# 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

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

It's all about figuring out

The Chance
WITH NO TREATMENT

vs

The Chance
WITH TREATMENT

# 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

# 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
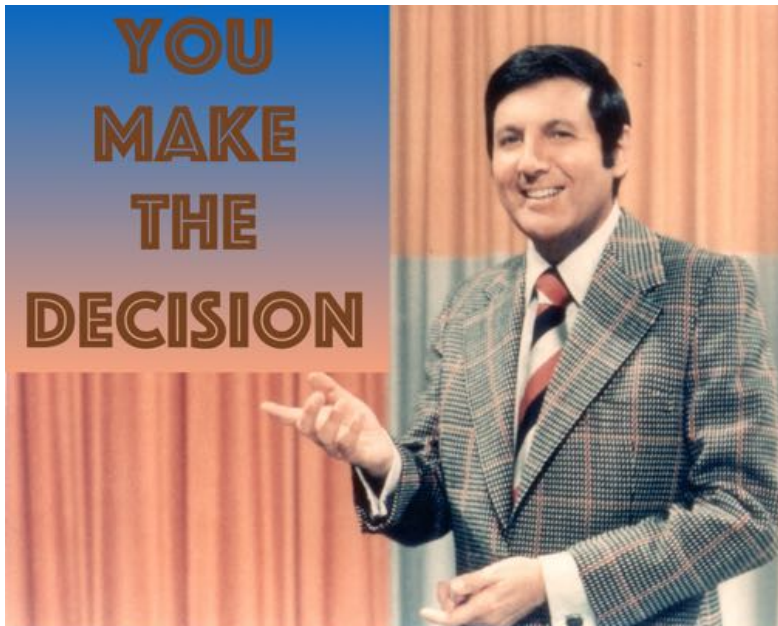
# What Will You Do?

You are approximately 50 y/o

You have been diagnosed "properly" with elevated blood pressure

You have tried non-drug measures for 6 months and still your blood pressure remains elevated

## QUESTION

ABOVE what systolic blood pressure would YOU take a drug every day for the next 5 years?

# What is your "scary" number?



130
140
145
150
155
160
165
170
175

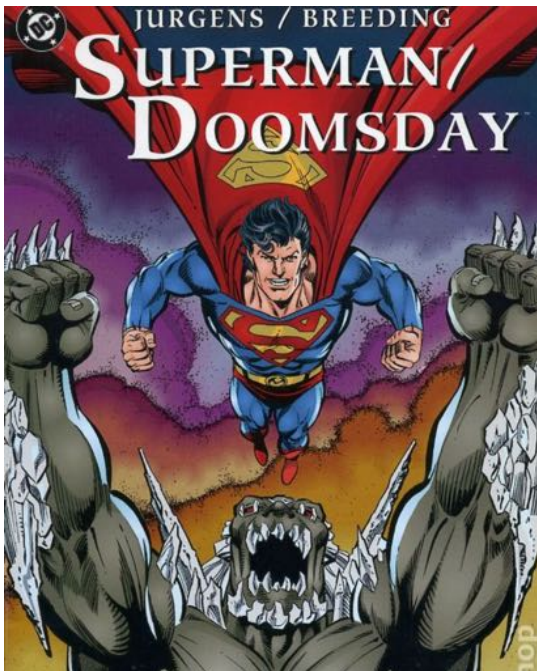# Numbers VS NUMBERS



Risk factor numbers

**VS**

# CVD

## Risk/benefit/harm

# Misguided beliefs

Patients believe CVD "prevention" drugs produce a 70% absolute benefit over 5 years when at most only ~ 20-30% benefit is possible over a lifetime

# 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)

## DIABETES
ACCORD, ADVANCE, VADT
(aggressive A1c lowering)
ROADMAP (olmesartan)
ORIGIN (insulin)
SAVOR-TIMI 53 (saxagliptin)
EXAMINE (alogliptin)
ALECARDIO (aleglitazar)

## BLOOD PRESSURE
ALTITUDE (aliskiren)
VAL-ISH, AASK, ACCORD
(aggressive BP lowering)

## GENERAL
ACTIVE (irbesartan/afib)
CRESCENDO (rimonabant)
VISTA-16 (varespladib)

182,000+
patients

EMPA-REG OUTCOME (empagliflozin) - 1.6% ARR over 3.1 years
SPRINT (120mmHg vs 140mmHg) - 1.6% ARR over 3.26 years
HOPE 3 - statins YES 1.4% ARR for CVD events over 5.6 years
- 1.8% ARR for kidney events over 3.3 years
BUT blood pressure no benefit
FINALLY!!!!!

