The Risky Business of Risk Factor modification

It's Just a Numbers Game And So Much More

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Objectives

Be able to explain what is meant by the various cardiovascular/fracture endpoints which drug therapy is aimed at improving.

Be able to select and use an appropriate risk estimation tool to help a patient understand their level of risk and chance of benefit.

Be able to conceptualize how this information could be applied to pharmacotherapeutic decision-making.

Risk …

Risk markers - associated with a bad outcome

Risk factors - modifiable?

Risky behaviors - smoking, nutrition, activity

Risk of disease - CVD, MI, strokes, fractures

Risk of treatment - harms, costs

Risk of over diagnosis - 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

Conditions requiring risk assessment

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

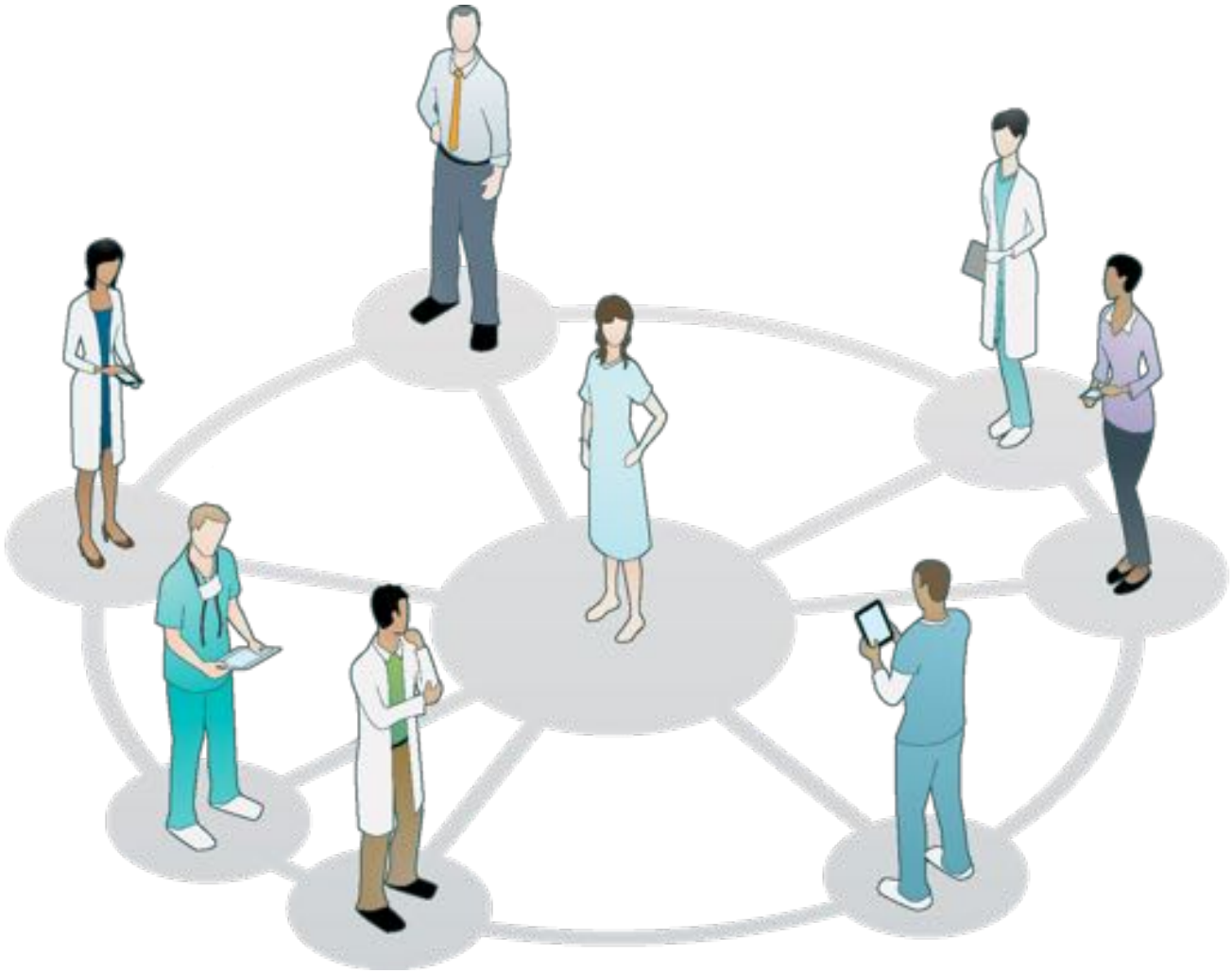
Figure out risk

Then figure out benefit

Include harm and costs and inconvenience

We are knowledge brokers

Patient centered



“Choice is a gift from the patient to the doctor, not the other way around”

BMJ 2000;320:874

It’s all about figuring out

The Chance
WITH NO TREATMENT

vs

The Chance
WITH TREATMENT


I'VE BEEN LABELLED
TYPE 2 DIABETES
IBD
BS
CVD
SILENT THIEF
SILENT KILLER
CRP
BMW
DOA
OSTEOPOROSIS
DSM 5
SAD
CHRONIC FATIGUE
GAD
HDL
METABOLIC SYNDROME
OSTEOPENIA
ADHD
IBS
CAD
ED
TLC
HIGH CHOLESTEROL
PRE-HYPERTENSION
DEPRESSION
PSA
POLYMYALGIA
GET MILK
TAKE OUT THE GARBAGE
LOW T
LDL
SBP
A1c
OBESE
SFA
WALK THE DOG
PRE-DIABETES
BMI
BMD
STD
CHD
FU
DBP

We need minimally disruptive medicine

The burden of treatment for many people with complex, chronic, comorbidities reduces their capacity to collaborate in their care. **Carl May, Victor Montori**, and **Frances Mair** argue that to be effective, care must be less disruptive

