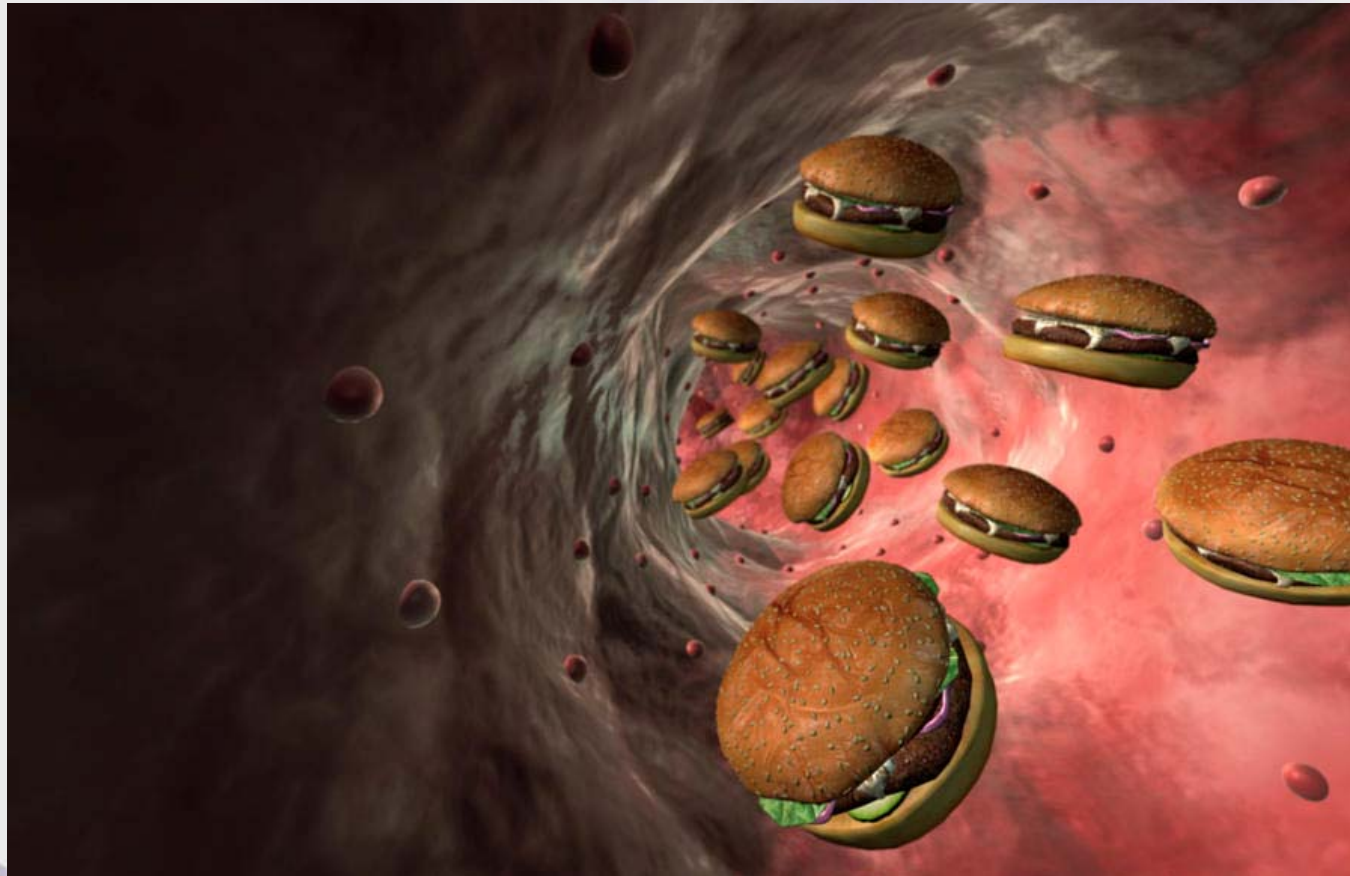# Moving from dyslipidemia to cardiovascular risk managament

## G Michael Allan

Professor and Director of EBM, Dept of Family, U of A.
Evidence & CPD Program, Alberta College of Family Physicians

Faculty/Presenter Disclosure

- **Faculty/Presenter: G Michael Allan**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Not applicable
  - **Speakers Bureau/Honoraria:** Not applicable
  - **Consulting Fees:** Not applicable
  - **Other:**
    - **Employed by University of Alberta, Alberta Health**
    - Non-profit sources including Alberta College of Family Physicians, TOP, IHE, CADTH, etc.

- **Chair a Primary Care Guideline on Lipid Management**

Cholesterol: A brief history
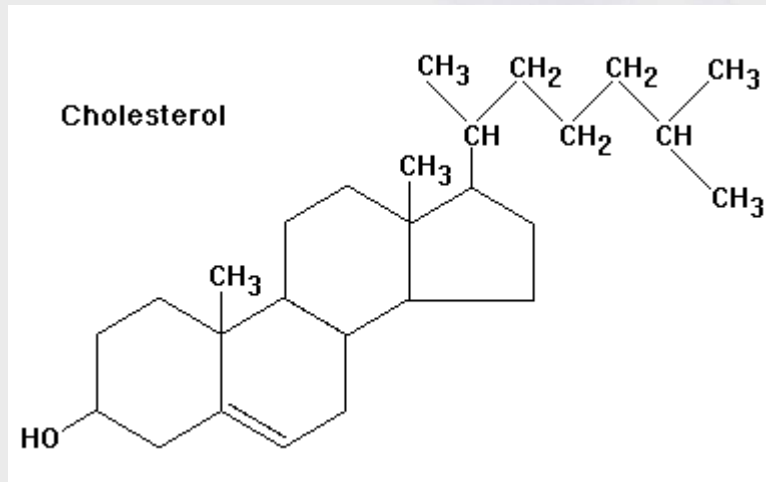
Testing Cholesterol

HEALTH

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

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

Dyslipidemia

Cardiovascular Risk Reduction

"Do I need to Fast Doctor?"

