Evidence for Statins in Secondary & Primary Prevention

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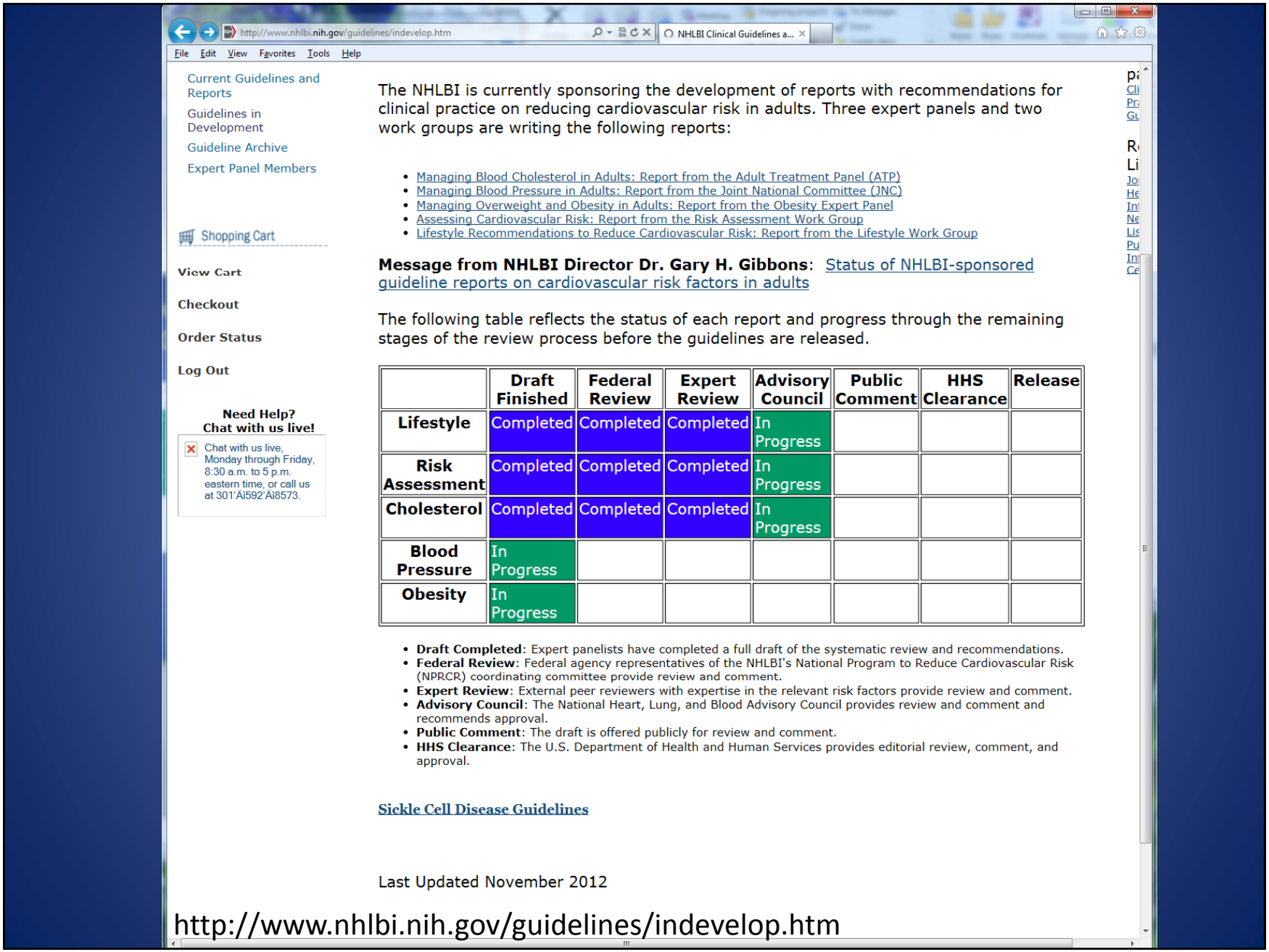
Disclosures

Vice-Chair for Clinical Applications, Cholesterol Adult Treatment Panel (ATP) IV

In the past year:

- Research grants to the institution from Amarin, Amgen, Daiichi-Sankyo, Genetech/Hoffman LaRoche, Glaxo-Smith Kline, Merck, Sanofi Aventis



http://www.nhlbi.nih.gov/guidelines/indevelop.htm

ATP IV used RCTs and meta-analyses of RCTs for guiding clinical practice guidelines

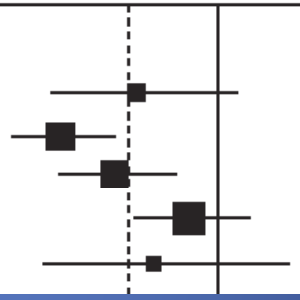
- Randomization results in an unbiased experiment comparing treatment(s) to control
- Well done RCTs objectively assess CVD outcomes and relatively common adverse effects
- Inclusion/exclusion criteria of the RCT allows definition of the population that:
  - Experiences a CVD risk benefit
  - Experiences adverse effects

Value of using RCTs and meta-analyses of RCTs for guiding clinical practice

- Not all RCTs and meta-analyses are of the same quality
  - Prospective definition of inclusion/exclusion criteria and individual level meta-analyses are higher quality than study level meta-analyses
- **While RCTs enroll a select study population which limits generalizability, nonetheless the inclusion/criteria also define the population in which the treatment is effective and safe**

High intensity statin (atorvastatin 80 mg) reduces CVD risk more than moderate intensity statin (atorva 10/simva 20-40/prava 40 mg)

	LDL-C reduction (mmol/L)	Events (% per annum)		Unweighted RR (CI)
		Statin/more	Control/less	
More vs less statin				
PROVE–IT	0·65	406 (11·3%)	458 (13·1%)	
TNT	0·62	889 (4·0%)	1164 (5·4%)	
IDEAL	0·55	938 (5·2%)	1106 (6·3%)	
SEARCH	0·39	1347 (3·6%)	1406 (3·8%)	
A to Z	0·30	257 (7·2%)	282 (8·1%)	

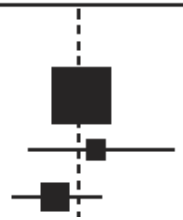


Trend: χ^2_1=12·4 (p=0·0004)

CTT 2010: Meta-analysis of data from 170,000 participants in 26 trials (CTT Collaboration 2010; 376: 1670-1681).

Statins reduce relative risk of major CVD* similarly in Primary and Secondary prevention

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL-C	Heterogeneity/ trend test
	Statin/more	Control/less		
Previous vascular disease				
CHD	8395 (4·5%)	10123 (5·6%)	0·79 (0·76–0·82)	χ^2_2=2·28 (p=0·3)
Non-CHD vascular	674 (3·1%)	802 (3·7%)	0·81 (0·71–0·92)	
Primary prevention	1904 (1·4%)	2425 (1·8%)	0·75 (0·69–0·82)	



*** Major CVD = first occurrence of any major coronary event (nonfatal MI, coronary death) , coronary revascularization, or stroke**

