Simplified Lipid Management: A truly primary care guideline

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Faculty/Presenter Disclosure

- **Faculty/Presenter: Mike, Mike & Tina**
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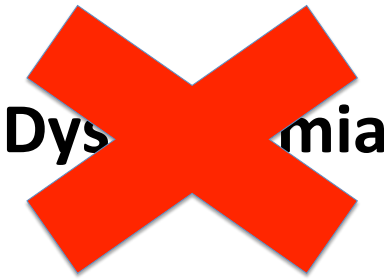


Cardiovascular Risk Reduction

Simplified Lipid Pathway

Separate Evidence Review
3 Family Doctors
2 Pharmacists

Peer Review
32 peer reviews
(mostly Family Doctors)

Evidence Review Group
Adrienne J Lindblad
Michael R Kolber
Scott Garrison
Candra Cotton
G Michael Allan

Lipid Pathway Committee
G Michael Allan
Marco Mannarino
Ann Comeau
John Coppola
Brianne Hudson
Cindy McMinis
Raj Padwal
Christine Schelstraete
Kelly Zarnke
Adrienne J Lindblad (non-voting member)

Pathway Review Group
Michael R Kolber
Christina Korownyk
Adrienne J Lindblad
G Michael Allan

Pathway Committee

2 Specialists,	1 Nurse Practitioner
1 Nurse	4 Family Doctors
1 Pharmacist	(chair & co-chair)

Our Questions

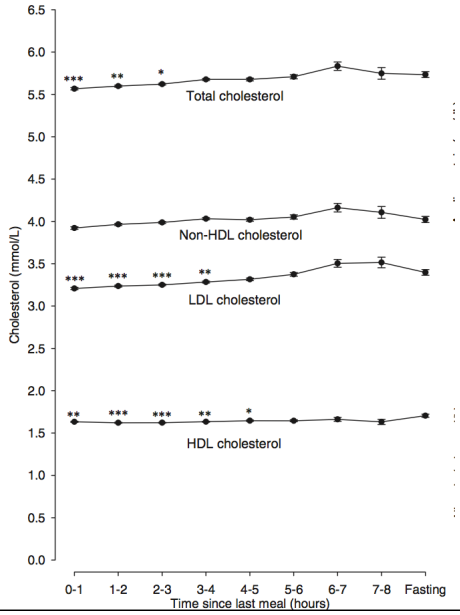
1. Do Patients need to fast for lipid testing?
2. Testing lipids: When to start & how often?
3. How do I decide who to treat?
   a) Risk factors and biomarkers
   b) Risk vs lipid levels
4. What drug(s) should I offer?
5. What dose should I offer?
6. What do I need to monitor?
7. How do I talk to patients?

"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

"Do I need to Fast Doctor?"



- Actual change in an estimated risk is <1%
- Bottom-Line: No meaningful difference in fasting vs non-fasting. Fasting is not required.

Circulation. 2008; 118: 2047-56.

Testing lipids: When to start & how often?

- Best evidence likely 40 males and 50 females
- 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. Always do risk assessment with each lipid test.

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

The Fallacy of Risk Factors

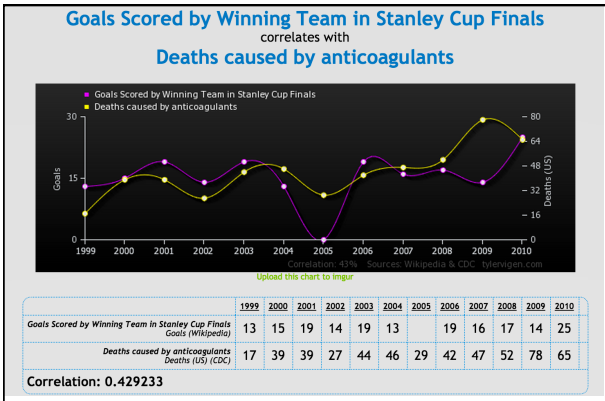
- There are >300 risk factors
- Associations versus causations
- Consider a few:

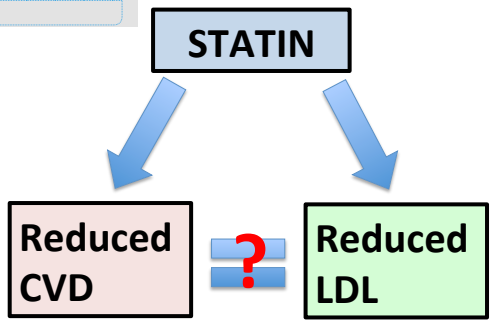
Homocystiene
CRP
Ear lobe creases?