- 2 large studies (33,000 Denmark, 200,000 Canada)
  - Without fasting:
    - LDL, Total Chol, HDL 0.1-0.2 lower & Trig 0.3 higher
    - Total Chol & HDL <2% change, at most ~10% LDL
- Non-fasting & fasting correlate equally with outcomes
- Biggest change in Trig (≤20%):
  - Contribute at 1/5 ratio to Total Chol.
  - O.5mmol/L change would change Total Chol 0.1

Circulation. 2008; 118: 2047-56. Arch Intern Med. 2012; 172:1707-1710. Tools for Practice #121 (Sept 15, 2014) https://www.acfp.ca/wp-content/uploads/tools-for-practice/1410799493_121non-fastinglipidsfv.pdf

# Testing lipids: When to start & how often?

- In Canada: Start at 40 males and 50 females
  - NZ: 45 males & 55 females (10 yrs early if risk/race)

- Lipid levels: Individual variance = 7%
  - Average annual increase 0.5-1%

- <10% move from low to high risk in ~10 yrs
  - Unclear what moving to moderate risk is?

Ann Intern Med 2008;148:656-61.   BMJ 2013;346:f1895

Testing lipids: When to start & how often?

- Bottom-Line: Start age 40 men and 50 women, and then every 5 years after. Fasting is generally not required. Always do risk assessment with each lipid test.

Ann Intern Med 2008;148:656-61.   BMJ 2013;346:f1895

How do we decide who to treat?
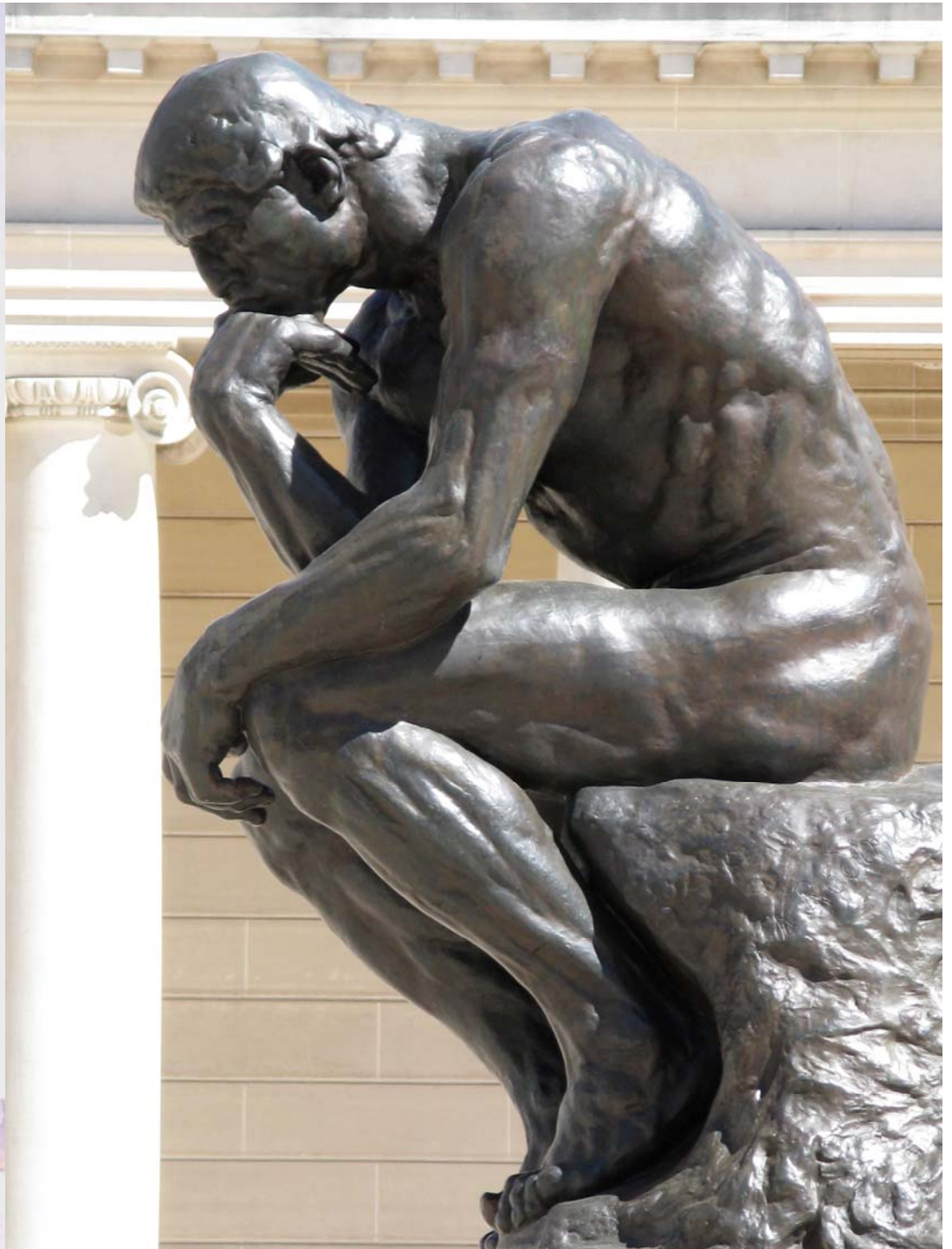
The Fallacy of Risk Factors

- There are >300 risk factors
- Associations versus causations
- Consider a few:

Homocystiene

CRP

Ear lobe creases?