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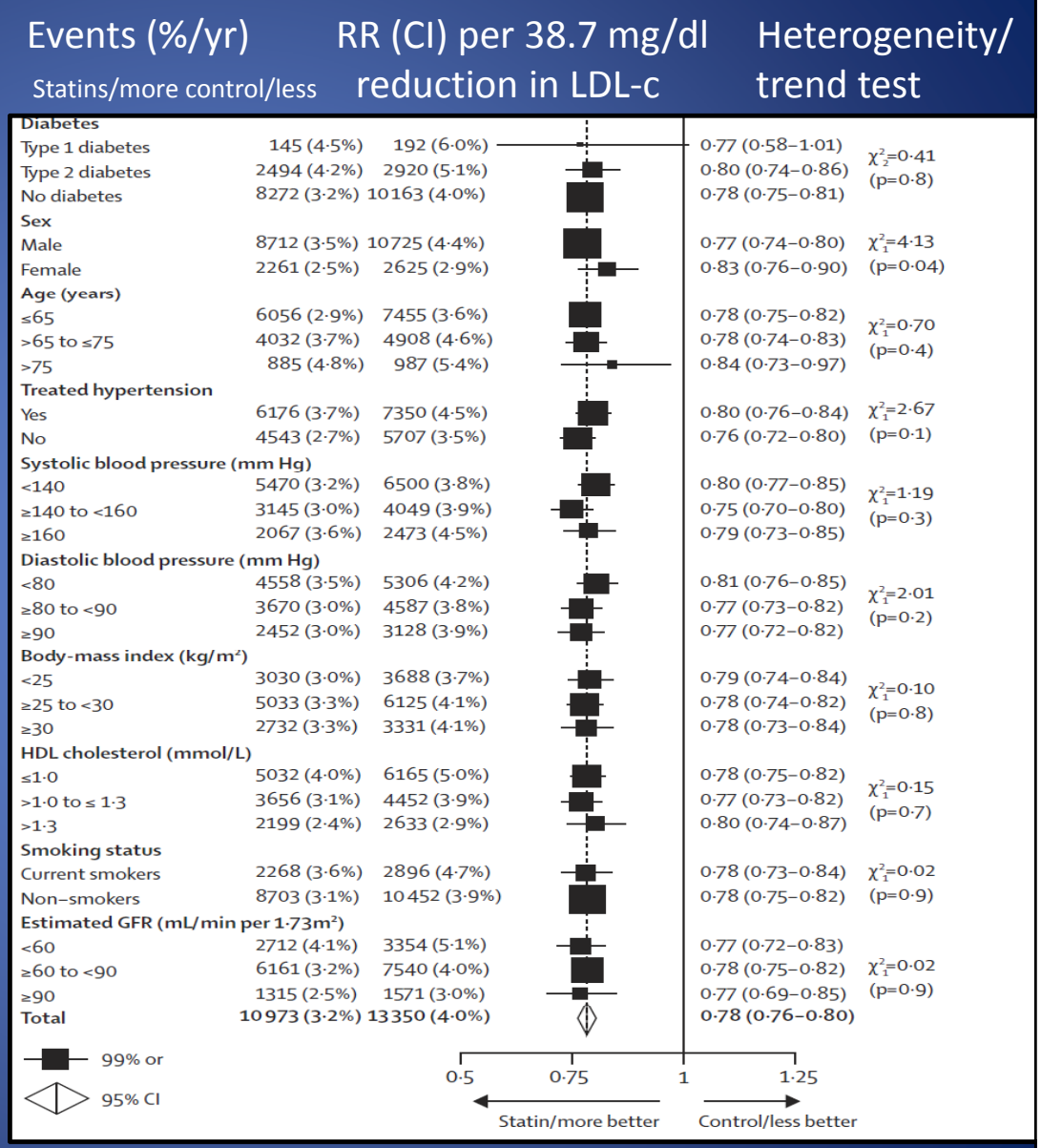
1 mmol/L = 39 mg/dL

Statins consistently reduce the relative risk of major CVD across subgroups

(Women have significant RRR major CVD, may be slightly less than men)



CTT Collaboration 2010; 376: 1670-1681

"Poly-portfolio" for secondary prevention

Risk factor and goal	Recommended Agent(s)	Change in risk factor	Relative risk reduction - Major CHD events	Relative risk reduction - stroke
LDL-cholesterol <70 mg/dl	High-dose statin + diet	≥↓50%	48%	38%
Blood pressure <140/90 mm Hg except <130/80 mm Hg with diabetes	3 drug combination Diuretic (1/2 dose) Beta-blocker ACE-inhibitor or calcium channel blocker	Systolic ↓20 mm Hg or Diastolic ↓10 mm Hg	46-49%*	63-66%*
Platelet function	Aspirin 75-81mg daily		CHD pts 42% Stroke pts 17%	CHD pts 25% Stroke pts 19%
Beta-blocker, post-MI	Non-cardioselective No intrinsic sympathomimetic activity		23% CHD death†	
ACE-inhibitor, post-MI	ACE inhibitor		20%‡	32%‡
Sudden death, post-MI	Omega-3 fish oil 1000 mg daily		30%§ 30% CHD death	
Cardiac rehabilitation	Individual prescription	↑Moderate aerobic physical activity	26% CHD death§	
Diet	Mediterranean	↑Fruits, vegetables, legumes, nuts, whole grains, fish, MUFAs	52-72%‖ 33% CHD death (25% total mortality)	

Robinson JG, et al. Am J Cardiol 2005; 95: 373-378

Estimated risk reduction from poly-portfolio

Secondary prevention

Estimated relative risk reduction over 5 years	TYPE of PATIENT		
	Any CHD	Post-MI	Stroke
Major CHD events with combined drug therapy	84% NNT = 10	91% NNT=9	77% NNT=11
Major CHD events with addition of lifestyle therapy	92% NNT=9	96% NNT=9	
CHD death with combined drug therapy		93% NNT=16	
CHD death with addition of lifestyle therapy		97% NNT=15	
Stroke with combined drug therapy	83% NNT=21		

Robinson JG, et al. Am J Cardiol 2005; 95: 373-378

Defining statin benefit

Primary prevention

Defining the lower limit for CVD reduction benefit & upper limit of harms

CTT 2012

Individual level meta-analysis of statins in those at lower risk of major CVD*

(27 trials, >134,000 participants)

* Major CVD = first nonfatal MI, coronary death, stroke, or coronary revascularization

CTT Collaborators. Lancet 2012; 380: 581-590

5 to <10% 5-year risk of major CVD* (n=24,082)

	Median predicted 5-year MVE risk	Estimated 5-year MVE risk					Total
		<5%	≥5% to <10%	≥10% to <20%*	≥20% to <30%	≥30%	
Statin vs control							
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Subtotal, 22 trials	13·7%	24 790 (421)	28 362 (1436)	38 504 (4699)	27 956 (5782)	14 925 (4362)	134 537 (16 700)

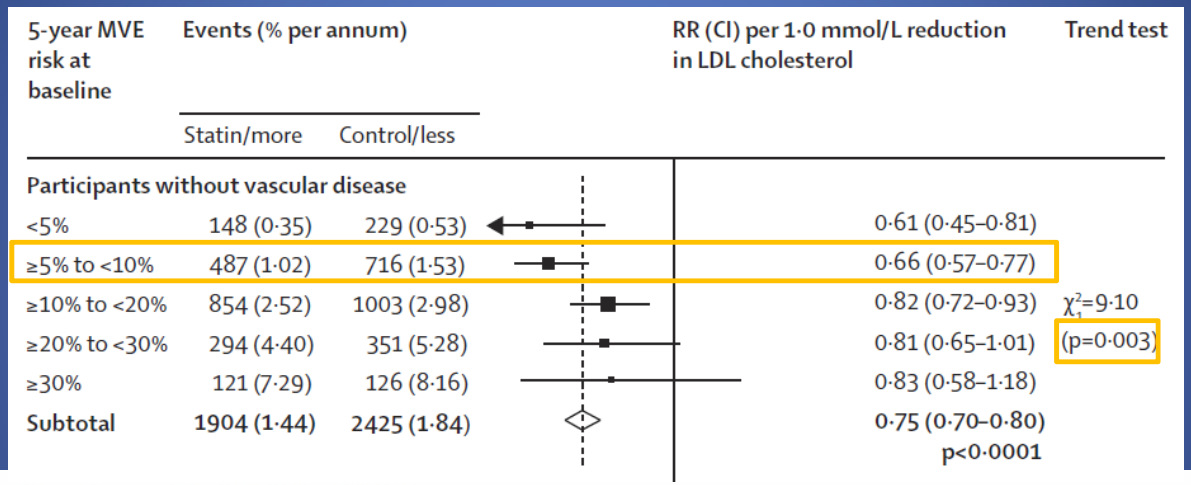
* Healthy individuals without serious comorbidities, including heart failure or chronic kidney disease