BMJ 2009;339:b2803

Risky Adjectives

HOW

low is low

moderate is moderate

high is high

Treatment thresholds are arbitrary

- Not based on patient preferences
- Not based on cost/benefit
- Seem to be primarily emotionally-based

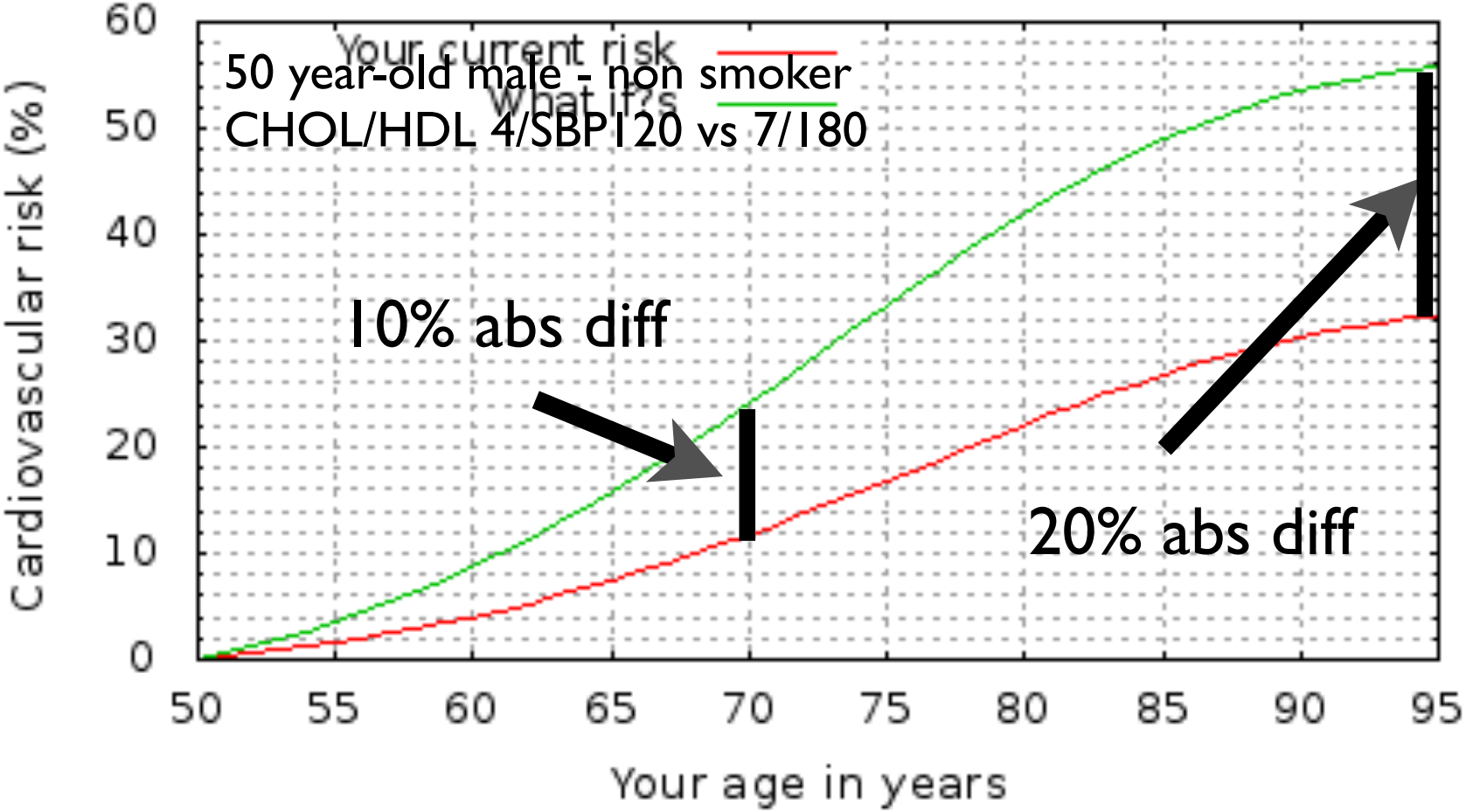
Misguided beliefs

Patients believe CVD “prevention” drugs produce a 70% absolute benefit over 5 years when at most only ~ 20% benefit is possible over a lifetime

Clin Med 2002;2:527-33

Prevention drugs

QRISK Lifetime risk of CVD



20 years ≈ 90% no benefit?

45 years ≈ 80% no benefit?

http://www.qrisk.org/lifetime/index.php

20 "NEGATIVE" STUDIES IN A ROW

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)

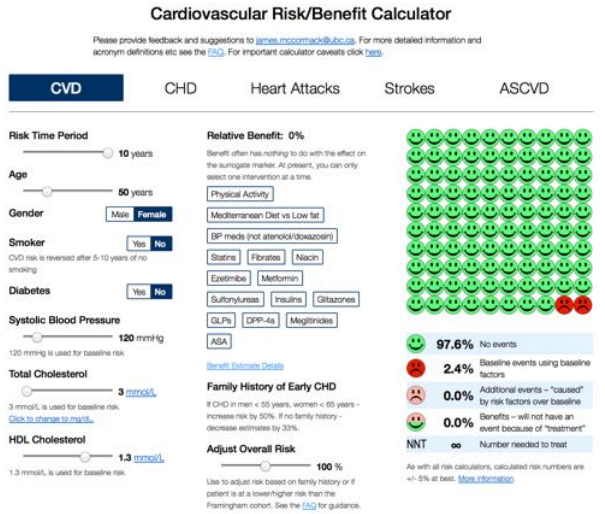
VISTA-16 (varespladib)