Biomarkers

- We identified 68 risk factors with ≥1 meta-analyses
    - 57 (84%) were positively associated in all analyses

- Get ~75% prediction with standard risk factors, & biomarkers add 0.01 - 0.40%
    - Example: best lipoprotein ≤0.18% vs WBC 0.36%

See Biomarker in Evidence review (Chapter 2).

Target Shooting

What do lipids tell us?

- Cholesterol is a risk factor for heart disease[1]
  - High levels (low HDL) associated with increase risk
  - Not always consistent (?worse if LDL <3.4 mmol/L)
- It can be very helpful to figure out CVD risk
  - We'll come back to that
- BUT,...
- It is not a disease (there are no symptoms).
- And causation is far from confirmed

1. Ann Intern Med. 2006;145:520-530.

What does it take to put an ugly fact through the heart of a beautiful hypothesis?

|

Narrative Review: Lack of Evidence for Recommended Low-Density Lipoprotein Treatment Targets: A Solvable Problem

Rodney A. Hayward, MD; Timothy P. Hofer, MD, MSc; and Sandeep Vijan, MD, MSc

Can we change the way we think?

ANALYSIS

The idolatry of the surrogate

Easier to measure surrogate outcomes are often used instead of patient important outcomes such as death, quality of life, or functional capacity when assessing treatments. **John Yudkin**, **Kasia Lipska**, **and Victor Montori** argue that our obsession with surrogates is damaging patient care

Understanding Risks

How do I decide who to treat?

- With every lipid test, Do a risk estimate.[1]
  - Biggest predictor of benefit is NOT lipid levels or statin type/dose (potency): It is Risk.[2]

- Example of trials with risk and lower lipids.
  - ASCOT: enrolled on hypertension.[3]
  - Jupiter: enrolled on CRP.[4]
  - TNT: enrolled with past CVD but low lipids.[5]

1) Curr Opin Lipidol. 2014 Aug;25(4):254-65 2) Lancet. 2012;380:581–590. 3) Lancet. 2003;361(9364):1149-58. 4) NEJM 2008;359:2195-2207. 5) N Engl J Med. 2005;352(14):1425-35

How do I decide who to treat?

- We must base it on overall risk.
  - So, Use a validated risk calculator.

- Doing Risk Assessment most important,…
  - My Recommendation: If you use one, keep using it.

- Understand: What risk and over how long?
  - They vary in duration (e.g. 5 vs 10 years)
  - They vary in outcome (MI and cardiac death, CVD mortality, All cardiovascular disease, etc)

Agreement in Risk Calculators
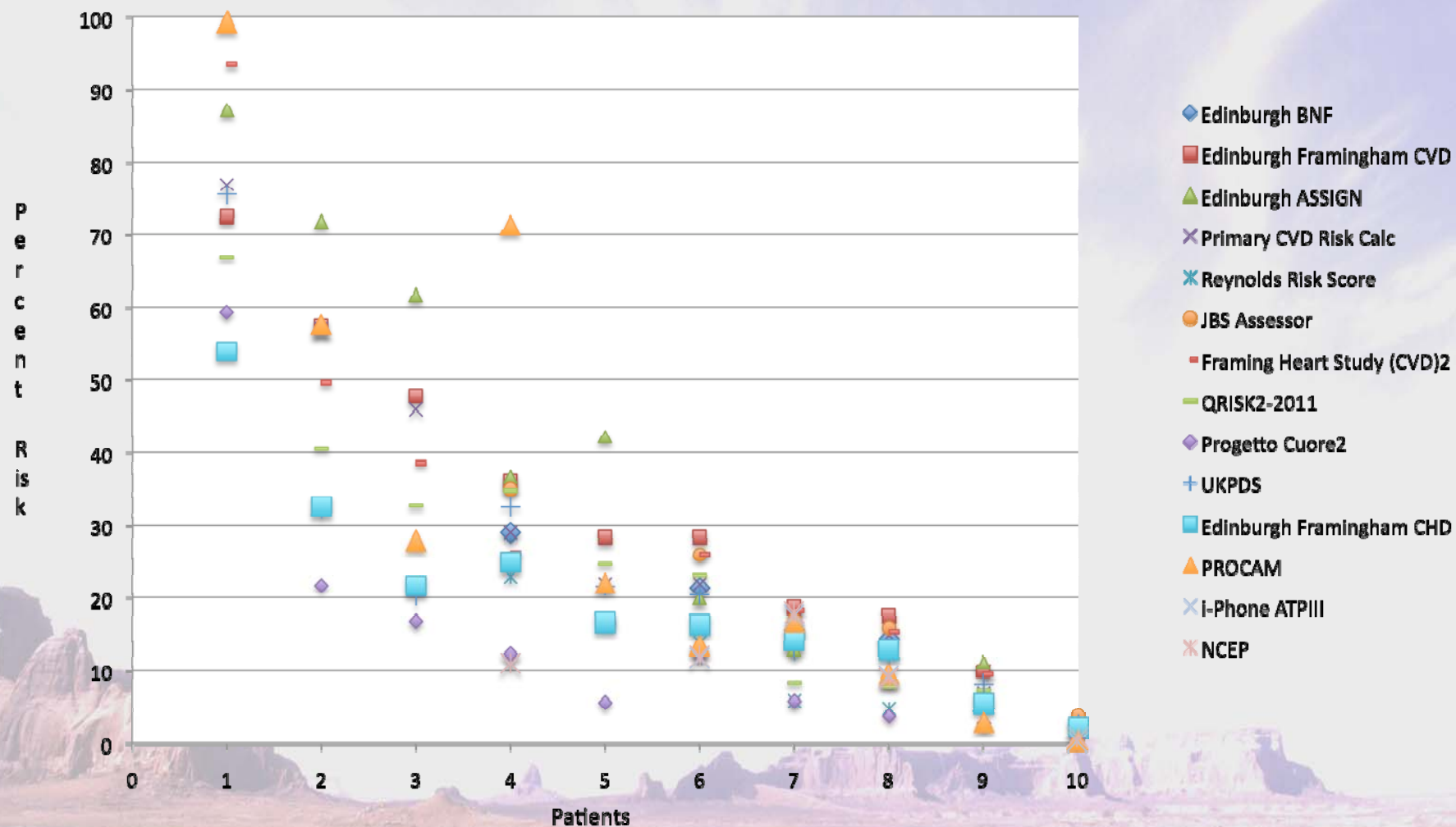
Variability in Calculating Risk