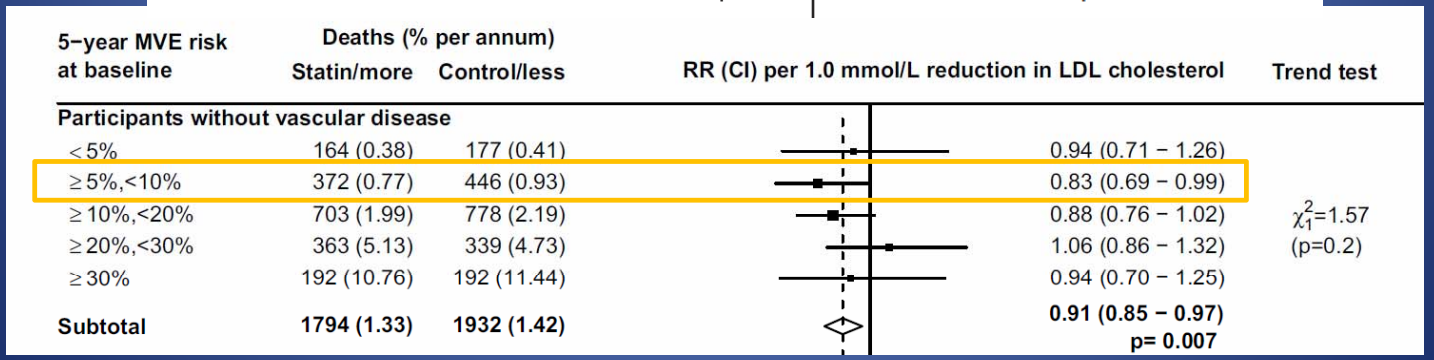
CTT Collaborators. Lancet 2012; 380: 581-590

Primary prevention 5 to <10% 5-year major CVD risk

Per 1 mmol reduction LDL-C with a statin*

- *Significantly greater 34% reduction in relative risk of major CVD* than higher risk groups
- *17% reduction in total mortality*





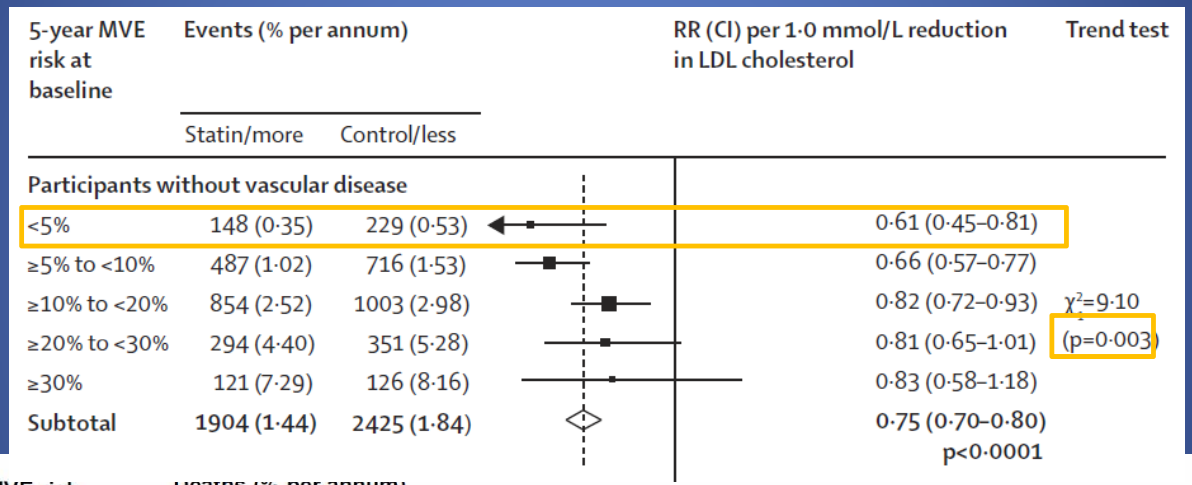
*1 mmol/L (39 mg/dl) LDL-C reduction was the average in the primary prevention RCTs excluding JUPITER

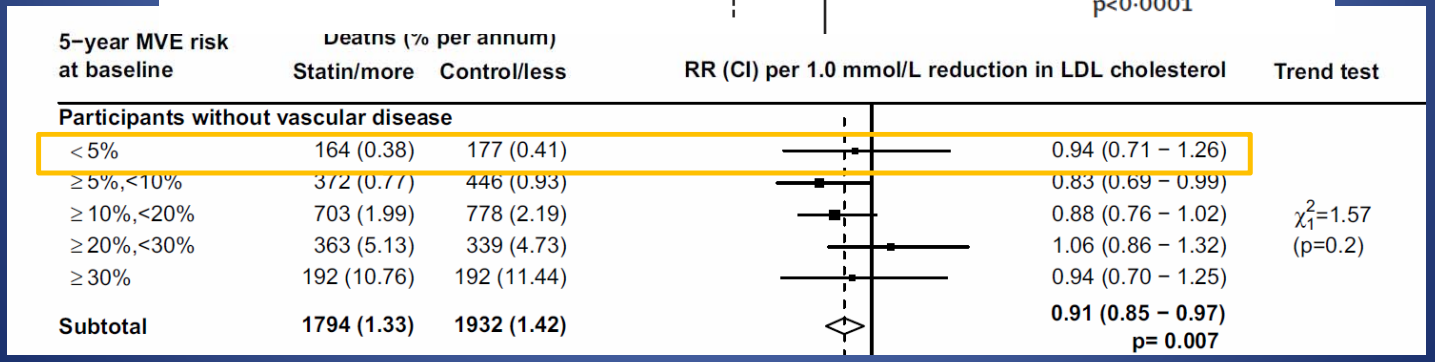
CTT Collaborators. Lancet 2012; 380: 581-590

Primary prevention <5% 5-year major CVD risk

Per 1 mmol reduction LDL-C with a statin*

- *39% reduction in relative risk of major CVD*
- *No reduction in total mortality*
- 88% of MEGA, 63% of JUPITER, 45% of AFCAPS/TexCAPS participants





*1 mmol/L LDL-C reduction was the average in the primary prevention RCTs

CTT Collaborators. Lancet 2012; 380: 581-590

Defining statin adverse effects

Statin adverse events

- **Excess risk of myopathy**
  - 0.5 per 1000 statin-treated persons over 5 years
    - Higher with simvastatin 80 mg (lower doses in Asians)
  - 5-year NNH = 2000
- **Excess risk of hemorrhagic stroke/1 mmol/L reduction in LDL-C**
  - 0.5 per 1000 statin-treated persons over 5 years
    - Might be higher in populations at ↑risk hemorrhagic stroke (eg Asian)
  - 5-year NNH = 2000

CTT Collaborators. Lancet 2012; 380: 581-590

Statin adverse events

- **Excess risk of new diabetes**
  - 5 per 1000 statin-treated persons over 5 years
    - Meta-analysis of mostly moderate intensity statin therapy
    - 5-year NNH = 200
  - 15 per 1000 statin-treated persons over 5 years
    - 54 per 8901 statin-treated persons over 2 years- Rosuvastatin 20 mg
    - All cases occurred in those with baseline impaired fasting glucose
    - 5-year NNH = 66

Sattar et al. Lancet 2010; 375: 735-742; Ridker Lancet 2012; 380: 565-571

Statin therapy
Conservative approach to adverse effects

- Low to Moderate intensity statin
  - 6 excess cases of adverse effects per 1000 statin-treated persons over 5 years
  - **NNH = 167**
- High intensity statin
  - 16 excess cases of adverse effects per 1000 statin-treated persons over 5 years
  - **NNH = 63**