182,000+ patients

Patient — Activity Nutrition

↓

Measure - BP (SBP) - Chol? — Risk of cardiovascular disease



↓

Patient decision

↓

Treatment
Thiazides
ACE inhibitors
Statins etc — EVIDENCE FOR, AND MAGNITUDE OF, THE reduction in cardiovascular outcomes

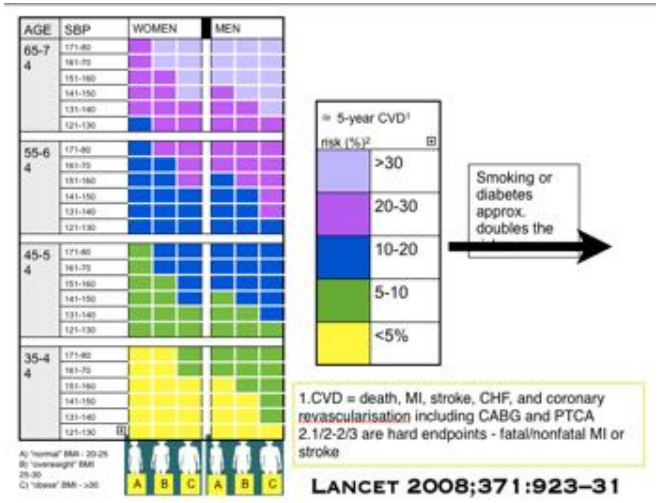
Side effects

↓

Repeat BP and chol??

↓

Reevaluate need



Relative Risk and Absolute Benefit - recap

Baseline Risk of a heart attack = 50% over 5 years
RR - Relative benefit = 0.8 or 20% reduction
With Treatment = 40%
Absolute difference = 10%
NNT = 10

Baseline Risk of a stroke = 2% per year
RR - Relative benefit = 0.25 or 75% reduction
With Treatment = 0.5%
Absolute difference = 1.5%
NNT = 67

Baseline risk of cancer = 10% lifetime
RR - Relative harm = 2.5 or 150% increase
With Treatment = 25%
Absolute difference = 15%
NNH = 7

Cardiovascular Endpoints

Risk of What and over How Long

WHAT

CVD is cardiovascular disease

Typically = CHD + cerebrovascular

CHD = coronary heart disease = fatal and non-fatal MIs and sometimes angina

Cerebrovascular disease = fatal and non-fatal strokes - and sometimes TIAs

CVD sometimes includes other conditions - heart failure, peripheral vascular disease

HOW LONG - 5 or 10 years

What a calculator should do

IDEALLY

“the calculator selected by a clinician should be derived from a population similar to the patient he or she sees or adjusted to match that, and then updated regularly”

“The calculator should give absolute risks, provide a graphic representation for patients, and preferably provide an estimate of the benefit of key interventions”

“all risk estimates, benefits, and harms of interventions should be used and discussed with patients as part of the shared decision-making process.”