- 95% Confidence Intervals (CI) around 10-year predictions of CHD

Framingham[1]	Baseline	<10%	10-20%			30-40%
	CI (+/-)	1.5%	3%			15%
Reynolds[2]	Baseline	10%	15%	20%		30%
	CI (+/-)	4%	5%	6%		7%

1. Am Heart J 1991; 121: 293-98.   2. J Cardiovasc Risk 2002; 9: 183-190.

How Relative Risk Weighting of the same Risk factors varies by Calculator

(50-year-old, Female, Smoker, 160 Systolic BP, 7 Total Chol, 0.8 HDL, Non-Diabetic).
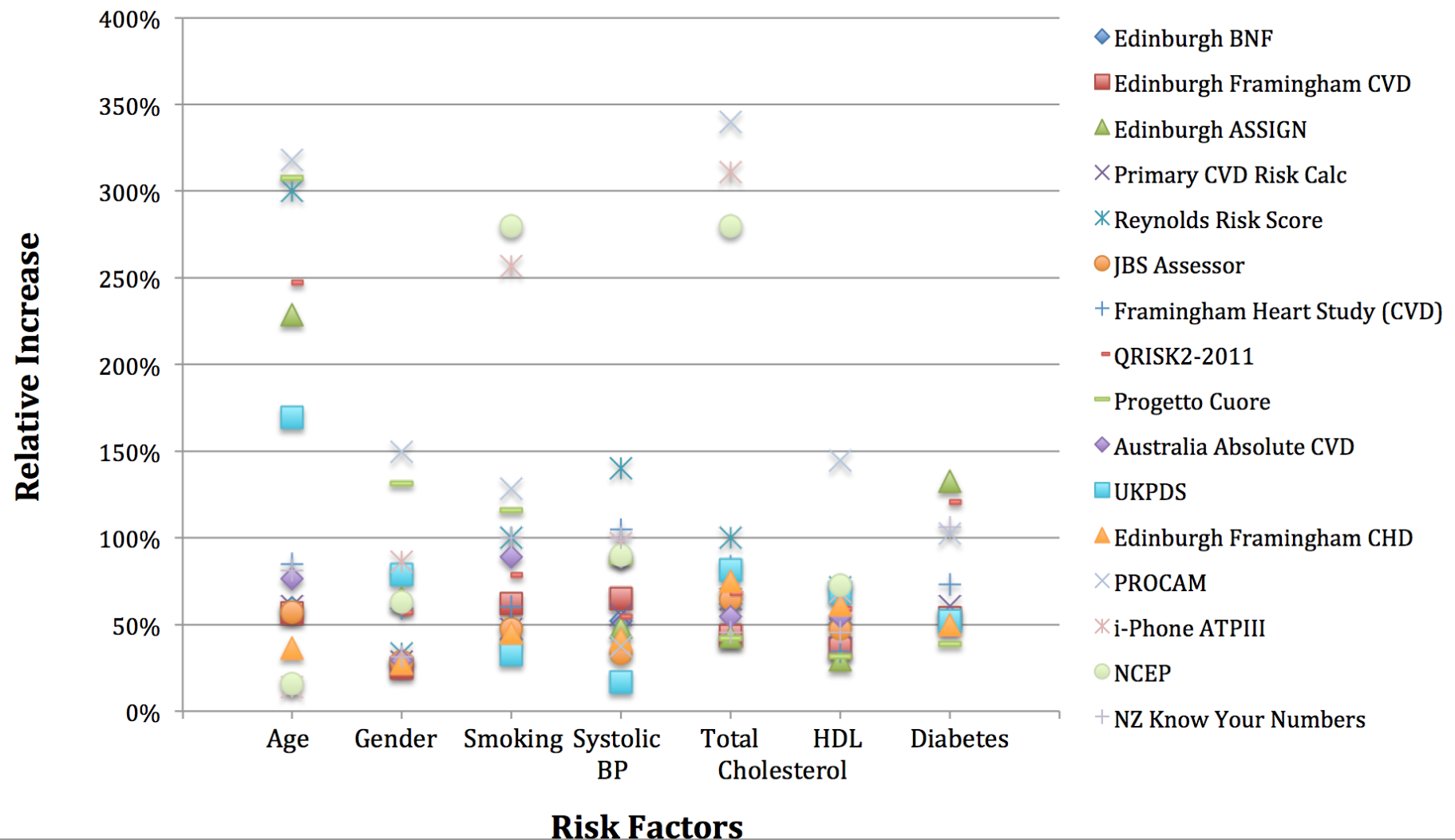
How do I decide who to treat?