Estimating net statin benefit

Primary prevention

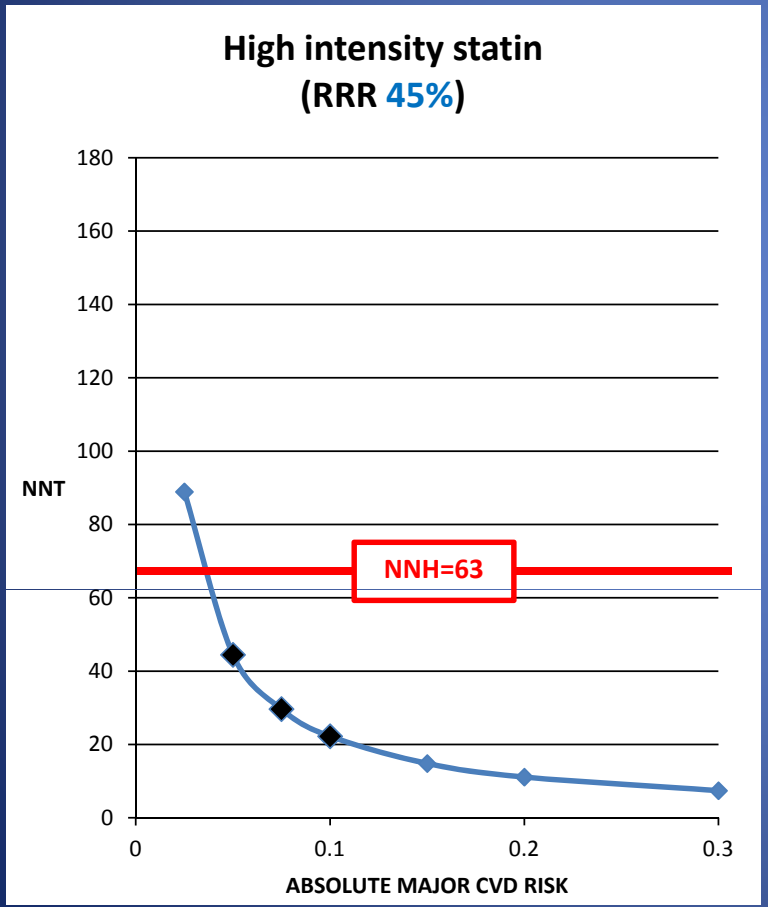
Estimating net benefit

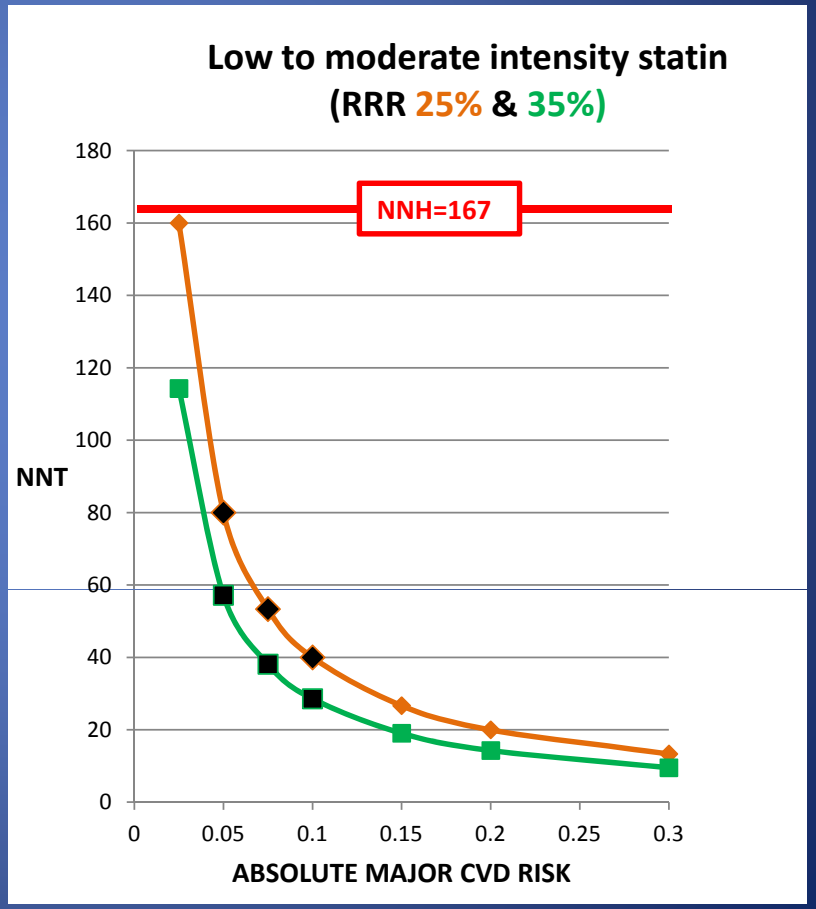
- Use absolute risk and relative risk reduction to estimate NNT to prevent one CVD event
- Use absolute risk (and relative risk increase) to estimate NNH to cause 1 excess adverse event
- NNT should exceed threshold for adverse events based on NNH
- Clinical application example:
  - Identification of candidates for primary prevention with statin therapy
  - Using data from CTT 2012 meta-analysis

Statins for primary prevention 5-<10% 5-year major CVD risk

Major CVD risk reduction benefits >> Adverse effects

Number-needed-to-treat (NNT) to prevent one major CVD event by level of absolute major CVD risk compared to number-needed to harm (NNH) over 5 years