A Swift Kick
in the Butt
$1.00

Patient — Activity / Nutrition

↓

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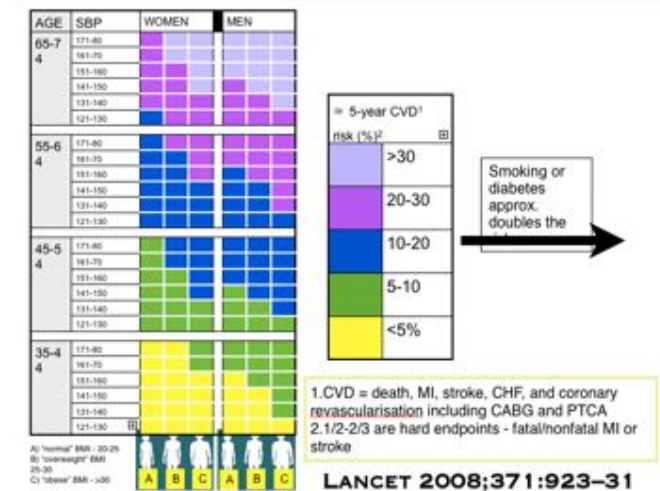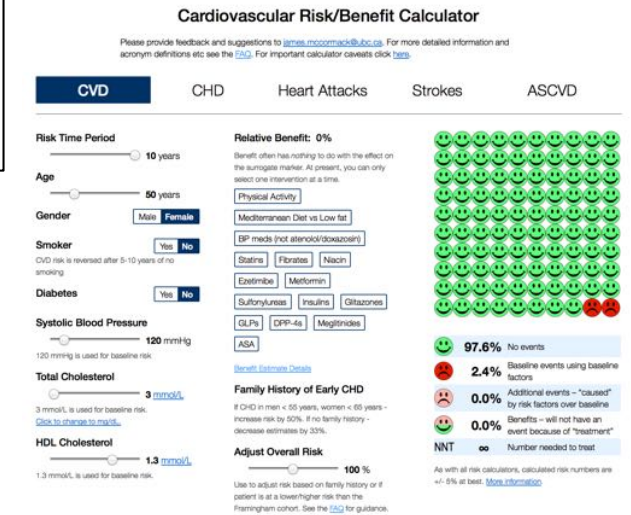
↓

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



Cardiovascular Risk/Benefit Calculator



LANCET 2008;371:923–31

# 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

# Evidence-based risk communication

"There is likely no single best method of communicating probabilities to patients but rather several good options with some better suited to certain risk scenarios."

# Recommended approaches

GENERAL SUGGESTIONS - these are "relative"
use percentages or natural
frequencies(numerator/denominator)
use absolute terms
add bar graphs or icon arrays
use incremental risk format with icon arrays in
the same array