- Use a validated risk estimation tool with every lipid test. Know what a patients risk of CVD is.

Examples

- Know your numbers
  - http://www.knowyournumbers.co.nz/

- Edinburgh Risk Calculator
  - http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp

- BS Medicine Calculator
  - http://chd.bestsciencemedicine.com/calc2.html#basic

Circulation. 2013; 127: 1948-1956

	Total	HDL	LDL	Age	Smoke	BP	DM
Mr Norm	4.9	1.0	2.6	55	Yes	140	Not

On the Case

Know your numbers: NZ
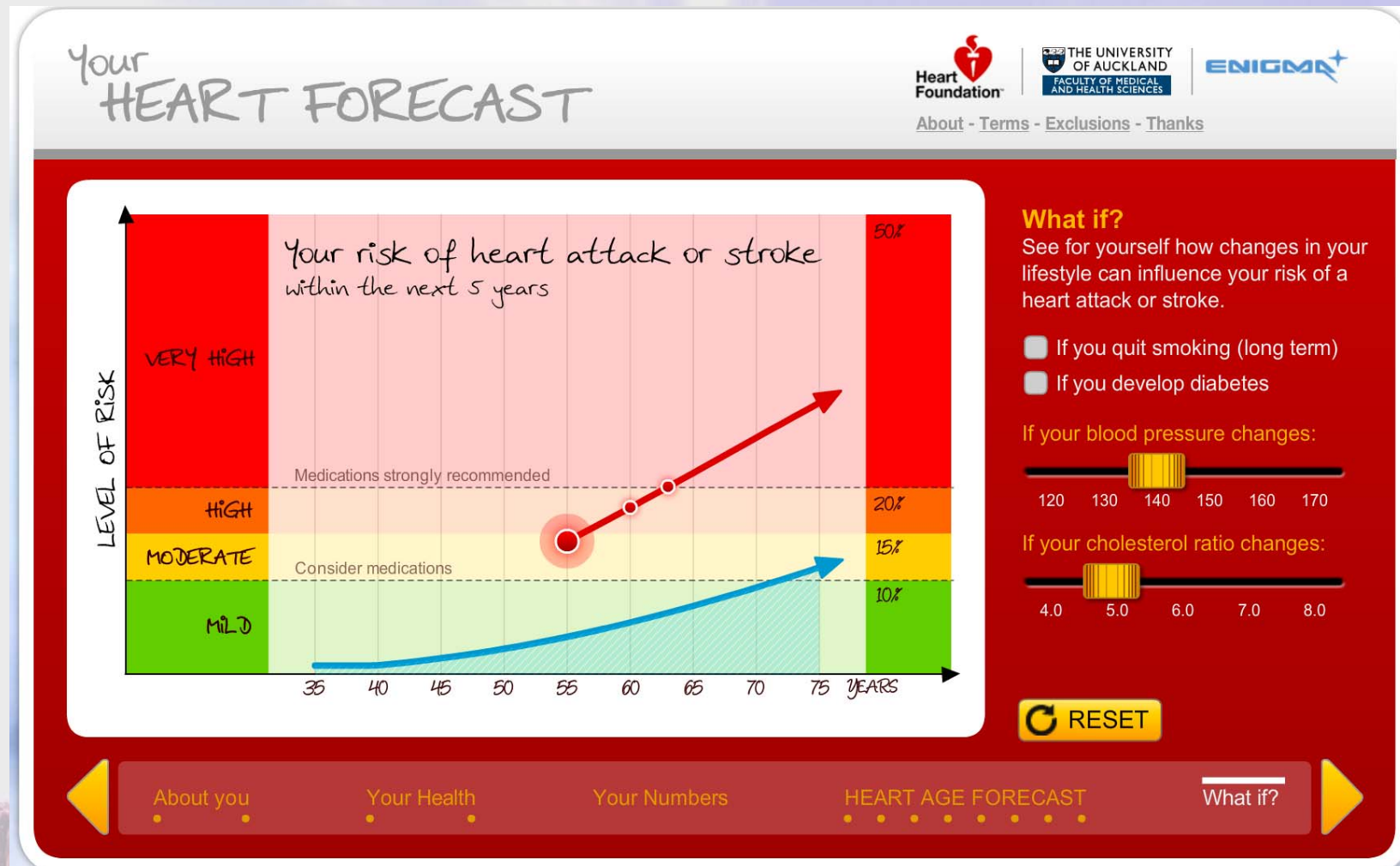
- **Good: Shows you how you compare to ideal**
  - **Also, heart age can be informative for some people.**
- **Bad: Uses cholesterol change to estimate risk / benefit**