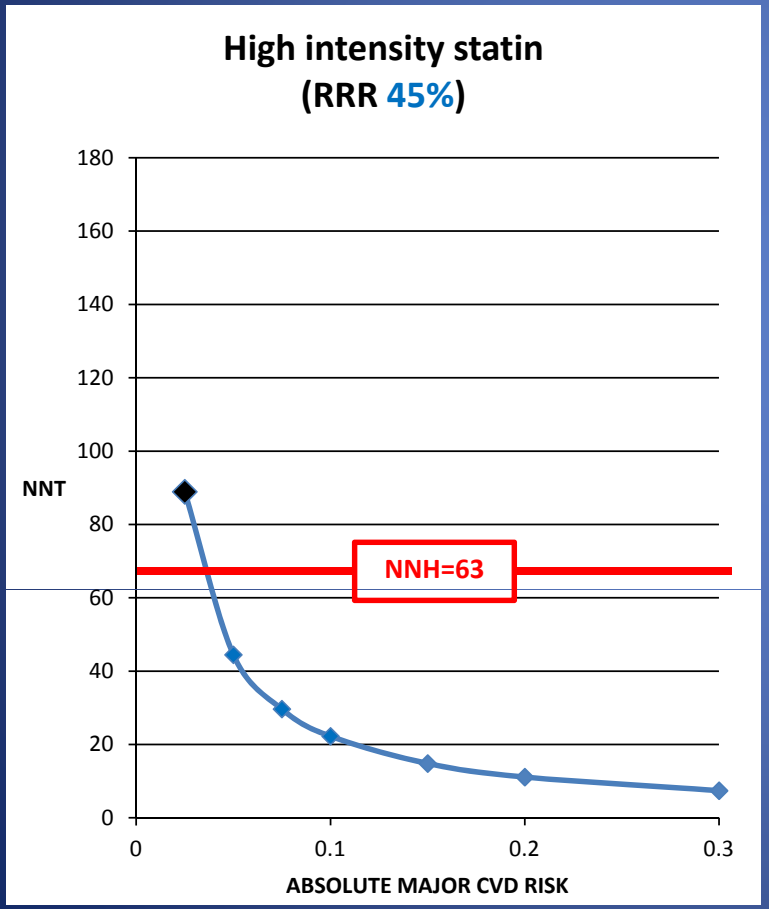


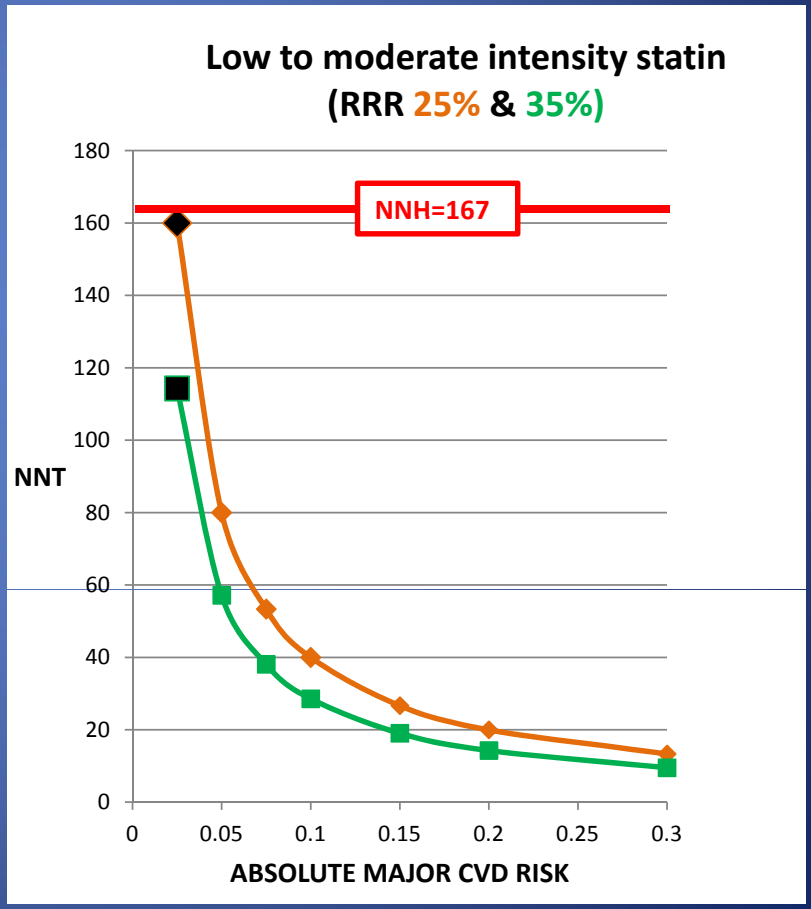
Using risk assessment in clinical decision-making

- 5 to <10% 5-year major CVD risk
  - Compelling indication to initiate statin therapy
  - Total mortality benefit
  - High or moderate intensity statin preferred
    - **45% RRR: NNT to prevent 1 major CVD event=22-44 vs. NNH=63**
    - **35% RRR: NNT to prevent 1 major CVD event=29-57 vs NNH=167**
    - 25% RRR: NNT to prevent 1 major CVD event=40-80 vs NNH=167

Statins for primary prevention <5% 5-year major CVD risk

Number-needed-to-treat (NNT) to prevent one major CVD event by level of absolute major CVD risk compared to number-needed to harm (NNH) over 5 years





Using risk assessment in clinical decision-making

- <5% 5-year major CVD risk
  - Less indication to initiate statin therapy
  - NNT to prevent one major CVD event ≥60
  - No total mortality benefit
  - Moderate intensity statin may be preferred if decide to treat 2.5-<5% 5-year major CVD risk
    - 45% RRR: NNT to prevent 1 major CVD event= >40-89 vs. NNH=63
    - **35% RRR: NNT to prevent 1 major CVD event= >57-114 vs NNH= >167**
    - 25% RRR: NNT to prevent 1 major CVD event= >80-160 vs NNH=167

Statins in primary prevention

- Statins reduce major CVD events and mortality in those at lower CVD risk
- Statins are cost-effective and socially beneficial
- Adherence is fundamental to achieving the CVD and mortality benefits of statin therapy

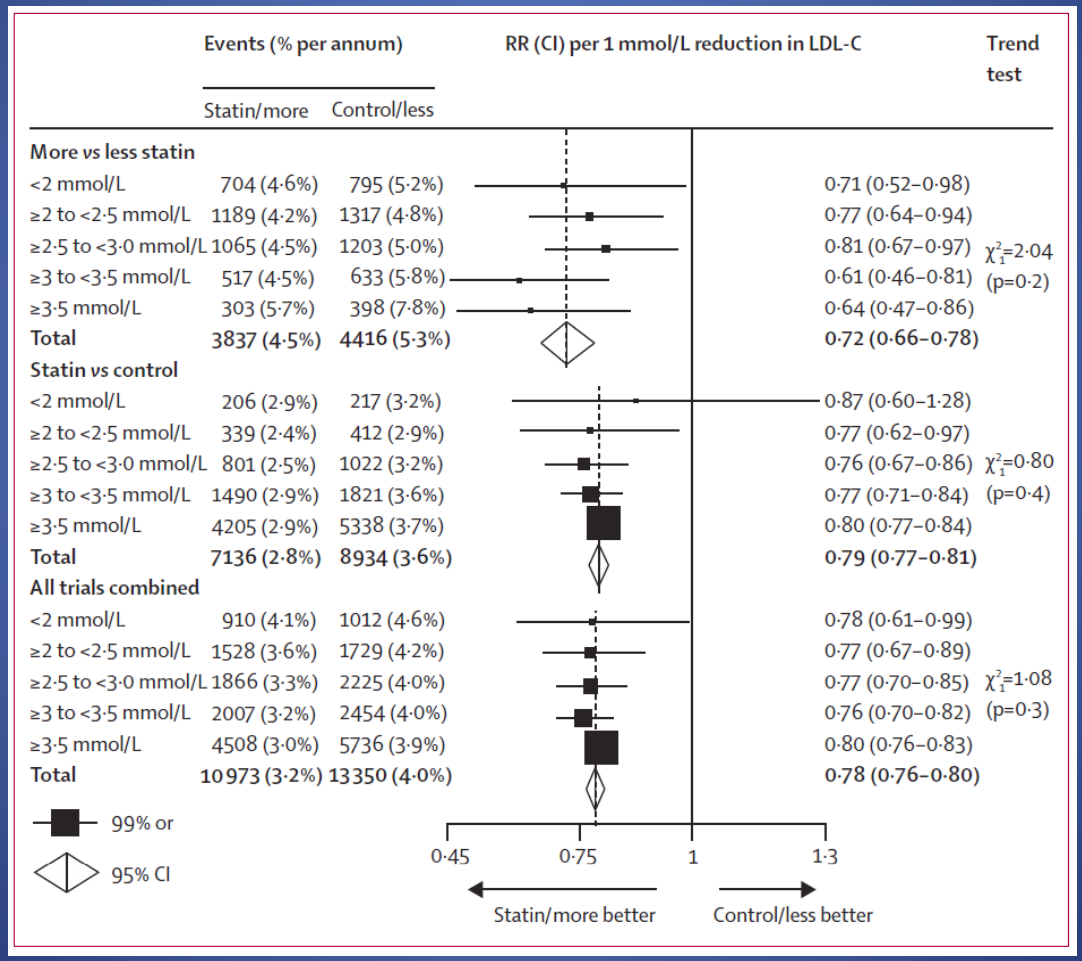
Pletcher MJ, et al. *Ann Intern Med.* 2009;150:243-254; Heart Protection Study Collaborative G. *Circ Cardiovasc Qual Outcomes.* 2009;2(2):65-72; Conly J, et al. *Can Med Assoc J.* 2011;183(16):E1180-E1188.
Grabowski DC, Lakdawalla DN, Goldman DP, et al. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. *Health Aff* 31;2276-2285

Statin treatment decisions based on absolute CVD risk

or,

What happened to LDL-C & risk factor treatment thresholds?