- avoid use of NNTs

if use relative risks add baseline risks

# 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

# How accurately can we predict risk?
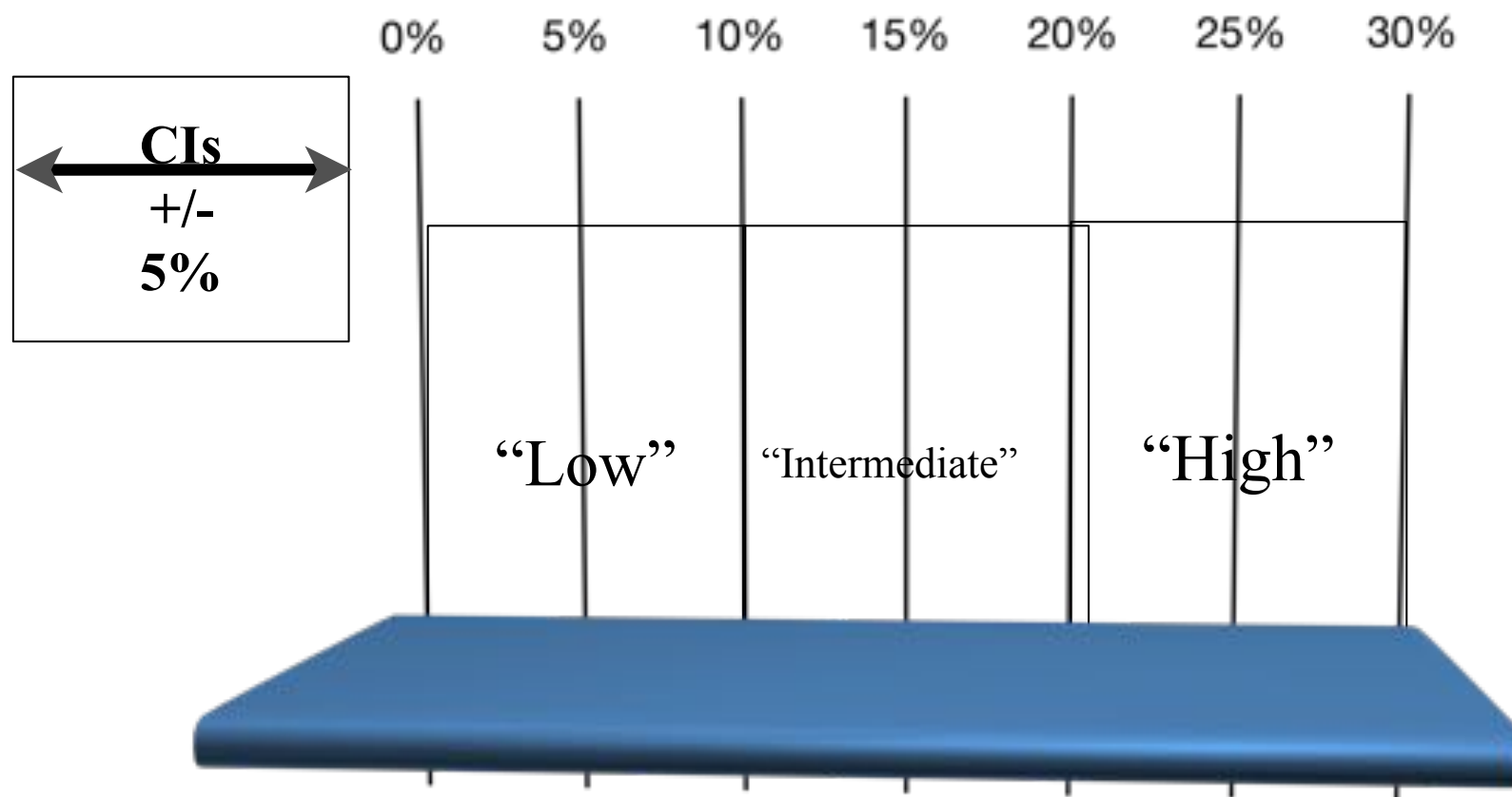


J Cardiovasc Risk 2002;9:183-90

# "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

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)

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 53%

ASCVD (HA, stroke) = 41%

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) = 8%

ASCVD (HA, stroke) = 2%

Wonder Woman
Age 40 (OK she ages well)
BP 120/70 mmHg
Total cholesterol 6.8(270)
HDL 1.6 (65)
LDL 5.0 (200)
Trigs 1
Diet mostly caiman and anaconda (rich in cholesterol)
Non-diabetic
Not a smoker (but still smokin')
PMH: Charles Bonnet Syndrome
(suffers from visual hallucinations that are pleasant: in this case, a jet)
Wears bracelets as a defence but otherwise dresses more than appropriately!

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 2%

ASCVD (HA, stroke) = 1%

S.M.+W.W
45 years old
Diabetics A1c 8.5
SBP 140 mm/Hg
Non smokers
Total cholesterol 4.5 (180)
HDL 1.2 (55)

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 12%/12%

ASCVD (HA, stroke) = 4%/2%

Superman
Age 74
Still quite physically active
BP 150/90 mmHg
Total cholesterol 5.2
HDL 1.4
BMI 35
A1C 15 = 5.4 on Krypton so OK
Prostate exam: very hard throughout
… almost steel-like?