Edinburgh CVD calculator

- **Good: Lots of Flexibility (time, display, equation)**
- **Bad: Uses cholesterol change to estimate risk / benefit**

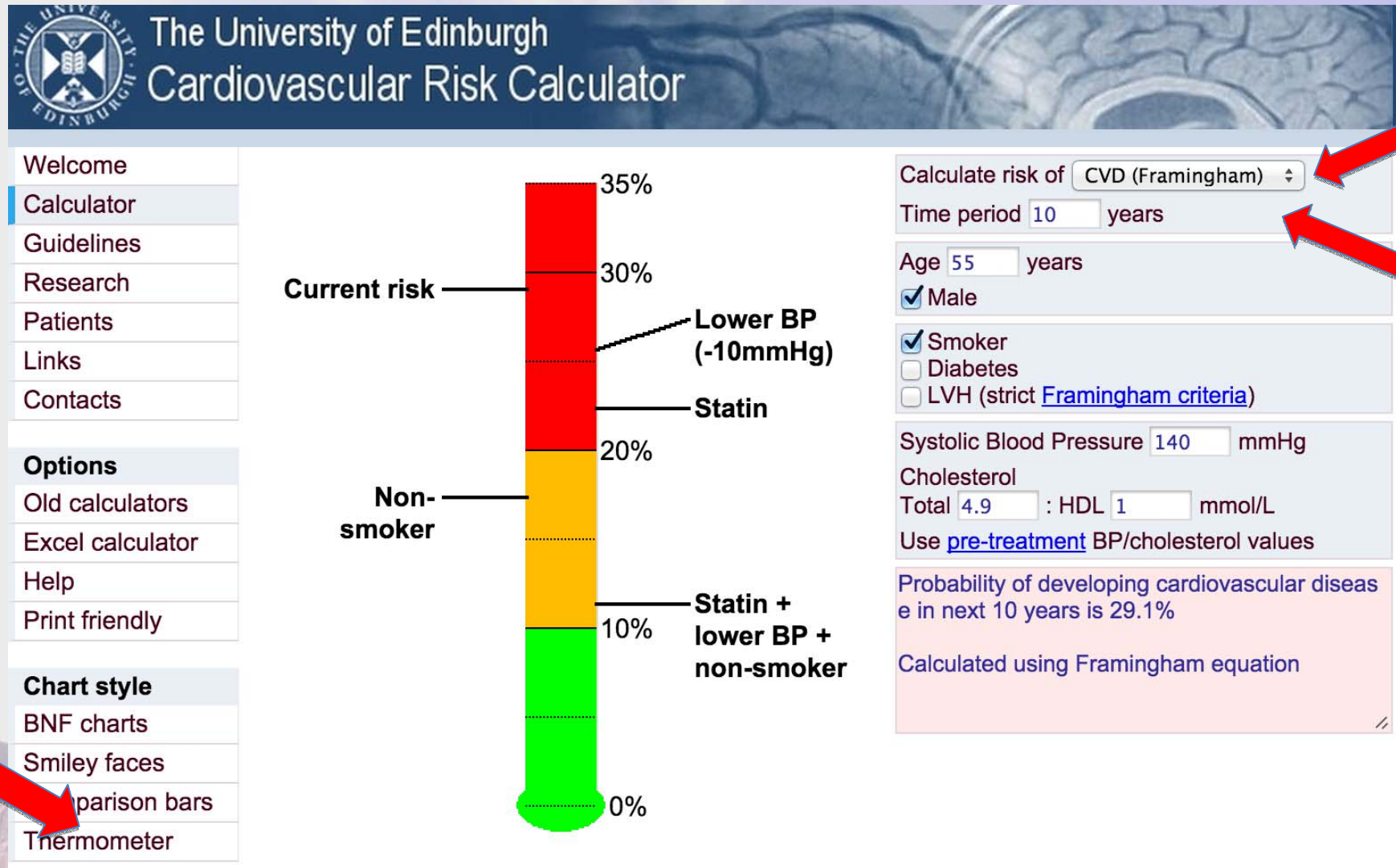**BS Medicine Calculator**

Framingham
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK®2-2014
Heart attacks + strokes

ACC/AHA ASCVD
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

Age 55 years

Gender ✔ Male | Female

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

Diabetes Yes | ✔ No

Systolic Blood Pressure 140 mmHg
Blood pressure should be prior to drug treatment
120 mmHg is used for baseline risk

Total Cholesterol 4.9 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 mmol/L
HDL should be prior to drug treatment
1.3 mmol/L is used for baseline risk

Family History of Early CHD 0 %
The amount of additional risk conferred from a

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
Low-mod intensity statins
High intensity statins
Smoking Cessation
ASA

Benefit Estimate Details

Risk Time Period
10 years
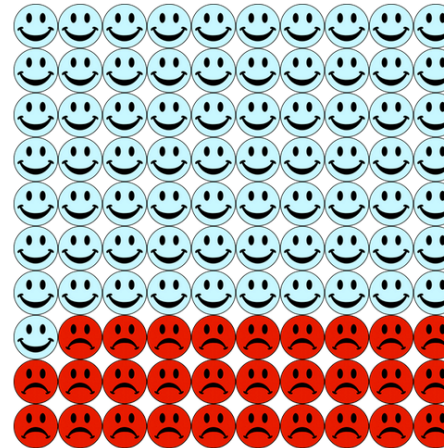
🙂 **70.9%** No event
🙁 **29.1%** Total with an event
🙂 **0.0%** Number who benefit from treatment
NNT ∞ Number needed to treat