Lowering LDL-C reduces CVD events across the range of LDL-C levels



CTT . Lancet 2010; 376: 1670-1681

NLA FH Statement

Treat All Adult FH Patients

- Untreated FH
  - Mean onset CVD
    - Men early 40's
    - Women in early 50's
  - 24 times higher risk of MI before age 40
- **Long-term statin treatment largely ameliorates excess CVD risk due to FH**
- Risk of long-term statin treated FH patients = Risk of general population

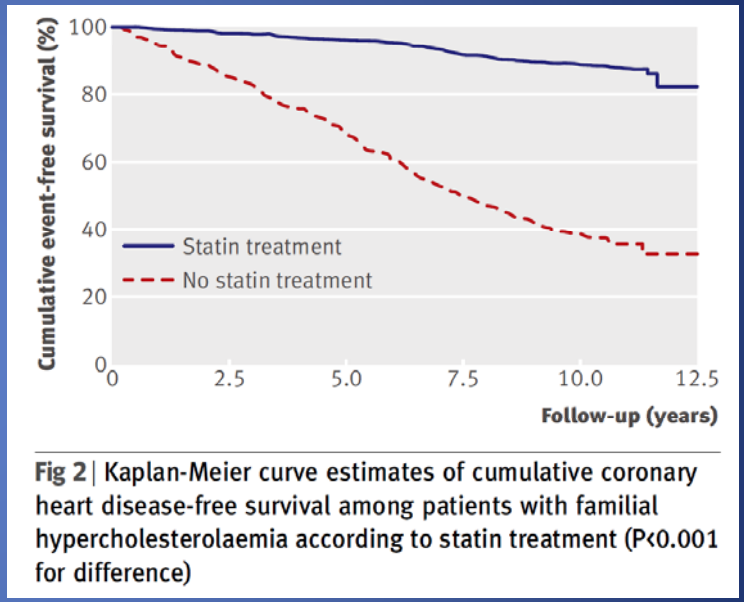


Fig 2 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

Versmissen J, et al BMJ 2008; 337: a2423

Goldberg A, et al. *J Clin Lipidol* 2011; 5(3, suppl 1):S1-8: Executive summary
Robinson JG, Goldberg A. *J Clin Lipidol* 2011; 5(3, suppl 1):S18-29

Statin primary prevention trials in healthy individuals

Broad eligibility criteria (Age, male sex, lower HDL-C, CRP≥2 mg/L, hypertension, multiple risk factors, diabetes, LDL-C <130, <160, ≥155 mg/dl), **range of 5-year major CVD risk**, and **different intensities of statin therapy**

	Median predicted 5-year MVE risk	Estimated 5-year MVE risk					Total
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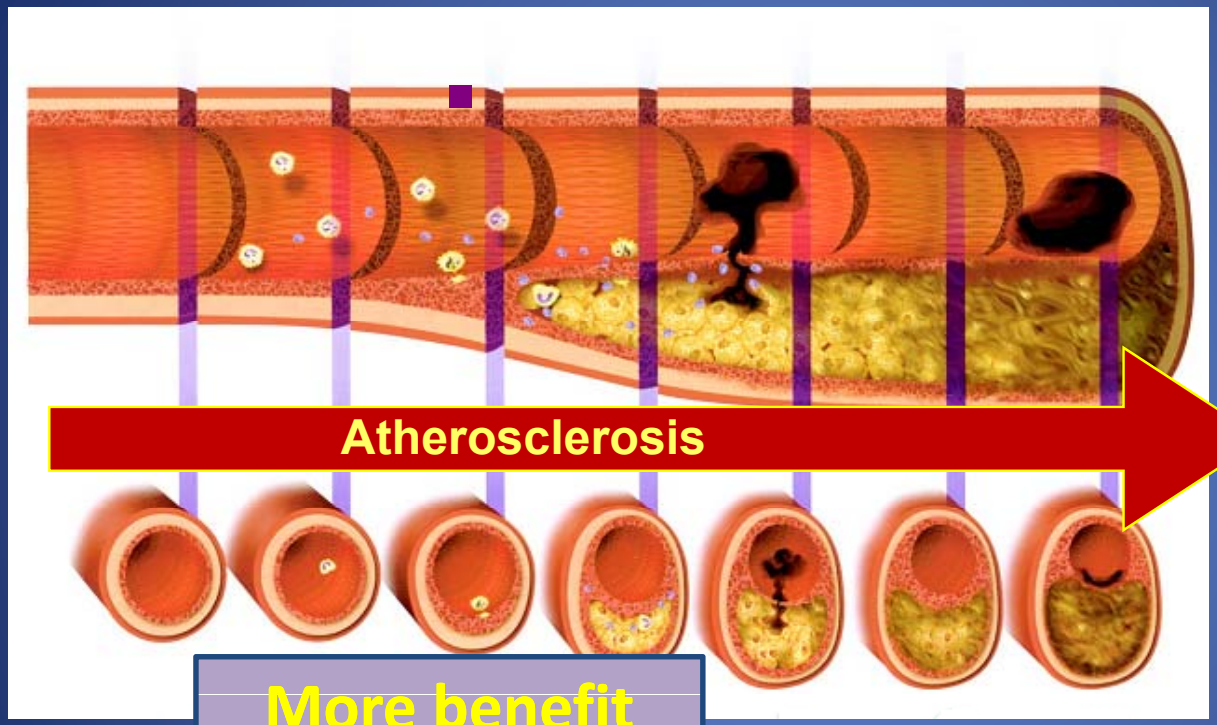
CTT Collaborators. Lancet 2012; 380: 581-590

Ever too late for statins/prevention?

- Statins do not reduce CVD
  - Heart failure (Class II-IV)
    - GISSI-HF, CORONA
  - End-stage renal disease – hemodialysis
    - 4D, AURORA
- Age?
  - Few clinical trial data >75 years
    - CHD or stroke populations: almost all <80 years
    - Primary prevention populations: Few >80 years
  - ? Net benefit with advancing age
    - Competing causes of mortality/morbidity, quality of life, safety

Kjekshus J, at al. 2007; 357: 2248-2261; GISSI-HF Investigators. Lancet 2008; 372: 1231-1239.
Wanner C, et al NEJM 2005; 353: 238-248; Fellstrom 2009; 360: 1395-1407
Robinson JG, et al. Stroke 2007; 38: 441-450

Atherosclerotic Cardiovascular Disease Progression Through the Lifespan



CVD EVENTS

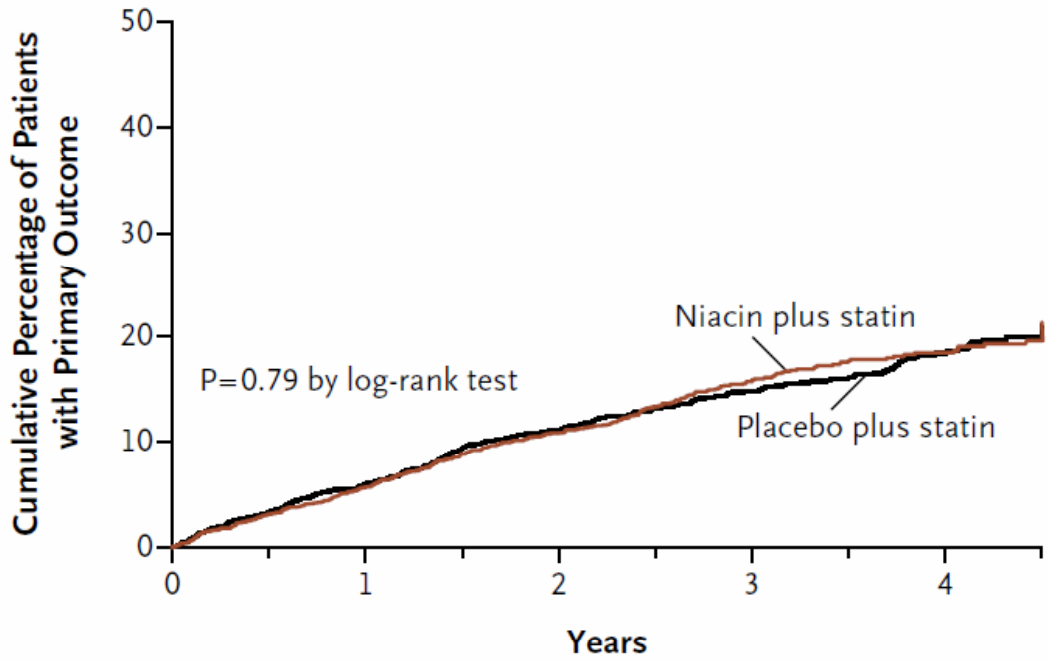
- MI/Unstable angina
- Ischemic stroke/TIA
- Critical leg ischemia
- Intermittent claudication
- CV death

More benefit
From earlier primary prevention with statins?