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 33%

ASCVD (HA, stroke) = 29%

# Risks over short time periods

Assume a 5% (5/100) reduction in CVD over 5 years

~ 1% (1/100) reduction over one year

~ 0.1% (1/1000) per month

~ 0.02 (1/5000) per week

**10 year risk**

Framingham (HA, angina, HF, stroke, int claud) = 53%

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) = 8%

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)



**10 year risk**

Framingham (HA, angina, HF, stroke, int claud) = 2%

ASCVD (HA, stroke) = 1%

Smokin' - NO TREATMENT
BP 120/70 mmHg - 0%
Total cholesterol 6.8(270) - 25% RR
HDL 1.6 (65)
LDL 5.0 (200)

| 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


A B C A B C
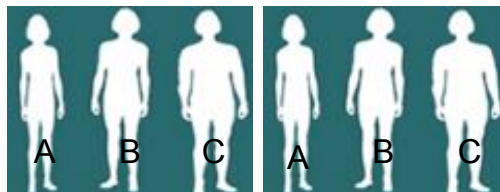
| $\simeq$ 5-year CVD[1] risk (%)[2] | |
|---|---|
| | >30 |
| | 20-30 |
| | 10-20 |
| | 5-10 |
| | <5% |

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

# Baseline 10-year risk (%) of CVD, blindness, amputation and ESRD(lifetime) based on A1c (1-3)

### (all numbers are ballpark approximations but provide at least a starting point for discussion)

## 65 year-old female patient
### with no CVD, BMI 27, diabetes for 4-6 years, non-smoker, CHOL/HDL ratio = 5, SBP = 140
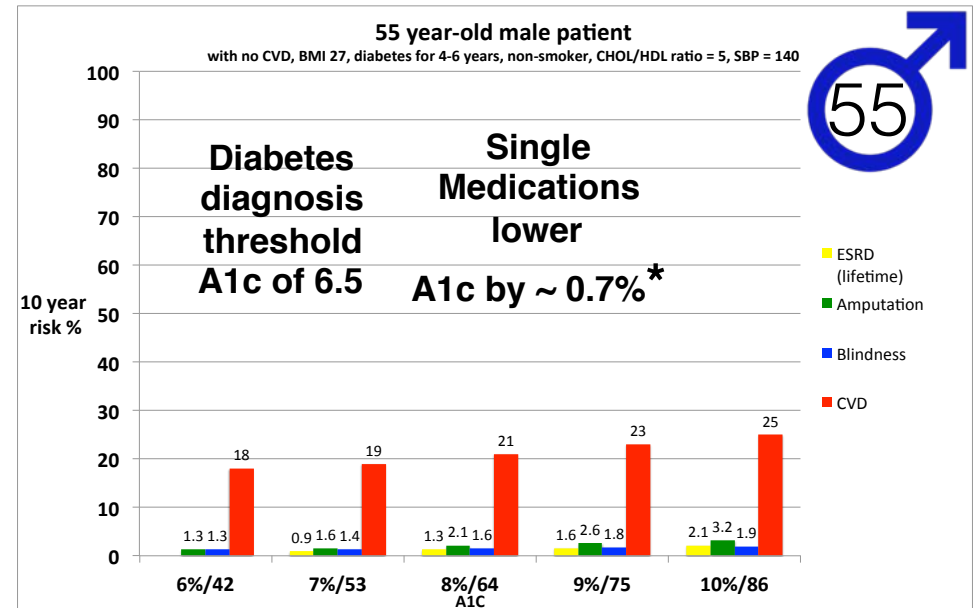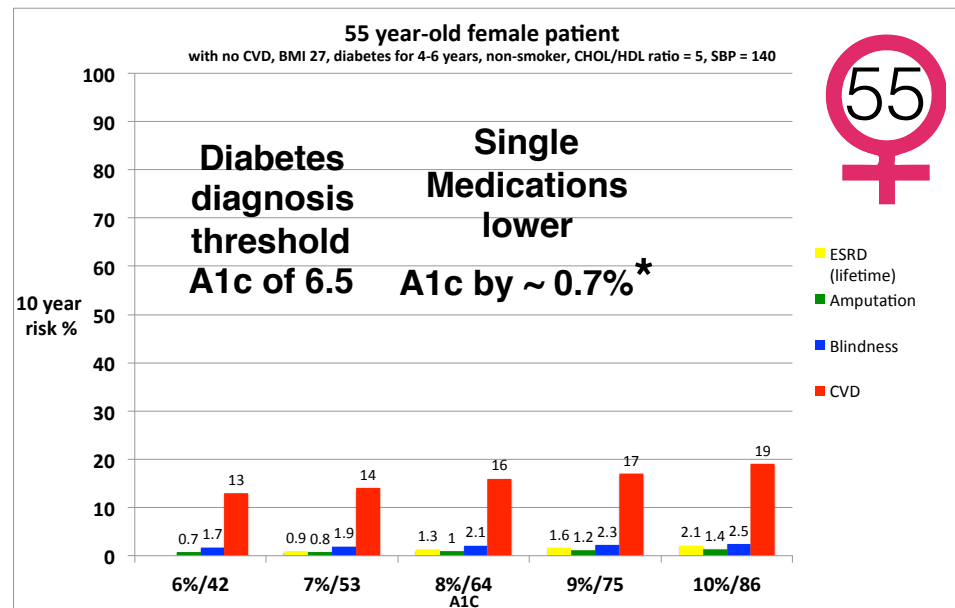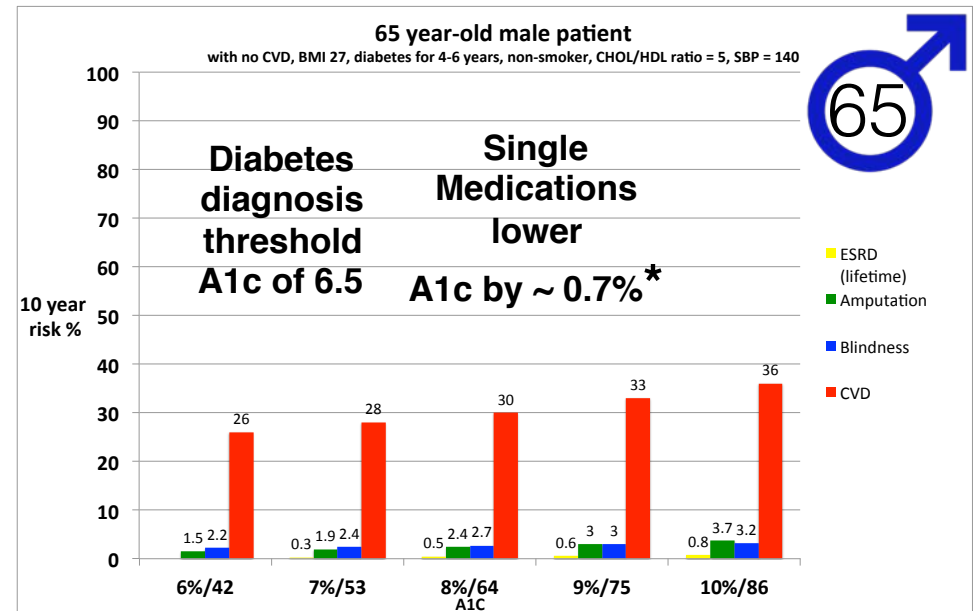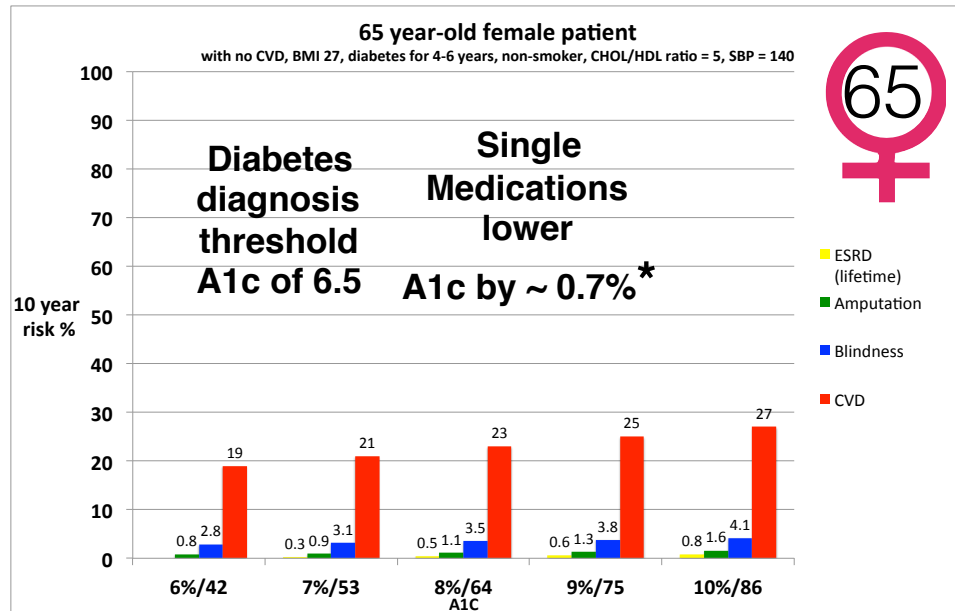
**Diabetes diagnosis threshold A1c of 6.5**