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

- **Good: Actual benefits from research**
- **Bad: Less options and no life-time risk**

Framingham
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK®2-2014
Heart attacks + strokes

ACC/AHA ASCVD
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

With benefit

Age

55 years

Gender

✔ Male | Female

Smoker

✔ Yes | No

CVD risk is reversed after 5-10 years of no smoking

Diabetes

Yes | ✔ No

Systolic Blood Pressure

140 mmHg

Blood pressure should be prior to drug treatment

120 mmHg is used for baseline risk

Total Cholesterol

4.9 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 mmol/L

HDL should be prior to drug treatment

1.3 mmol/L is used for baseline risk.

Family History of Early CHD

0 %

The amount of additional risk conferred from a

Relative Benefit: **35%**

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

Low-mod intensity statins

High intensity statins

Harm of Intervention

- Muscle aches and stiffness NNH 10-20 (similar to placebo in most studies)
- Increased liver function tests (3x normal) NNH 150
- Severe muscle/kidney damage NNH 10,000
- Nausea, constipation, diarrhea
- Drug Cost

Smoking Cessation

ASA

Benefit Estimate Details

Risk Time Period

10 years

🙂	**70.9%**	No event
☹️	**18.9%**	Total with an event
😃	**10.2%**	Number who benefit from treatment
NNT	**10**	Number needed to treat

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

Good Drugs?

What drug(s) should I offer?

- Reduce CVD and/or mortality.

- Lifestyle first: Samples of interventions over 2 yrs
  - Smoking: NNT for death in high risk =11
  - Activity: NNT for any CVD in high risk = 6
  - Diet (Mediterranean): NNT for CVD in high risk = 12

1) Chest 2007; 131: 446–52 Ann Intern Med. 2005;142:233-9. 2) Circulation 2004;109:1371-8. Cochrane 2011;(7):CD001800. J Am Coll Cardiol 2012;60:1521–8. 3) Lancet 1994; 343: 1454-59. Lancet 2002;360(9344):1455-61. N Engl J Med 2013; 368:1279-1290

Things that change Cholesterol!!

Drug/Intervention	RCTs	LDL	HDL	Trig	CVD (relative risk)	Mortality (relative risk)
Torcetrapib	2	++	+++		+25%	+50%
Low/modified fat diet	>20	+		+	inconsistent	Ø
Omega 3	>20			+	Ø	Ø
Dalcetrapib	1		++		Ø	Ø
Add Niacin*	2	+	+	++	Ø	Ø
Add Fibrate*	1			+++	Ø	Ø
Fibrates alone	10+	+		++	Ø (just MI)	Ø
Ezetimibe	5	++ - ++++			-6%*	Ø
Statin	18	+++			-25%	-14%
Mediterranean diet	3				-30%+	Insign or better

* To a statin

Things that change Cholesterol!!

Drug/ Intervention	RCTs	LDL	HDL	Trig	CVD (relative risk)	Mortality (relative risk)
Torcetrapib	**2**	++	+++		**+25%**	**+50%**
Low/modified fat diet	>20	+		+	inconsistent	∅
Omega 3	>20			+	∅	∅
Dalcetrapib	1		++		∅	∅
Add Niacin*	2	+	+	++	∅	∅
Add Fibrate*	1			+++	∅	∅
Fibrates alone	10+	+		++	∅ (just MI)	∅
Ezetimibe	**5**	++ - ++++			**-6%***	**∅**
Statin	**18**	+++			**-25%**	**-14%**
Mediterranean diet	3				-30%+	Insign or better

* To a statin

Things that change outcomes!!