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%

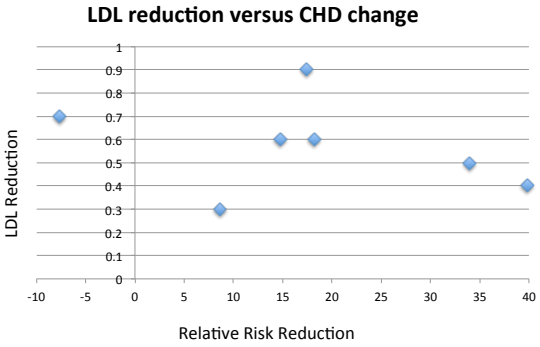
See Biomarker in Evidence review (Chapter 2).





What do non-statin trials say about CHD & LDL reduction?

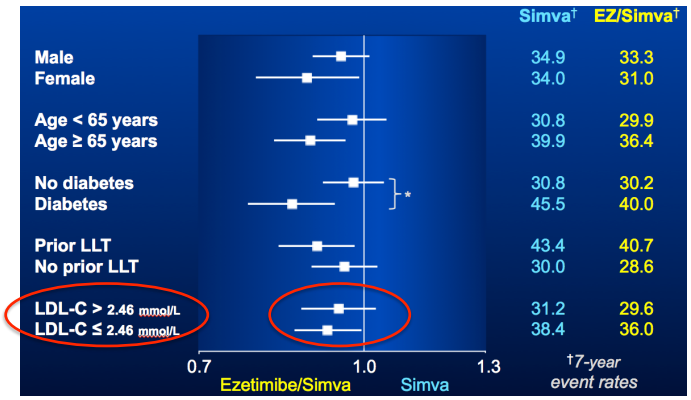
STUDY	INTERVENTION	Relative Risk Reduction in CHD	LDL Reduction
DART	Diet	8.6%	0.3
Upjohn	Resin	39.8%	0.4
Helsinki	Gemfibrozil	34.0%	0.5
WHO	Clofibrate	18.2%	0.6
CDP	Niacin	14.7%	0.6
Minnesota	Diet	-7.7%	0.7
LRC	Resin	17.4%	0.9



Examining the largest (>2,000 participants) non-statin RCTs with at least two years duration from the Law meta-analysis

(BMJ. 2003 Jun 28;326(7404):1423).

Proving it with IMPROVE-IT?



LDL level: LDL level had no effect on how well Ezetimibe worked. *If anything, ezetimibe had a slightly better CVD reduction with lower starting LDL (not at all significantly)*

IMPROVE-IT slides from American Heart Association (AHA) 2014 Scientific Sessions (accessed 2014 Dec 16): www.my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469669.pdf

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.

Who really benefit from treatment?

	Total	HDL	LDL
Mrs Fats	7.5	1.0	5.2
Mr Norm	4.9	1.0	2.6

- Who gets meds by guidelines?
- Who is higher risk?

Who really benefit from treatment?

	Total	HDL	LDL	Age	Smoke	BP
Mrs Fats	7.5	1.0	5.2	35	No	120
Mr Norm	4.9	1.0	2.6	55	Yes	140

- Who gets meds by guidelines?
- Who is higher risk?

Lipid vs Risk?

	Risk* (x10 yrs)	Med	Treating (statin) 5 years		
			Risk	Benefit (~28%)	New risk
Mrs Fats	1.7%	Yes	0.6%	0.17%	0.4%
Mr Norm	13.6%	No	6.2%	1.7%	4.5%

- The patient who "should" be treated get 10% of the benefit the patient not treated could get!

