WITH NO clinical trial evidence around CVD risk

individual nutrients
most aspects of nutrition
all supplements (Omega 3s?)
all vitamins
all herbs

"We found no evidence to support antioxidant supplements for primary or secondary prevention. Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A"
CD007176 2012

Treatments WITH clinical trial evidence showing NO CVD risk benefit

a number of medications that lower cholesterol, blood pressure and many that lower glucose

When someone does something wrong, don’t forget all the things they did right.