Current Opinion in Lipidology 2014;25:254-65

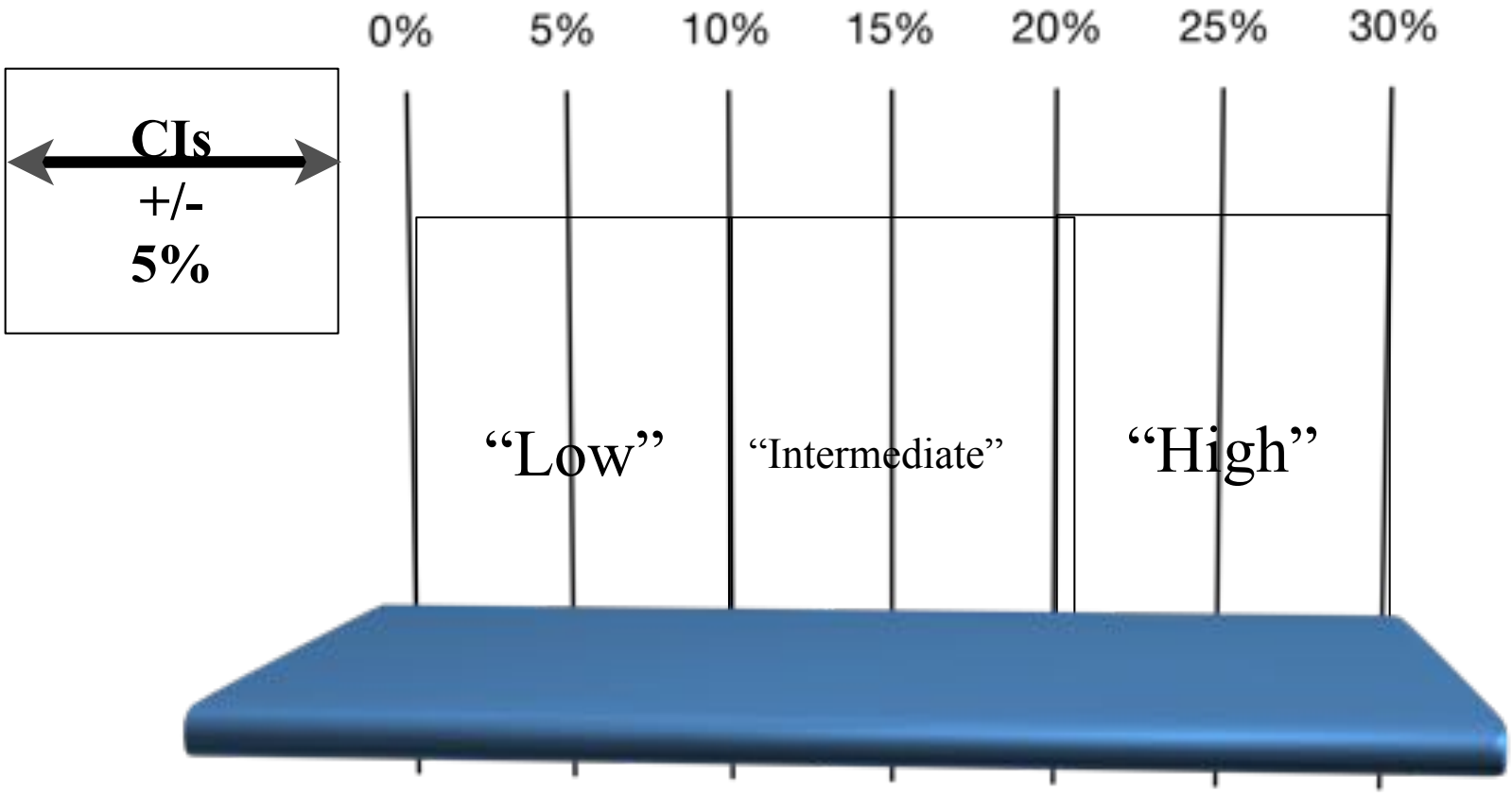
Epidemiology and Prevention

Agreement Among Cardiovascular Disease Risk Calculators

G. Michael Allan, MD; Faeze Nouri, MD; Christina Korownyk, MD; Michael R. Kolber, MD, MSc; Ben Vandermeer, MSc; James McCormack, PharmD

Circulation 2013;127:1948–56

How accurately can we predict risk?



J Cardiovasc Risk 2002;9:183-90

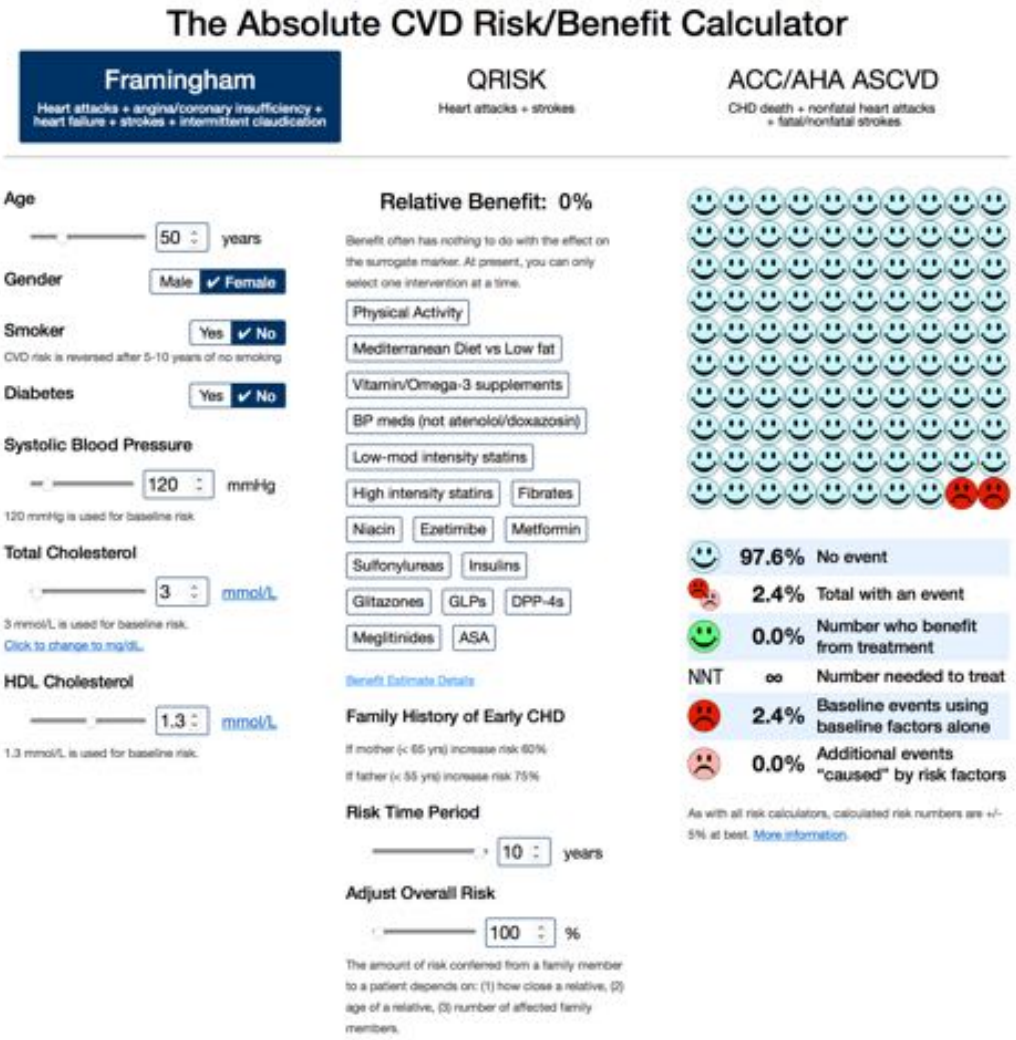
“Non-traditional” Risk Factors

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

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

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

For Primary Prevention



cvdcalculator.org

55 y/o white M

BP 145/90 BMI 27 (172 cm, 80kg)

TChol 5.0. HDL 1.0. CRP 5.0

PMH: none

fam CV hx: none

67 y/o white F

BP 135/85. BMI 33 (160 cm, 82kg)

TChol 6.1. HDL 1.3. CRP 8.5

PMH: type 2 diabetes x 3y (HgB A1C 7.5%)

fam CV hx: none

“I find this one of the best risk calculator tools available.