How do I decide who to treat?

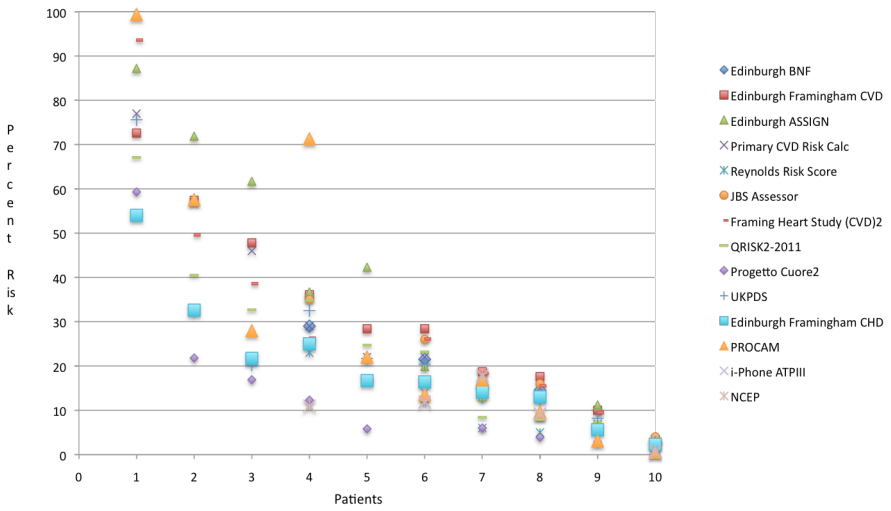
- With every lipid test, Do a risk estimate.[1]
  - Without risk estimate, determining CVD risk is tough
  - Biggest predictor of benefit is NOT lipid levels or statin type/dose (potency): It is Risk.[2]
- Example of trials with risk and lower lipids.
  - ASCOT: enrolled on hypertension.[3]
  - Jupiter: 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



Circulation. 2013; 127: 1948-1956

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 do I decide who to treat?

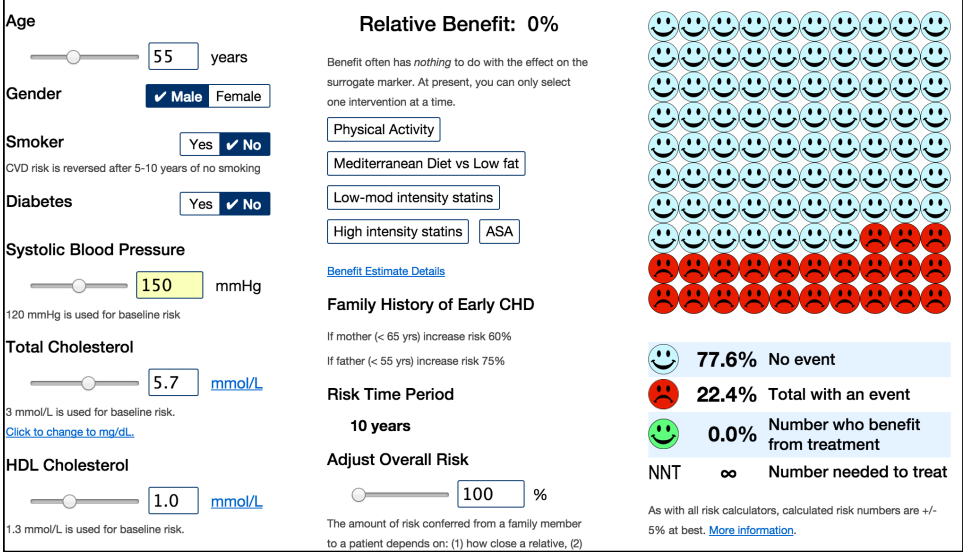
- Use a validated risk estimation tool with every lipid test. Know what a patients risk of CVD is.