Illustration Adapted from Libby P. *Circulation.* 2001;104:365-372.

Non-statin therapies

AIM-HIGH: 2 strategies equivalent titrated to mean LDL-C 65-70 mg/dl



No. at Risk

Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

Figure 1. Kaplan–Meier Curve for the Primary End Point.

The AIM-HIGH Investigators. NEJM 2011; 365: 2255-67

AIM-HIGH lipid/apo/lipoprotein changes

	On treatment - mean or median @ 1 year Change from baseline (difference between groups)								
Adjusted to achieve LDL-C 40-80 mg/dl	**HDL-C** mg/dl	**TG** mg/dl	**LDL-C** mg/dl	**Non-HDL-C** mg/dl	**Apo B** mg/dl	**Apo A-I** mg/dl	**Lp(a)** nmol/L	**HDL2-C** mg/dl	**HDL3-C** mg/dl
Niacin 1.5 to 2 g + simva ±EZE	43.6 23.3% (**14.2**%)	121 -28.2% (**-23.2**%)	66.4 -10.0% (**-5.7**%)	94.3 **-16.3%** (-**10.1**%)	71.4 **-14.2%** (-**10**%)	132.2 **+7.9%** (**4.9**%)	27.1 **-24.9%** (-**18.5**%)	10.2 **+67.2%** (**49.7**%)	33.4 **+16.4%** (**9.5**%)
Placebo/Niacin IR 50 mg + simva ±EZE	38.4 9.1%	155 -5.0%	70.4 -4.3%	105.0 -6.2%	79.3 -4.2%	127.4 3.0%	30.6 -6.4%	HDL2-C 7.4 17.5%	HDL3-C 31.0 6.9%

The AIM-HIGH Investigators. NEJM 2011; 365: 2255-67

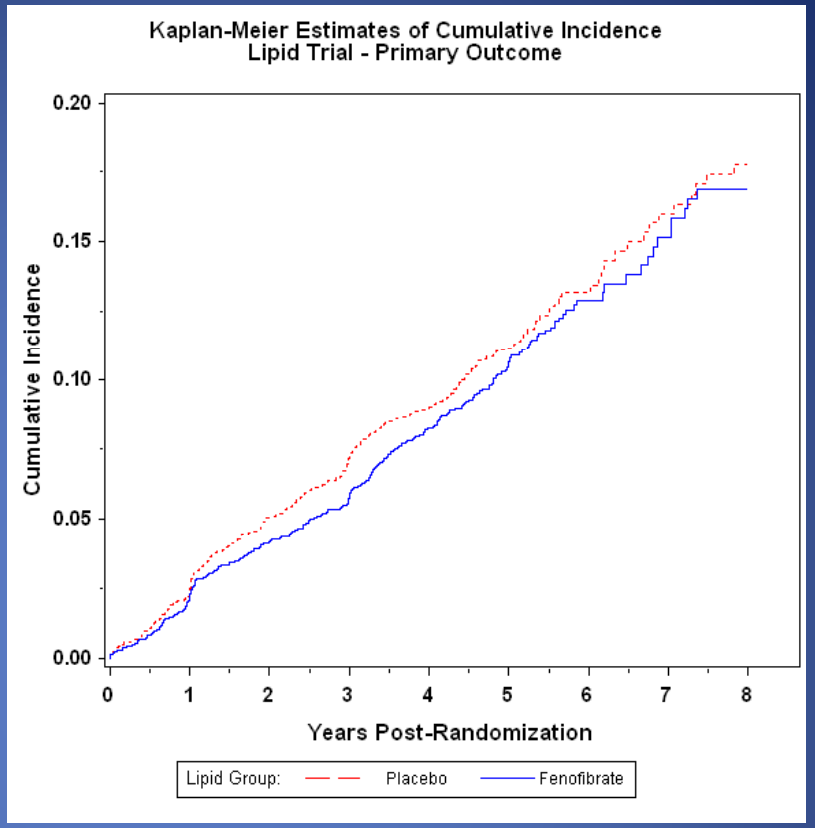
HPS-2 THRIVE

- Results to be reported at ACC March 2013
- Niacin/laropriprant added to simvastatin therapy
  - No CVD benefit
  - Significantly increased the risk of nonfatal but serious side effects

http://www.mercknewsroom.com/press-release/prescription-medicine-news/merck-announces-hps2-thrive-study-tredaptive-extended-release

ACCORD

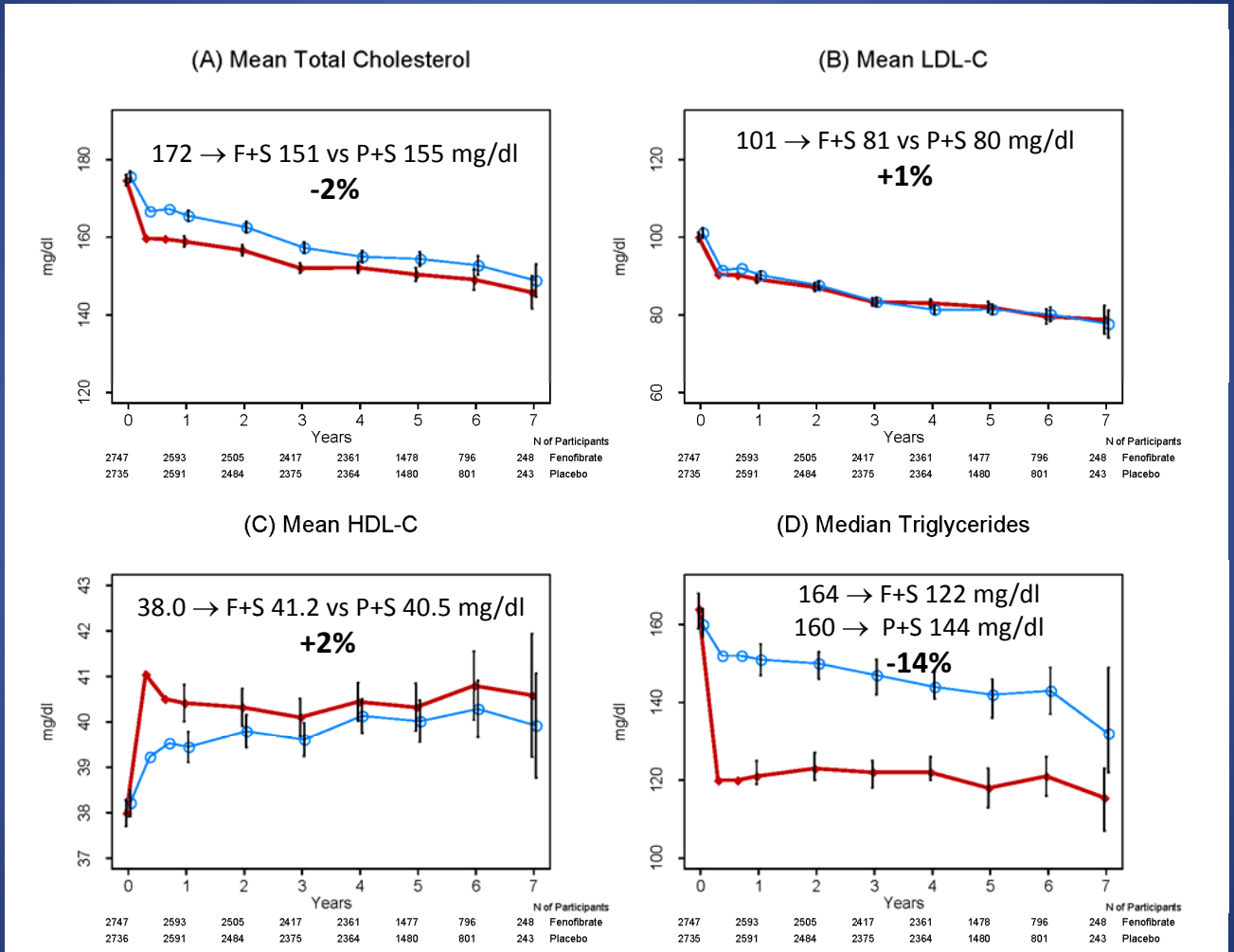
Fenofibrate - No benefit added to simvastatin in high risk diabetic patients