It’s easy to use and to understand, the user can select to use the Framingham or the AHA/ACC risk model, and to predict various outcomes (CHD, MI, Stroke, ASCVD).

The background material is also excellent – providing data on how the risks were calculated.

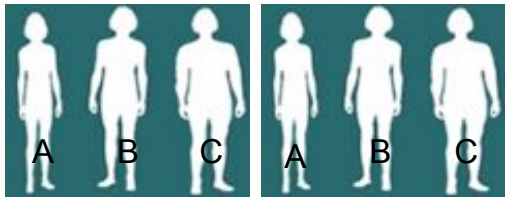
I also love the way you can explore the effect of various interventions, and the simple, intuitive way that the effects of interventions are displayed.

I think this is one of the best sites to use if you want to show patients a visual of how their risk might change with interventions.”

Deborah Grady
Deputy Editor of JAMA Internal Medicine

AGE	SBP	WOMEN				MEN		
65-74	171-80							
	161-70							
	151-160							
	141-150							
	131-140							
	121-130							
55-64	171-80							
	161-70							
	151-160							
	141-150							
	131-140							
	121-130							
45-54	171-80							
	161-70							
	151-160							
	141-150							
	131-140							
	121-130							
35-44	171-80							
	161-70							
	151-160							
	141-150							
	131-140							
	121-130							

A) “normal” BMI - 20-25
B) “overweight” BMI 25-30
C) “obese” BMI - >30



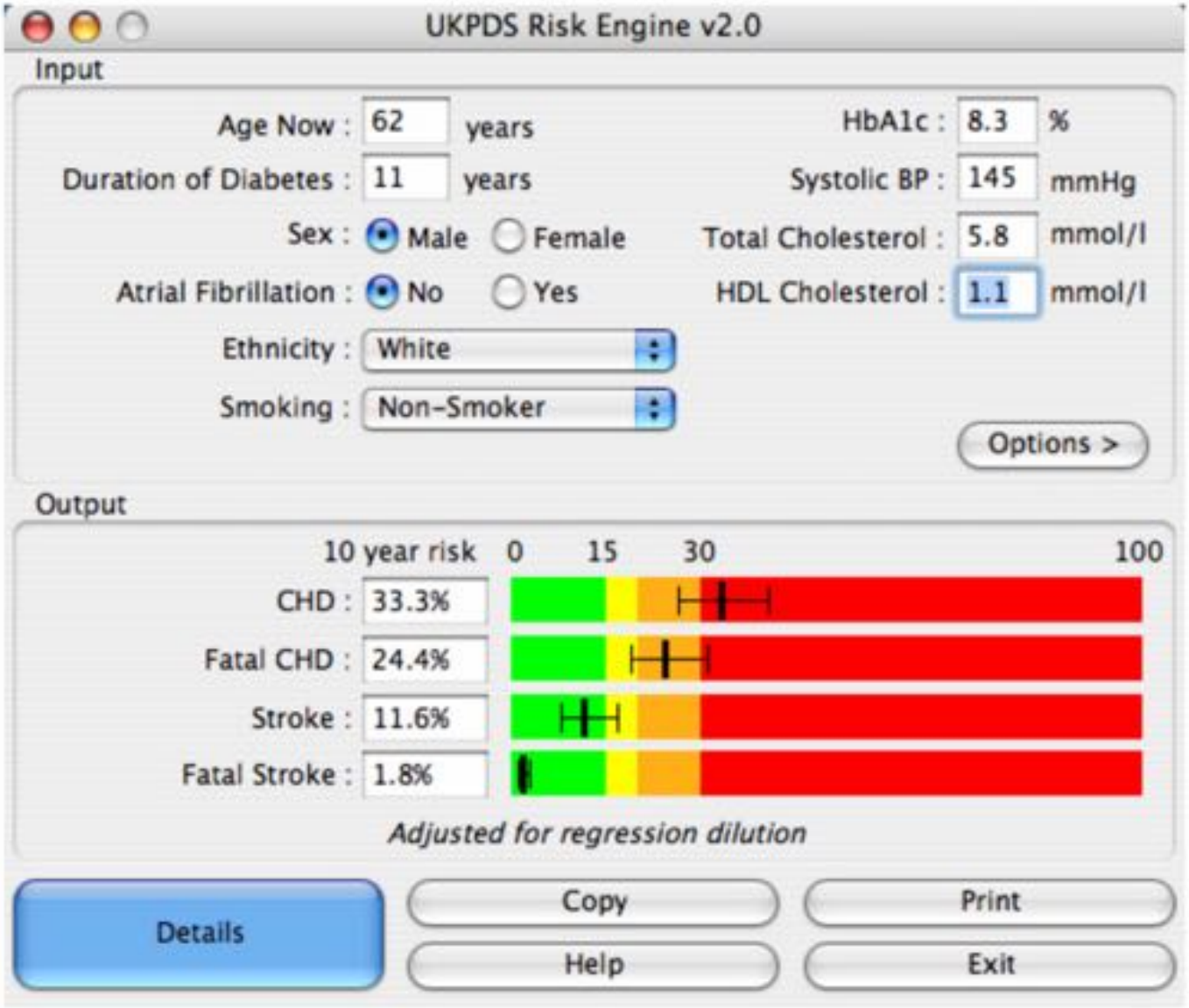
≃ 5-year CVD[1] risk (%)[2]	
	>30
	20-30
	10-20
	5-10
	<5%