Examples

- Edinburgh Risk Calculator
  - http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp
- QRISK2
  - http://www.qrisk.org/
- BS Medicine Calculator
  - http://chd.bestsciencemedicine.com/calc2.html#basic

Circulation. 2013; 127: 1948-1956

Risk Estimation



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!!

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Torcetrapib	**2**	**++**	**+++**		**+25%**	**+50%**
Low/modified fat diet	>20	+		+	inconsistent	ø
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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 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.

What dose should I offer?

- Data on dose in primary preventions is inadequate
- In secondary prevention
  - Low dose vs placebo: Relative ~25%, NNT CHD = 27
  - High dose vs low: Relative ~10%, NNT CHD = 91
- Maximizing dose increases withdrawal: NNH 47
- Bottom-Line: Most of the benefit with statins come at low/moderate dose. Maximizing dose/potency (intensity) increases benefit slightly more. It may be worth trying to maximize the intensity of statins, but not at the cost of compliance.

Tools for Practice, #67, May 22, 2012.
http://www.acfp.ca/wp-content/uploads/tools-for-practice/1397838022_20120522_090852.pdf

What do I need to monitor: LFT/CK

- Systematic review: Statin vs Placebo.
  - LFT >3x normal. 0.3% vs 0.2%
  - Liver failure, CK (>10x normal), myalgia, myopathy (bad enough to stop med), Rhabdo – None significantly increased
- Another Sys Rev: RCTs with >80,000
  - LFT >3ULN : 1% High intensity vs 0.3% Low intensity (0.7% diff)
  - Myopathy Sx + CK >10ULN: 0.7% High vs 0.3% Low (0.4% diff)
  - Rhabdomyolysis: 0.038% vs 0.025%
- Liver: Normal baseline + statin <2% increase (<10x N)
  - Elevated at baseline and followed: 4.6% increased on statins vs 6.4% increased without statins.

Am J Cardiol 2006. 97(8A) 52C-60C. Eur J Prev Cardiol. 2014 Apr;21(4):464-74. Gastroenterology 2004;126:1287-1292

What do I need to monitor: Sugar & Lipids

- Diabetes: Increase glucose 0.1mmol/L
  - Cause DM: 1 in 100 -250 over around 4 years.
- Lipids: Not on meds: q 5 yrs.
  - If on Statin: STOP.
    1) There is no evidence for lipid targets,
    2) You've done all you can,
    3) Once on statins, risk estimation unreliable.

Can Fam Physician. 2013 Jul;59(7):e311. Tools for Practice #122, Sept, 29, 2014.
https://www.acfp.ca/wp-content/uploads/tools-for-practice/1412004531_tfplipoproteinsfv.pdf

What do I need to monitor?

- Bottom-Line:
  - We suggest not ordering baseline ALT or CK and not monitoring unless you have clinical suspicion. Moderate quality so recommendation is weak.
  - Don't monitor Lipids after starting a statins.
  - Don't use other biomarkers or target them. The evidence does not support that they have predictive value above risk estimation.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease

Use risk to target treatment, **No lipid targets**

Nothing But Statins **No lipid monitoring**

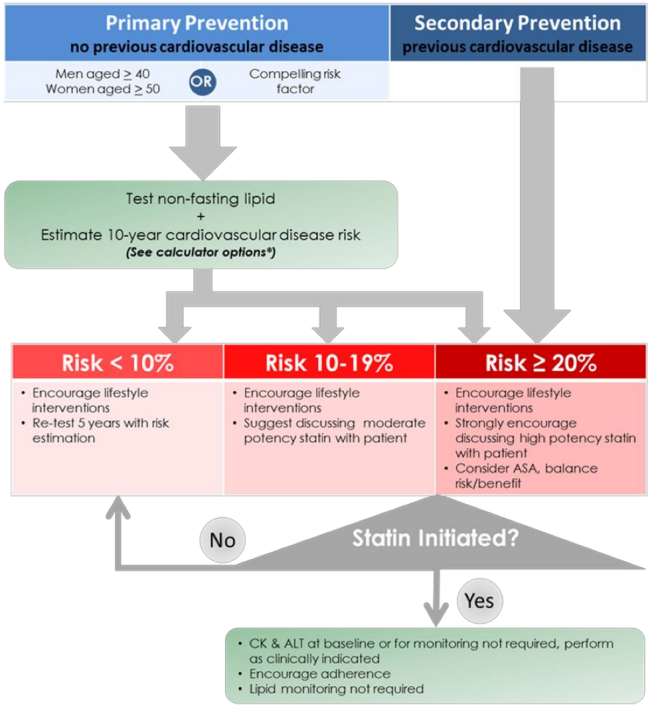
Annals of Internal Medicine CLINICAL GUIDELINE