**Single Medications lower A1c by ~ 0.7%***

10 year risk %

- ESRD (lifetime)
- Amputation
- Blindness
- CVD

| A1C | ESRD | Amputation | Blindness | CVD |
|---|---|---|---|---|
| 6%/42 | | 0.8 | 2.8 | 19 |
| 7%/53 | 0.3 | 0.9 | 3.1 | 21 |
| 8%/64 | 0.5 | 1.1 | 3.5 | 23 |
| 9%/75 | 0.6 | 1.3 | 3.8 | 25 |
| 10%/86 | 0.8 | 1.6 | 4.1 | 27 |

## 65 year-old male patient
### with no CVD, BMI 27, diabetes for 4-6 years, non-smoker, CHOL/HDL ratio = 5, SBP = 140

**Diabetes diagnosis threshold A1c of 6.5**

**Single Medications lower A1c by ~ 0.7%***

10 year risk %

- ESRD (lifetime)
- Amputation
- Blindness
- CVD

| A1C | ESRD | Amputation | Blindness | CVD |
|---|---|---|---|---|
| 6%/42 | | 1.5 | 2.2 | 26 |
| 7%/53 | 0.3 | 1.9 | 2.4 | 28 |
| 8%/64 | 0.5 | 2.4 | 2.7 | 30 |
| 9%/75 | 0.6 | 3 | 3 | 33 |
| 10%/86 | 0.8 | 3.7 | 3.2 | 36 |

## 55 year-old female patient
### with no CVD, BMI 27, diabetes for 4-6 years, non-smoker, CHOL/HDL ratio = 5, SBP = 140

**Diabetes diagnosis threshold A1c of 6.5**

**Single Medications lower A1c by ~ 0.7%***

10 year risk %

- ESRD (lifetime)
- Amputation
- Blindness
- CVD

| A1C | ESRD | Amputation | Blindness | CVD |
|---|---|---|---|---|
| 6%/42 | | 0.7 | 1.7 | 13 |
| 7%/53 | 0.9 | 0.8 | 1.9 | 14 |
| 8%/64 | 1.3 | 1 | 2.1 | 16 |
| 9%/75 | 1.6 | 1.2 | 2.3 | 17 |
| 10%/86 | 2.1 | 1.4 | 2.5 | 19 |

## 55 year-old male patient
### with no CVD, BMI 27, diabetes for 4-6 years, non-smoker, CHOL/HDL ratio = 5, SBP = 140

**Diabetes diagnosis threshold A1c of 6.5**

**Single Medications lower A1c by ~ 0.7%***

10 year risk %

- ESRD (lifetime)
- Amputation
- Blindness
- CVD

| A1C | ESRD | Amputation | Blindness | CVD |
|---|---|---|---|---|
| 6%/42 | | 1.3 | 1.3 | 18 |
| 7%/53 | 0.9 | 1.6 | 1.4 | 19 |
| 8%/64 | 1.3 | 2.1 | 1.6 | 21 |
| 9%/75 | 1.6 | 2.6 | 1.8 | 23 |
| 10%/86 | 2.1 | 3.2 | 1.9 | 25 |