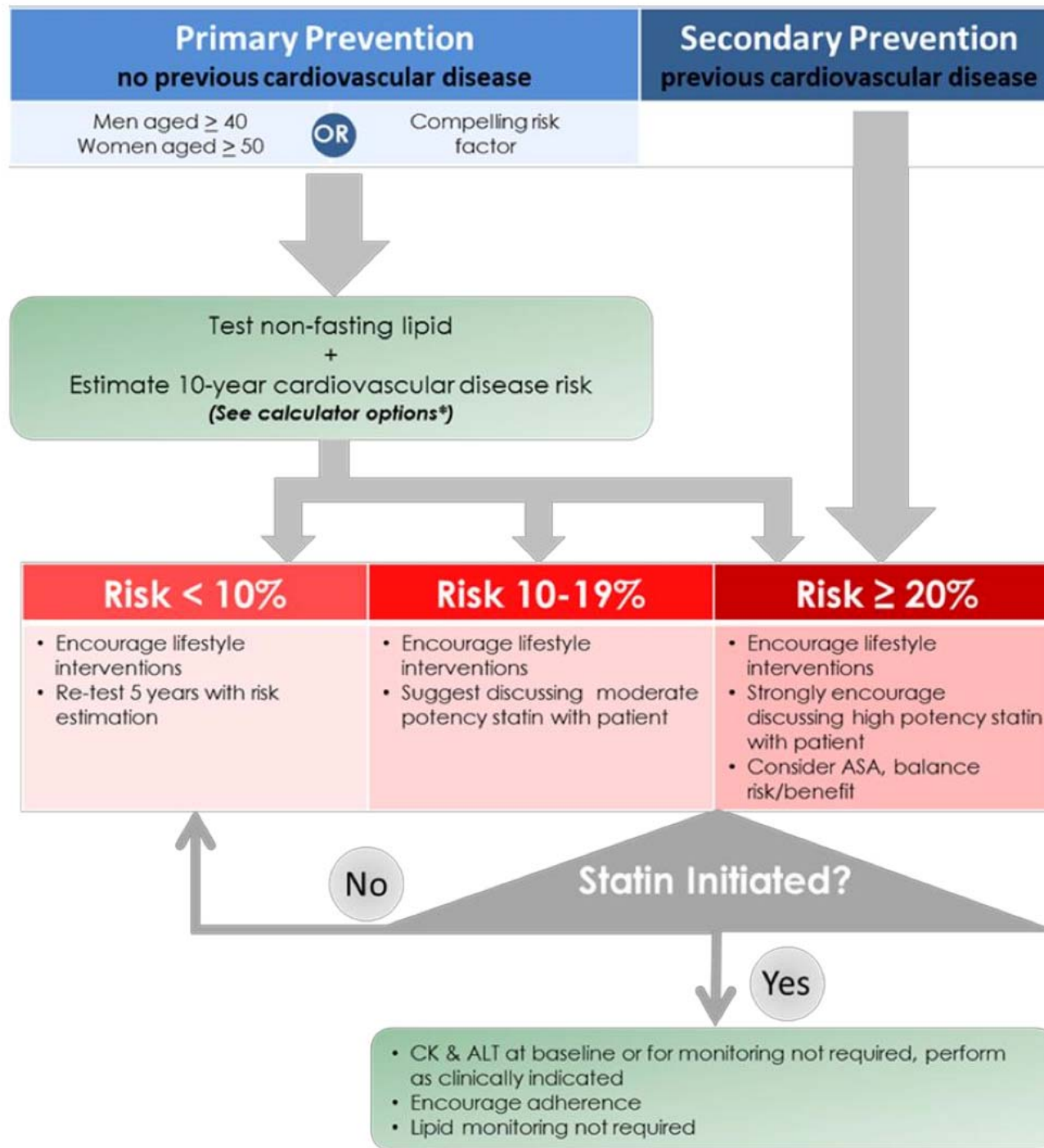| Drug/ Intervention	RCTs	LDL	HDL	Trig	CVD (relative risk)	Mortality (relative risk)
Torcetrapib	2	++	+++		+25%	+50%
Low/modified fat diet	>20	+		+	inconsistent	Ø
Omega 3	>20			+	Ø	Ø
Dalcetrapib	1		++		Ø	Ø
Add Niacin*	2	+	+	++	Ø	Ø
Add Fibrate*	1			+++	Ø	Ø
Fibrates alone	10+	+		++	Ø (just MI)	Ø
Ezetimibe	5	++ - ++++			-6%*	Ø
Statin	**18**	**+++**			**-25%**	**-14%**
Mediterranean diet	**3**				**-30%+**	**Insign or better**

* To a statin

What drug(s) should I offer?

- Bottom-Line: Regarding medications, only statins have a large body of consistent evidence showing meaningful reduction in CVD and small reductions in mortality.

Primary Prevention
no previous cardiovascular disease

Secondary Prevention
previous cardiovascular disease

Men aged ≥ 40
Women aged ≥ 50

OR

Compelling risk factor

Test non-fasting lipid
+
Estimate 10-year cardiovascular disease risk
(See calculator options*)

Risk < 10%

- Encourage lifestyle interventions
- Re-test 5 years with risk estimation

Risk 10-19%

- Encourage lifestyle interventions
- Suggest discussing moderate potency statin with patient

Risk ≥ 20%

- Encourage lifestyle interventions
- Strongly encourage discussing high potency statin with patient
- Consider ASA, balance risk/benefit

Statin Initiated?

No

Yes

- CK & ALT at baseline or for monitoring not required, perform as clinically indicated
- Encourage adherence
- Lipid monitoring not required

Intensity	Statin Options
Low Intensity	Pravastatin 10-20mg; Lovastatin 10-20 mg; Simvastatin 5-10mg; Atorvastatin 5mg; Rosuvastatin 2.5mg
Moderate Intensity	Pravastatin 40-80mg; Lovastatin 40-80mg; Simvastatin 20-40mg; Atorvastatin 10-20mg; Rosuvastatin 5-10mg
High Intensity	Atorvastatin 40-80mg; Rosuvastatin 20-40mg

Therapy		Estimating benefit (relative risk reduction)	Example if baseline risk estimated at 20% over 10 years		
			Absolute Risk Reduction	Number Needed to Treat (NNT)	New Risk Estimate
Smoking Cessation		Recalculate without smoking.	9%*	12*	11%*
Mediterranean Diet		30%	6%	17	14%
Exercise		30%	6%	17	14%
Statin Intensity	Low	25%	5%	20	15%
	Moderate	30%	6%	17	14%
	High	35%	7%	15	13%
ASA		12%	2%	50	18%

* Example used a 53 year old male smoker with total cholesterol 5, HDL 1.2 and systolic BP 128, estimated ris

If dietary cholesterol doesn't matter,…