Management of Dyslipidemia for Cardiovascular Disease Risk Reduction: Synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline

John R. Downs, MD, and Patrick G. O'Malley, MD, MPH

Summary of our pathway

- Start screening at 40 men, 50 women
- Test every 5 years (generally non-fasting)
- Estimate risk, explain risk to patient, advise of potential benefits of interventions (encourage lifestyle)
- If goes on statin, don't retest lipids further
- If does not go on statin, retest every 5 years.
- Monitoring CK and/or LFT lacks evidence. Base on clinical grounds.



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

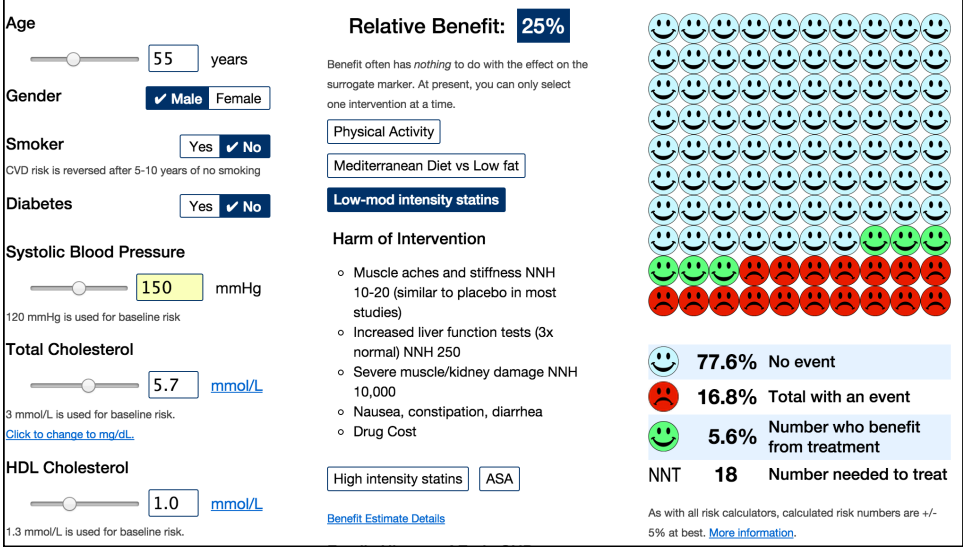
Therapy		Estimating benefit (relative risk reduction)	Example if baseline risk estimated at 20% over 10 years		
			Absolute Risk Reduction	Number Needed to Treat (NNT)	New Risk Estimate
Smoking Cessation		Recalculate without smoking.	9%*	12*	11%*
Mediterranean Diet		30%	6%	17	14%
Exercise		30%	6%	17	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

How do we talk to patients?

- Calculate Risk, tell them risk (over 10 years), and then tell them benefit (25-35%).
- Consider sale prices. If something is $20, but it is 25% off, how much do you save.
  - $5 off and final price is $15
- Monitoring: "We've found that although cholesterol can effect your chance of heart attack or stroke, changing it with most medicines doesn't do anything. For this medicine, it reduces you chance of heart attack or stroke regardless. Think of it like taking an aspirin a day (except it works two and half times better!)."

Risk/benefit estimation with Treatment



Advantages

- Less lipid testing and non-fasting
- Less/no lab (CK / LFTs) monitoring once on statins
- No monitoring lipids chasing targets once on statins
- More shared informed decision-making
- Less medicines being taken
- Right people on meds: more CVD prevented for less medication burden.