\* does not imply a reduction in risk as most individual studies of medications that lower glucose don't show reductions in risk of CVD endpoints - a meta-analysis suggests glucose control reduces major CVD by 5%(0.95RR) Lancet Diabetes Endocrine 2015;3:356–66

\* hypoglycaemia risks vary between medications but are roughly 1-2%/year (severe) and 5-10%/year (overall)

1) CVD from UKPDS risk engine calculator - v3.0b2 - unreleased beta - 2012
2) Amputation/blindness from http://www.qdiabetes.org/amputation-blindness/index.php - 2015
3) ESRD from Ann Int Med 1997;127:788-95 - lifetime risk and authors didn't break down numbers based on gender or other risk factors

| ALL LOWER GLUCOSE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RED - no effect on clinical outcomes | 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 | UKPDS COMBO | 4-11 | | 3% | | | |
| INSULIN | 12,000/6 4,000/10 | UKPDS COMBO | None done | | | | | |
| DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Alogliptin (Nesina) | 5,000/1.5 16,000/2 1,500/2 | vs glimiperide | None done | | | | | |
| GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia) | 4,400/4 5,200/3 | ? | 42 | ?CHF harm | ? | ? | ? | |
| GLPs - Exenatide (Byetta) Liraglutide (Victoza), Dulaglutide (Trulicity) | ? - not studied | | ? | | ? | ? | ? | |
| MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm) | ? - not studied | | ? | | ? | ? | ? | |
| SGLT2 - Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance) | Empag (7000/3) Others? | 1.6% | ? | | ? | ? | ? | |
| 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

# 10 mmHg reduction in SBP

|  | NNT over ten years |
|---|---|
| Mortality | 32 |
| CVD events | 26 |
| CHD events | 55 |
| Stroke events | 25 |
| Retinopathy | 45 |
| Albuminuria | 11 |

# 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

Age 76
# A fib
150/70 mmHg
No CHF
No Prev stroke/TIA
No diabetes

### PERCENT PER YEAR

| THERAPY | Stroke / Embolism | | Major Bleeding | |
|---|---|---|---|---|
| | CHADS2 | CHA2DS2-VASc | Pop.Avg. | HAS-BLED |
| NO THERAPY | 3.6% | 4.3% | 0.6% | |
| ASPIRIN | 2.8% | 3.4% | 1.1% | |
| ASPIRIN+CLOP | 2.0% | 2.4% | 3.8% | |
| WARFARIN | 1.2% | 1.4% | 3.8% | 2.2% |
| DABIGATRAN 110 | 1.2% | 1.4% | 3.0% | 1.8% |
| DABIGATRAN 150 | 0.8% | 0.9% | 3.8% | 2.2% |
| RIVAROXABAN | 1.2% | 1.4% | 3.8% | 2.2% |
| APIXABAN | 0.9% | 1.1% | 2.6% | 1.5% |
| EDOXABAN 30 | 1.2% | 1.4% | 1.8% | 1.0% |
| EDOXABAN 60 | 1.2% | 1.4% | 3.0% | 1.8% |

| | | | | |
|---|---|---|---|---|
| DABIGATRAN 150 | 0.9% | 0.2% | 3.8% | 1.2% |
| RIVAROXABAN | 0.4% | 0.2% | 3.8% | 1.2% |
| APIXABAN | 0.3% | 0.2% | 2.6% | 0.8% |
| EDOXABAN 30 | 0.4% | 0.2% | 1.8% | 0.6% |
| EDOXABAN 60 | 0.4% | 0.2% | 3.0% | 1.0% |

**percent per year**

http://www.sparctool.com

# An easy A fib table

| CHADS$_2$ Score | Patient's ANNUAL risk (%) of ischemic stroke | | | Difference in benefit between ASA and OAC |
|---|---|---|---|---|
| | 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

| CHADS$_2$ Score | Patient's ~ ANNUAL risk (%) of ischemic stroke | | | Difference in benefit between ASA and OAC |
|---|---|---|---|---|
| | 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 |