Smoking or diabetes approx. doubles the risk

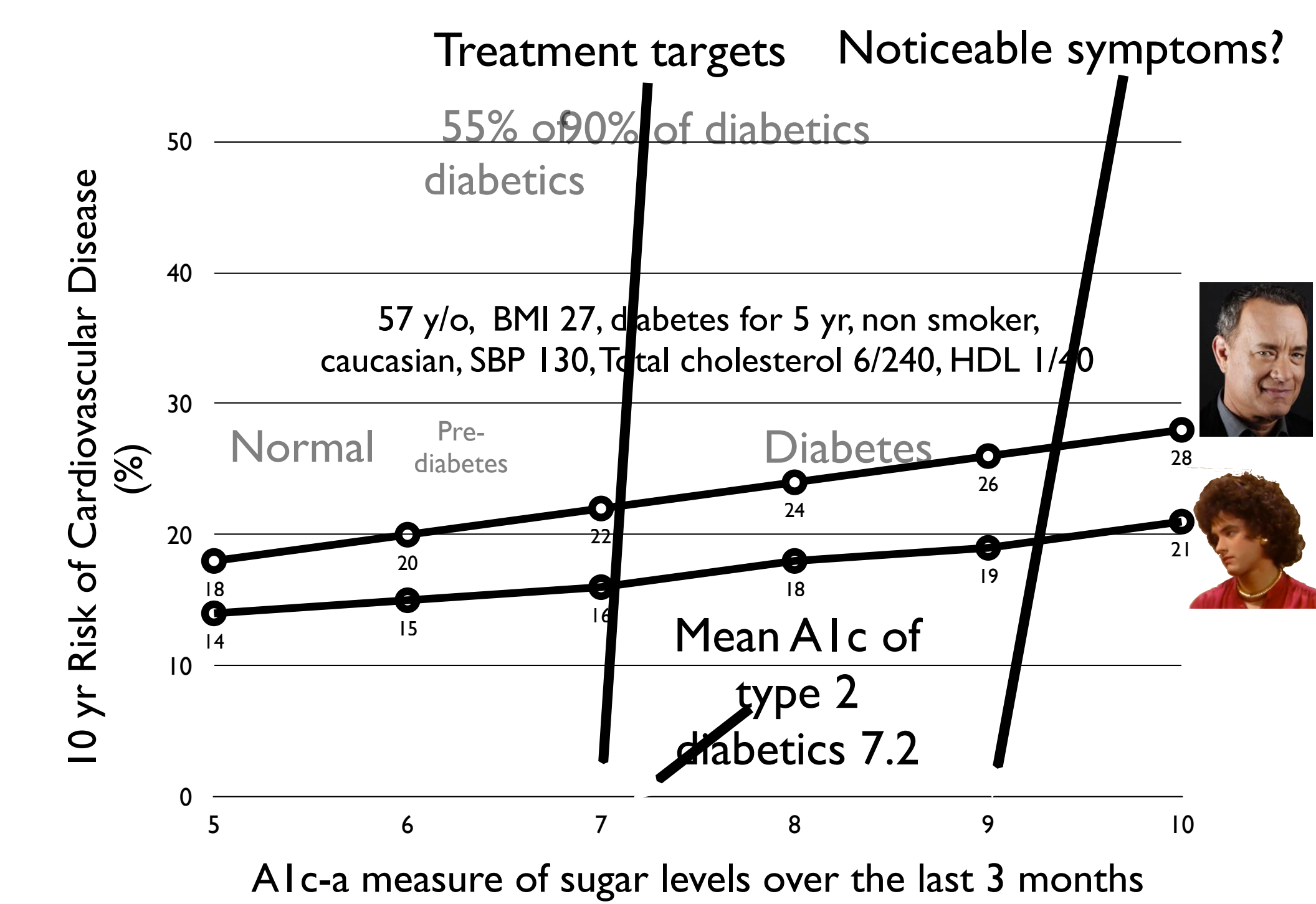
1.CVD = death, MI, stroke, CHF, and coronary revascularisation including CABG and PTCA
2.1/2-2/3 are hard endpoints - fatal/nonfatal MI or stroke

Lancet 2008;371:923–31

For Type 2 diabetes (A1c)