	Fenofibrate + simvastatin (N=2765)		Placebo + simvastatin (N=2753)			
	N of Events	Rate (%/yr)	N of Events	Rate (%/yr)	HR (95% CI)	P Value
Primary Outcome:						
Major Fatal or Nonfatal Cardiovascular Event	**291**	**2.24**	**310**	**2.41**	**0.92 (0.79 - 1.08)**	**0.32**

Ginsberg H, et al. *N Engl J Med* 2010: online ahead of print March 14, 2010 (10.1056/NEJMoa1001282

ACCORD - Plasma Lipid Levels



Non-HDL-C 113.2 vs 109.8 mg/dl **-3%**

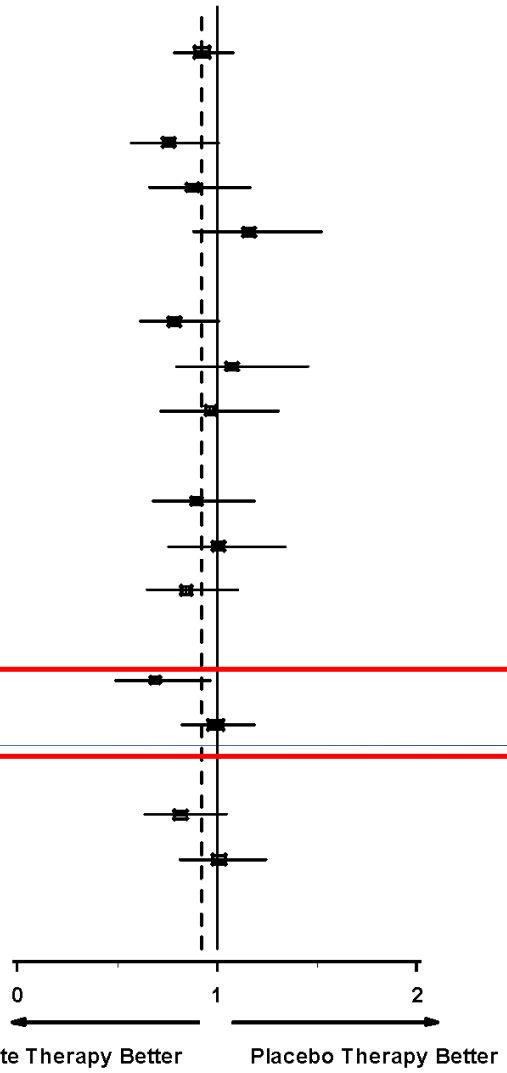
Action to Control Cardiovascular Risk in Diabetes
ACCORD

Ginsberg H, et al. *N Engl J Med* 2010: online ahead of print March 14, 2010 (10.1056/NEJMoa1001282; Appendix 1

ACCORD Primary Outcome By Baseline Subgroups

Fenofibrate + simvastatin beneficial in dyslipidemia?

Subgroup	Fenofibrate % Events (# in grp)	Placebo % Events (# in grp)	Interaction P-Value
Overall	10.5% (2765)	11.3% (2753)	
LDL-c Tertile			
<=84 mg/dl	9.4% (938)	12.2% (891)	0.1212
85-111 mg/dl	9.9% (934)	11.2% (922)	
>=112 mg/dl	12.4% (877)	10.6% (927)	
HDL-c Tertile			
<=34 mg/dl	12.2% (964)	15.6% (906)	0.2374
35-40 mg/dl	10.1% (860)	9.5% (866)	
>=41 mg/dl	9.1% (925)	9.0% (968)	
Triglyceride Tertile			
<=128 mg/dl	9.9% (891)	11.3% (939)	0.6422
129-203 mg/dl	10.5% (924)	9.9% (913)	
>=204 mg/dl	11.1% (934)	12.8% (888)	
Trig/HDL combination			
TG204+ /HDL<=34	12.4% (485)	17.3% (456)	0.0567
All Others	10.1% (2264)	10.1% (2284)	
A1c Median			
A1c <= 8.0	8.7% (1324)	10.6% (1335)	0.2045
A1c 8.1+	12.2% (1435)	11.9% (1415)	

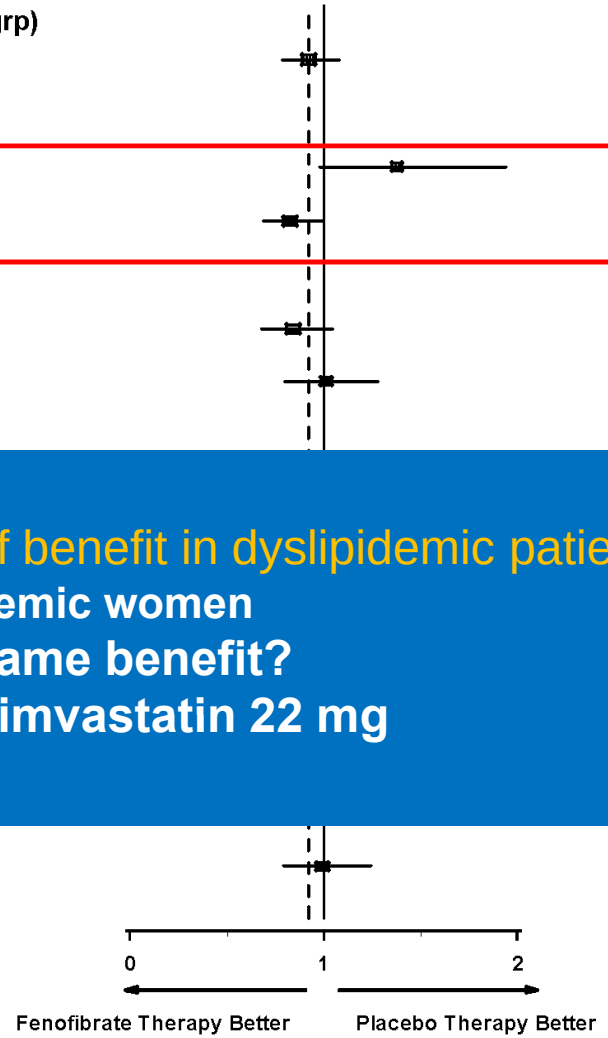


Ginsberg H, et al. *N Engl J Med* 2010: online ahead of print March 14, 2010 (10.1056/NEJMoa1001282

ACCORD Primary Outcome By Subgroup

Fenofibrate + simvastatin harmful in women?

Subgroup	Fenofibrate % Events (# in grp)	Placebo % Events (# in grp)	Interaction P-Value
Overall	10.5% (2765)	11.3% (2753)	
Sex			
Women	9.1% (851)	6.6% (843)	
Men	11.2% (1914)	13.3% (1910)	0.0106
Age			
Age < 65	8.1% (1838)	9.5% (1822)	0.2530
Age 65+	15.3% (927)	14.7% (931)	
Race			
Pric			
Gly			
Int Glycemia	10.9% (1374)	10.9% (1383)	



ACCORD conclusions

Fenofibrate+ simvastatin might be of benefit in dyslipidemic patients

- **Although maybe NOT dyslipidemic women**

Compared to high-dose statin – same benefit?

-ACCORD mean dose of simvastatin 22 mg

Need more information

Ginsberg H, et al. *N Engl J Med* 2010: online ahead of print March 14, 2010 (10.1056/NEJMoa1001282

Conclusions from RCTs

- Focus on statin therapy to reduce CVD risk
- Benefits of high intensity statin therapy appear to exceed risks except in lower risk primary prevention
- Statins reduce CVD risk for all patient subgroups
- Net benefits from non-statin / statin combination therapy are unclear
  - Maximize statin therapy