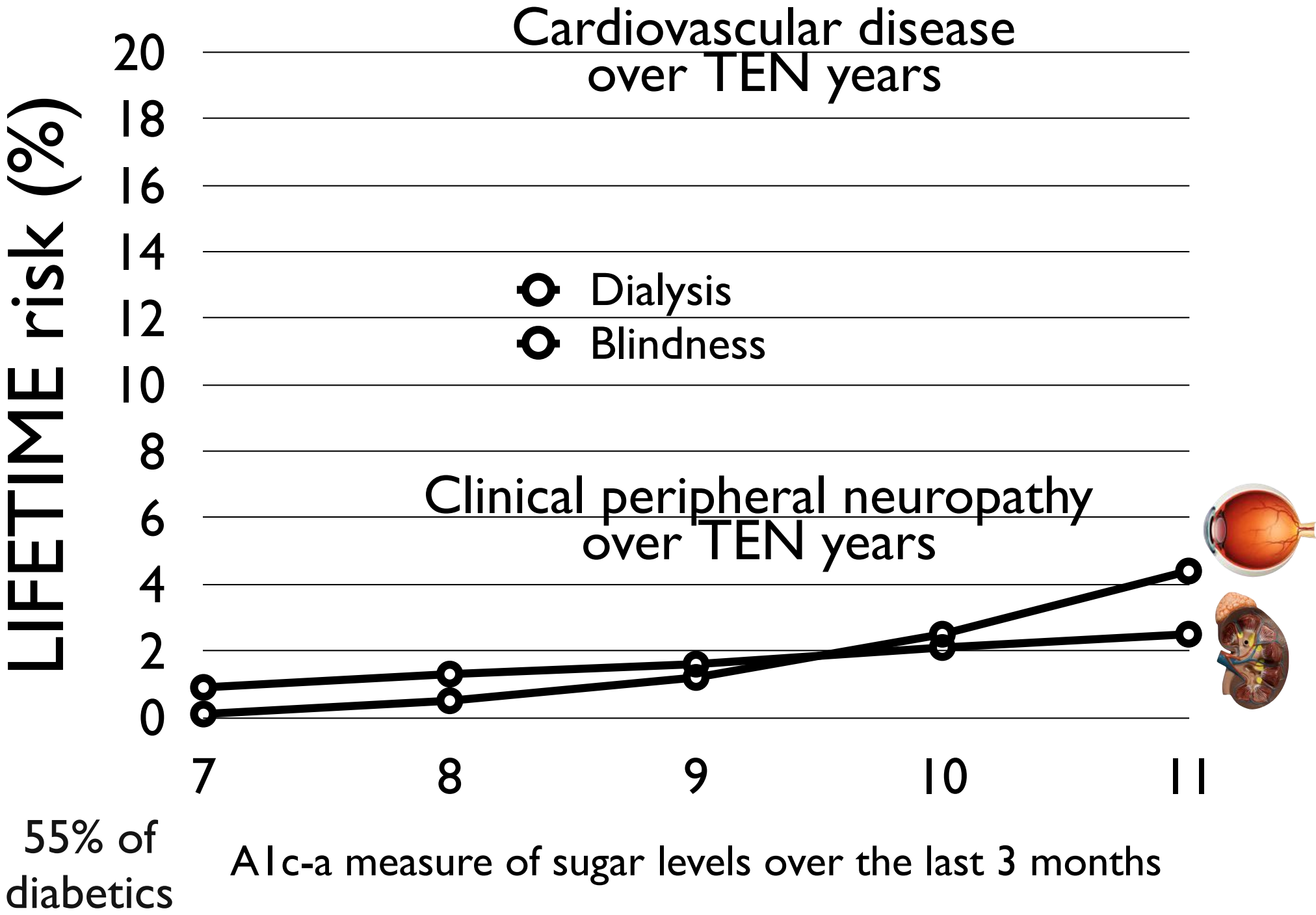
http://www.dtu.ox.ac.uk/riskengine/



http://youtu.be/jOxxHbdyXcg

Diabetes Care 2008;31:81–6

UKPDS RISK ENGINE



55% of diabetics

Ann Intern Med 1997:127:788-95

ALL LOWER GLUCOSE							
	Key RCTs patients/years		MA (# of studies)				
METFORMIN - Glucophage, Glumetza, generic	700/11	7%	13				
SULFONLYUREAS - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)	4,000/10	COMBO	4-11		3%		
INSULIN	12,000/6 4,000/10	COMBO	None done				
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin	5,000/1.5 16,000/2		None done				
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	4,400/4 5,200/3	?	42	?CHF harm	?	?	?
GLPs - Exenatide (Byetta) Liraglutide (Victoza)	? - not studied		?		?	?	?
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	? - not studied		?		?	?	?
Tight control	10,000/3.5 1,800/5.5 11,000/5	? Mortality harm	3		2%	2%	2%

T2DM - Lifetime Treatment Benefits - absolute risk reduction

	Age	ESRD	Vision Loss	Amputation	First MI
Metformin at diagnosis	45	6.5	2.1	2.7	2.6
	55	4.2	1.6	2.2	4.0
	65	2.1	1.0	1.5	3.7
	75	0.7	0.5	0.8	2.7
Switch to Insulin after 10 years	45	1.3	0.4	0.4	1.0
	55	0.7	0.2	0.3	0.8
	65	0.3	0.1	0.2	0.6
	75	0.1	0	0.1	0.3

UKPDS - most optimistic

JAMA Intern Med. doi:10.1001/jamainternmed.2014.2894

Relative risk reductions with different interventions in DM2

	Treat BP	Treat Lipid	Treat Sugar
CVD events	~ 50%	~20-25%	~ 12.5%
Mortality	16%	8%	NSS

Diabetes Care 2010;33(1): S11-61, Ann Intern Med 2008;148:846-54, Lancet 2009;373:1765–72, Lancet 2008; 371:117–25, Ann Intern Med 2003;138:587-92

Afib
Stroke Endpoints

For Afib and stroke

SPARC - Stroke Prevention in Atrial Fibrillation Risk Tool
for estimating risk of stroke and benefits & risks of antithrombotic therapy in patients with chronic atrial fibrillation
references/notes
version 6.21, March 2013
Developed by Peter Loewen, ACPR, Pharm.D., FCSHP
peter.loewen@ubc.ca

In your patient with atrial fibrillation, which of the following stroke or bleeding risk factors are present?

CHADS2 CRITERIA

- CHF/LV dysfunction (diagnosed at any time in the past)
- Hypertension (controlled or uncontrolled)
- Age > 75
- Diabetes (Type I or II) controlled or uncontrolled
- TIA or stroke at any time in the past

CHADS2 SCORE (0-6):0

CHA2DS2-VASc CRITERIA

- Prior MI, peripheral artery disease, or aortic plaque
- Age 65-75
- Female

CHA2DS2-VASc SCORE (0-9):0

HAS-BLED CRITERIA*

- Abnormal renal function
- Abnormal liver function
- History of major bleeding (any cause)
- History of labile INR (time in therapeutic range <60%)
- Current "excess" use of alcohol
- Currently taking antiplatelet drug(s) or NSAID(s)

HAS-BLED SCORE (0-9)*:0

*no studies have observed major bleeding in patients with score>5, so these must be interpreted as "risk probably >10%".

	PERCENT PER YEAR			
	Stroke / Embolism		Major Bleeding	
THERAPY	CHADS2	CHA2DS2-VASc	Pop.Avg.	HAS-BLED
NO THERAPY	1.2%	0.7%	0.6%	
ASPIRIN	0.9%	0.5%	1.1%	
ASPIRIN+CLOP	0.7%	0.4%	3.8%	
WARFARIN	0.4%	0.2%	3.8%	1.2%
DABIGATRAN 110	0.4%	0.2%	3.0%	1.0%
DABIGATRAN 150	0.3%	0.2%	3.8%	1.2%
RIVAROXABAN	0.4%	0.2%	3.8%	1.2%
APIXABAN	0.3%	0.2%	2.6%	0.8%

http://www.sparctool.com

An easy A fib table

	Patient's ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
$CHADS_2$ Score	No therapy	ASA	OAC	
0	1.9	1.5	0.6	0.9
1	2.8	2.2	0.9	1.3
2	4	3.1	1.3	1.8
3	5.9	4.6	1.9	2.7
4	8.5	6.6	2.8	3.8
5	18	14	6	8

http://www.sparctool.com

An even easier A fib table

	Patient's ~ ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
$CHADS_2$ Score	No therapy	ASA	OAC	
0	2	1.5	0.5	~1
1	3	2.5	1	~1.5
2	4	3	1	~2
3	6	5	2	~3
4	9	7	3	~4
5	18	14	6	~8

Patient

Risk of having osteoporosis

Risk of fracture without knowing BMD

Patient decision

Exercise
Calcium
Vit D
HRT

Screening BMD

Patient decision

Risk of fracture knowing BMD

Treatment
Bisphosphonates
Raloxifene etc

EVIDENCE FOR, AND MAGNITUDE OF, THE
reduction in vertebral fractures
reduction in non-vertebral
reduction in hip fractures

Side effects

Repeat BMD

Does your patient have osteoporosis?

(Osteoporosis Self-assessment Tool)

Age – weight (kg) = ????
CHANCE OF OSTEOPOROSIS
> 20 – approx 50-60%
0-20 – approx 15-20%
<0 – less than 5%

An example
60 years old
130 lbs = 60 kg
Score = 0

Valid in men as well
Mayo Clin Proc 2003;78:723-7

Mayo Clin Proc. 2002;77:629-637
The Singapore Family Physician Jul-Sep 2003;29:12
MOH Osteoporosis clinical practice guidelines - Singapore Mar 2002

RISK FACTORS	Zero			One			Two		
t-score	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5
Female									
50	4	5/1	9/4	6	8/2	14/7	8	12/3	21/11
60	7	10/2	16/6	10/1	14/3	23/9	14/1	20/5	32/14
70	9/1	13/3	21/7	12/1	18/4	30/11	16/2	25/6	41/16
80	13/3	18/6	29/14	17/6	26/12	40/24	24/10	35/20	52/37
Male									
50	4	5/2	11/6	5	8/3	16/10	8/1	12/5	24/16
60	6/1	9/3	15/8	8/1	12/4	21/11	12/2	18/6	29/17
70	6/2	10/4	16/8	9/3	14/6	22/13	12/4	19/10	31/20
80	7/3	11/5	16/9	11/5	16/9	23/16	15/9	22/15	32/25

A simple tool for assessing the chance of your patient having osteoporosis

Does your patient have osteoporosis?

(Osteoporosis Self-assessment Tool)

Age – weight (kg) = ????

CHANCE OF OSTEOPOROSIS

> 20 – approx 50-60%

0-20 – approx 15-20%

<0 – less than 5%

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Fracture Endpoints

A simple tool for estimating chance of fractures without a BMD

Simple is better

"Simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of hip, major osteoporotic, and clinical fracture as well as more complex FRAX models"

Arch Intern Med 2009;169:2087-94

http://www.shef.ac.uk/FRAX/tool.aspx?country=19

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero				One				Two			
BMI	35	30	25	20	35	30	25	20	35	30	25	20
Female												
50	2	3	3	3	4	4	5	5	6	6	7	8/1
60	5	6	6	7/2	7	9	10/1	10/4	11/1	13/2	14/2	16/6
70	8/1	9/2	10/2	11/4	11/2	13/3	15/4	17/7	16/4	18/6	21/7	25/12
80	14/4	16/5	19/7	16/11	20/8	23/10	27/13	24/20	28/14	33/18	38/22	35/32
Male												
50	2	2	2	2	3	3	4	4	4	5	6	6
60	3	4	4	4	5	6	6	7/1	7	8	10/1	10/2
70	4	5/1	6/1	6/2	6	7	8/2	9/4	8	10	12/4	13/6
80	6/2	7/3	9/4	9/5	9/4	11/5	13/7	14/10	13/7	16/9	19/12	21/16

Risk factors - Previous fracture “atraumatic”, Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

A simple tool for estimating chance of fractures with a BMD

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero			One			Two		
t-score	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5
Female									
50	4	5/1	9/4	6	8/2	14/7	8	12/3	21/11
60	7	10/2	16/6	10/1	14/3	23/9	14/1	20/5	32/14
70	9/1	13/3	21/7	12/1	18/4	30/11	16/2	25/6	41/16
80	13/3	18/6	29/14	17/6	26/12	40/24	24/10	35/20	52/37
Male									
50	4	5/2	11/6	5	8/3	16/10	8/1	12/5	24/16
60	6/1	9/3	15/8	8/1	12/4	21/11	12/2	18/6	29/17
70	6/2	10/4	16/8	9/3	14/6	22/13	12/4	19/10	31/20
80	7/3	11/5	16/9	11/5	16/9	23/16	15/9	22/15	32/25

Risk factors - Previous fracture “atraumatic”, Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
Teriparatide	~ 70%	~ 40%	NS
Vitamin D usually with calcium	~15-25%	~15-25%	~15-30%
Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 90% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention