Hyperlipidemia: Lowering the Bar on the Lipid Limbo

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Hyperlipidemia is a common problem

- Nearly 50% of men in the over the age of 20 in the US have an LDL > 130 mg/dl (~45% for women)
- Approximately 20% of men and 17% of women have an LDL cholesterol > 160 mg/dl
- An estimated 40 million Americans have CHD, PVD, CVD, or DM

Topics for Today

- What should our targets be for cholesterol lowering– a review of the NCEP /ATP III guidelines
- What are the data supporting use of medications to lower cholesterol in primary prevention and secondary prevention
- What do we still need to know—unanswered questions?

High Blood Cholesterol

Detection

Evaluation

Treatment

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Final Report

NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Evolution of the NCEP Guidelines

- **MRFIT**
- LRC-CPPT
- Coronary Drug Project
- Helsinki Heart Study
- Framingham
- CLAS (angio)

- Angiographic Trials
  - (FATS, POSCH, SCOR, STARS, Ornish, MARS)
- Meta-Analyses
  - (Holme, Rossouw)

- 4S, WOSCOPS, CARE, LIPID, AFCAPS/TexCAPS, VA-HIT, others

ATP III/NCEP Recommendations

- Measurement of fasting lipid panel
- Determine 10 year risk for CHD
- Identification of clinical atherosclerotic coronary heart disease (CHD) ; or
- CHD *risk equivalents* -- symptomatic carotid disease, peripheral arterial disease, AAA, diabetes
- Determine presence of major risk factors for CHD-smoking, HTN, Age, +FH, low HDL

CHD risk equivalents

- Patients with known CHD have a 10 year risk of recurrent events of >20%
- Patients with CHD *risk equivalents* -- symptomatic carotid disease, peripheral arterial disease, AAA, diabetes -have a similar risk of >20% for "hard' CHD (CHD death or MI)

Assessing 10 year CHD risk

- Estimated CHD risk is based on Framingham Data
- Patients with known CHD or CHD equivalent have a 10 yr risk of >20%
- Patients with 0-1 risk factors have a 10 year risk of <10%
- Patients with 2 or more risk factors have a 10 year risk between 0 and 20%

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD Risk Equivalents (10-year risk >20%)	<100	≥100	≥130 (100–129: drug optional)
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10–20%: ≥130
			10-year risk <10%: ≥160
0–1 Risk Factor	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

Therapeutic Lifestyle Changes (TLC)

- TLC Diet
  - Saturated fat < 7%, cholesterol <200 mg/day
  - Consider increased fiber, plant stanols/sterols
- Weight management
- Increased physical activity
- For most patients, maximum decrease in LDL on this regimen is ~ 30%

Case 1

A 64 y/o male patient presents for an initial clinic visit.

PMH is notable for CHD (s/p IMI 2 years ago) HTN, smoking

Current Meds :ASA 81 mg po qd, atenolol 50 mg po qd, lisinopril 10 mg po qd, omeprazole 20 mg po qd.

Fasting lipid profile
LDL 95, HDL 45, TG 150, Total cholesterol 185

Should he be on a statin ?

How ⬇ Low should we go?

- Two distinct issues
- 1) Should patients with low baseline LDL (<100) and known CHD be treated?
- 2) For patients on lipid lowering medication, what should our treatment target be?
  - 100 mg/dl,
  - 70mg/dl,
  - 40 mg /dl
  - 0 mg/dl

How ↓ should we go? Low (continued)

- Major lipid lowering trials have generally compared a single statin dose vs. placebo rather than comparing specific treatment target LDL levels
- Target LDL levels have been inferred based upon 1)epidemiological data demonstrating a curvilinear relationship between LDL and CHD; 2)baseline and post-treatment LDL levels that have been associated with reduction in clinical endpoints in lipid lowering trials

“My Drug Study Sounds Catchier than Yours”

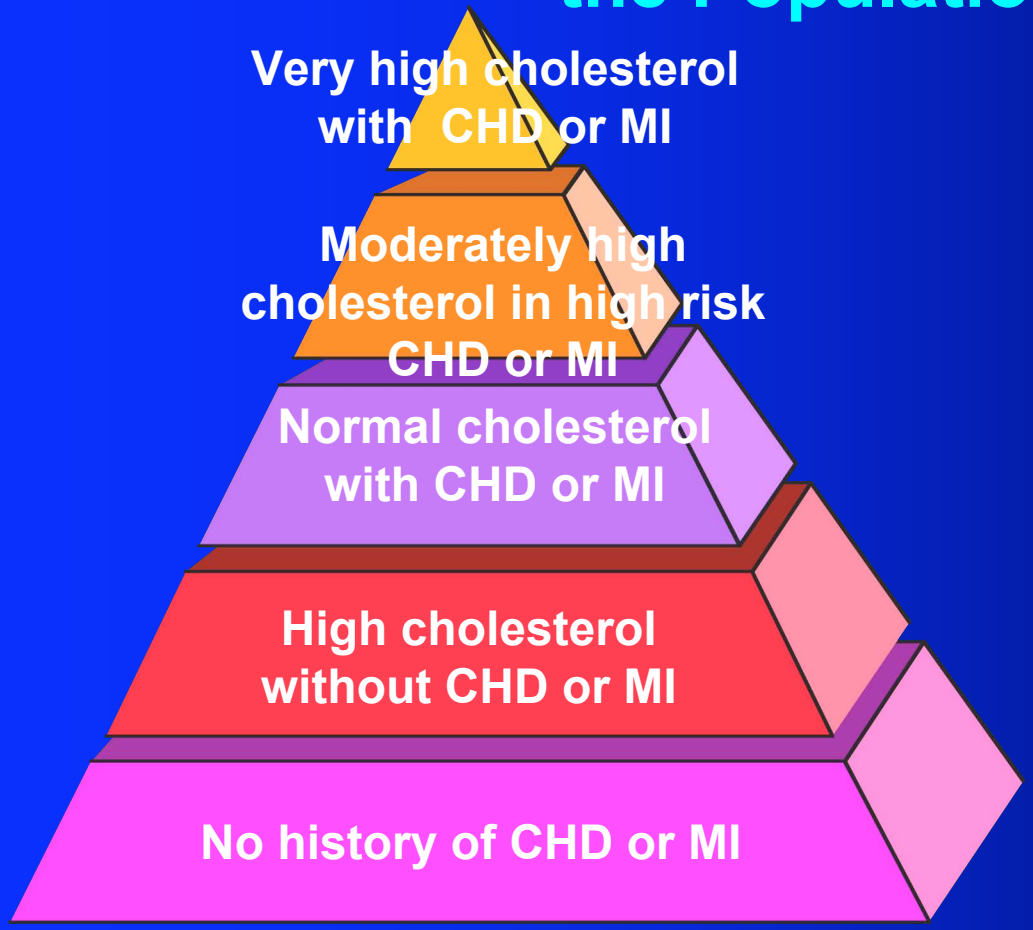
- 4S
- CARE
- LIPID
- WOSCOPS
- REVERSAL
- PROVE-IT
- SEARCH
- TNT
- TOAST

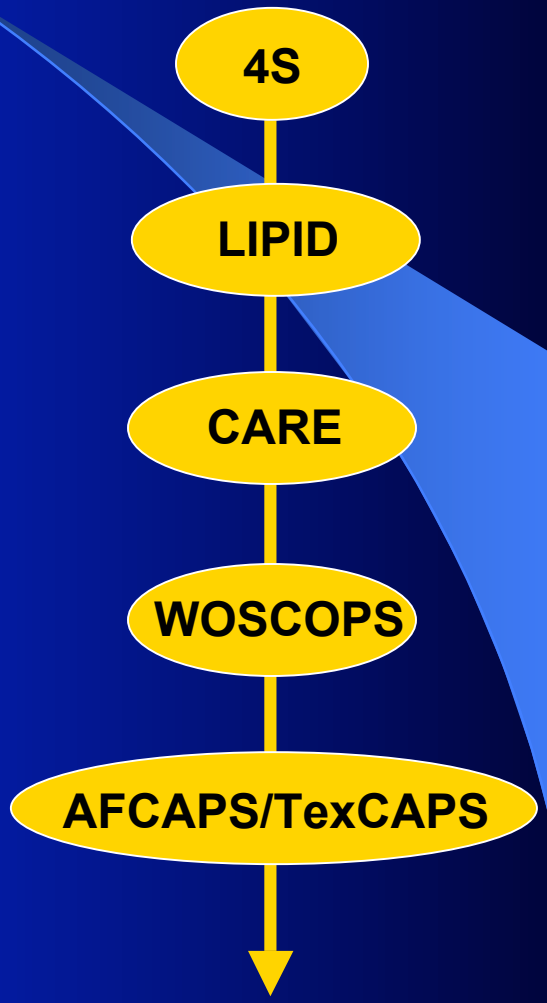
Prevention Strategies

- Primary Prevention
  - Prevention of events in patients without known heart disease
  - Mortality of acute MI approaches 25%
- Secondary prevention
  - Prevention of recurrent events in individuals with known disease

The Pyramid of Recent Trials

Relative Size of the Various Segments of the Population

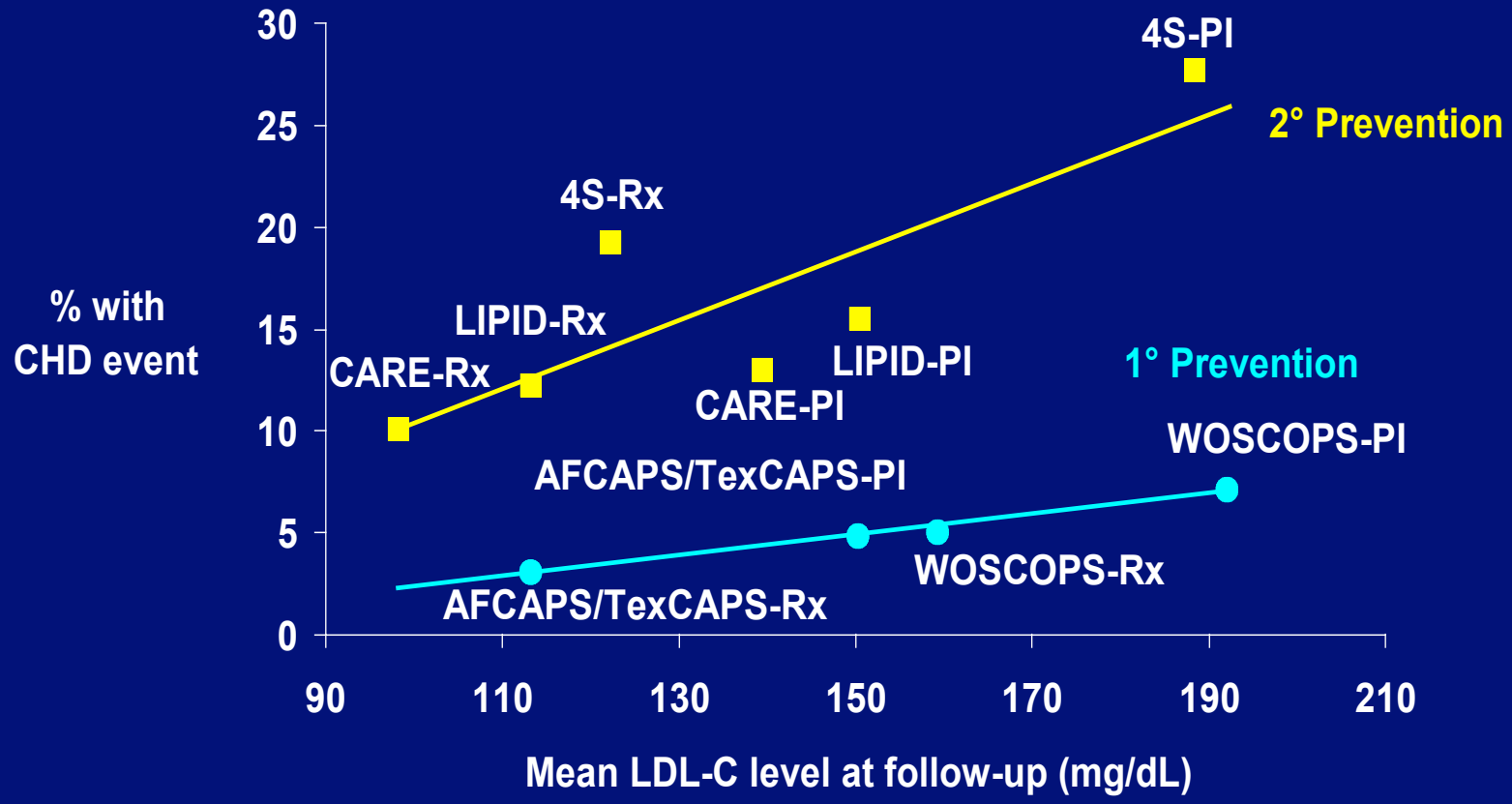




Summary Data Statin Trials

Trial	Initial LDL	Final LDL	LDL% Change	Event Rate Statin	Event Rate-Placebo	RRR %	ARR %	NNT
4S	188	122	35	19.4	28.0	34	8.6	12
LIPID	150	112	25	12.3	15.9	24	3.6	28
CARE	139	98	32	10.2	13.2	24	3.0	34
WOSCOPS	192	159	26	5.3	7.5	29	2.2	46
AFCAPS/ TEXCAPS	150	115	25	3.5	5.5	37	2.0	50

Relation Between CHD Events and LDL-C in Recent Statin Trials

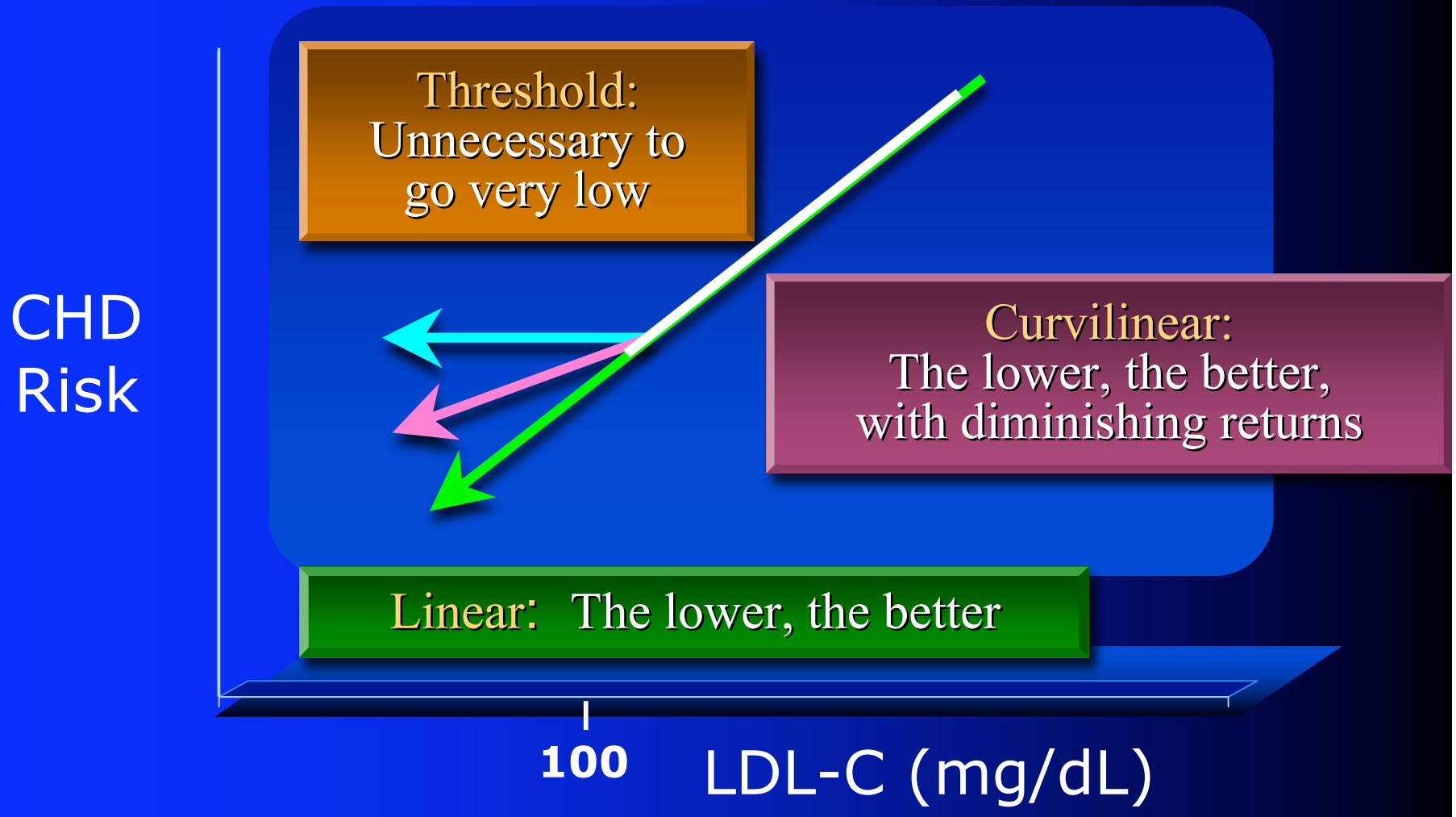


PI=placebo; Rx=treatment

Shepherd J et al. *N Engl J Med.* 1995;333:1301-1307.
4S Study Group. *Lancet.* 1995;345:1274-1275.
Sacks FM et al. *N Engl J Med.* 1996;335:1001-1009.
Downs JR et al. *JAMA*. 1998;279:1615-1622.
Tonkin A. Presented at AHA Scientific Sessions, 1997.

NLEC™

Possible Relationship between LDL-C Levels and CHD Risk (2001)



Rationale for ATP III's 2001 Low LDL-C Goal <100 mg/dL

- Epidemiology and clinical trial evidence congruent down to LDL-C at least as low as 100 mg/dL (2001)
- No clinical trial evidence of benefit from achieving very low LDL-C
- Practical goal with standard statin doses
- Safety of high statin doses not documented in large clinical trials

Post–ATP III Clinical Trials

- **HPS** (simvastatin 40)
- **PROSPER** (pravastatin 40)
- **ALLHAT-LLT** (pravastatin 40)
- **ASCOT-LLA** (atorvastatin 10)
- **PROVE IT** (pravastatin 40 vs. atorvastatin 80)

ATP III Update*

- Adds “therapeutic options” for very high risk and moderate high risk
- Very high risk patients: LDL goal of <70 mg/dl
- Moderate risk (10-20%) CHD: LDL goal of <100 mg/dl
- Target LDL reduction should be 30-40% in these groups

*Circulation 2004; 110:227-239

Candidates for Very Low LDL-C Goal of <70 mg/dL

- Very high risk patients
  - Established atherosclerotic CVD
    - + multiple risk factors (esp. diabetes)
    - + severe and poorly controlled risk factors (e.g., cigarette smoking)
    - + metabolic syndrome (high TG, low HDL-C)
    - + acute coronary syndromes (PROVE IT)

Considerations and Limitations for Achieving Very Low LDL-C Levels

- Dangers from very low LDL-C (unlikely)
- Side effects of high drug doses (still under study)
- High baseline LDL-C levels (>150 mg/dL)
  - Maximum drug lowering: about 50%

Heart Protection Study

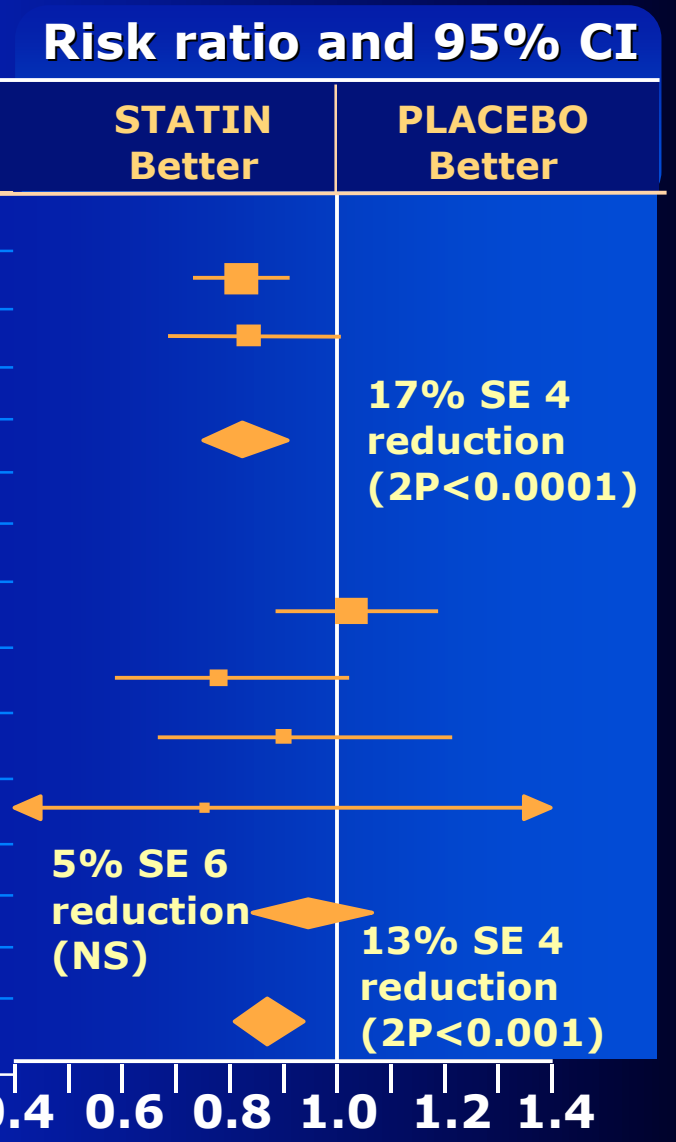
- Secondary prevention study in the UK
- 20,356 adults
- Age 40-80 at entry, 5 year follow up
- PMH + for CHD, PVD, DM or Males> 65 with HTN
- Total cholesterol>135 mg/dl (~3500 had baseline LDL <100)
- 40 mg simvastatin vs. placebo

Heart Protection Study Endpoints

- Coronary events: MI, coronary death
- Stroke
- Revascularization
- Cause- specific mortality
- All cause mortality

Simvastatin: Cause-Specific Mortality

Cause of Death	Simvastatin (10,269)	Placebo (10,267)
Vascular		
Coronary	587	707
Other vascular	194	230
ANY VASCULAR	781 (7.6%)	937 (9.1%)
Nonvascular		
Neoplastic	359	345
Respiratory	90	114
Other medical	82	90
Nonmedical	16	21
NONVASCULAR	547 (5.3%)	570 (5.6%)
ALL CAUSES	1328 (12.9%)	1507 (14.7%)



Heart Protection Study Collaborative Group. *Lancet* 2002;360:7–22.
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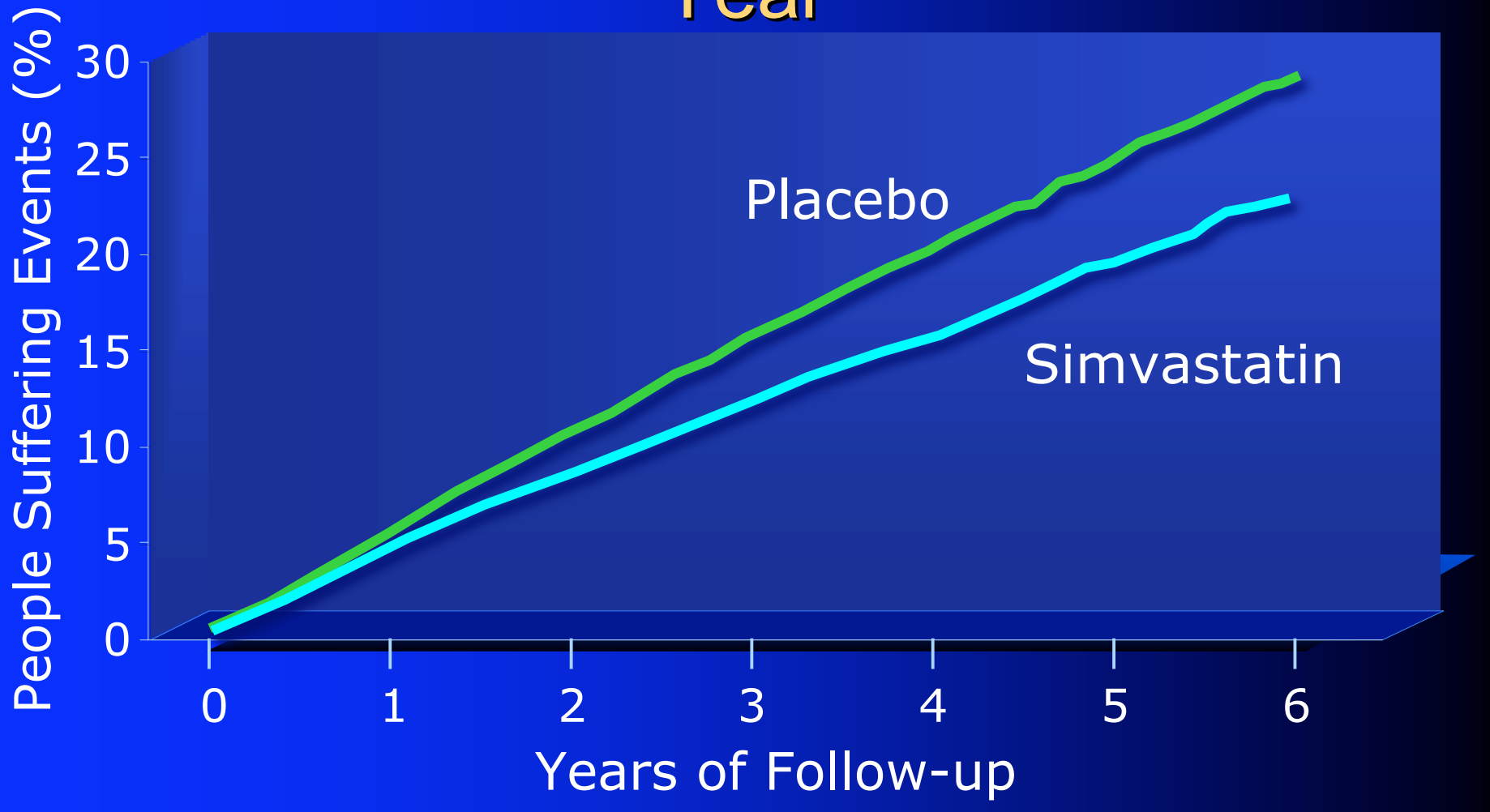
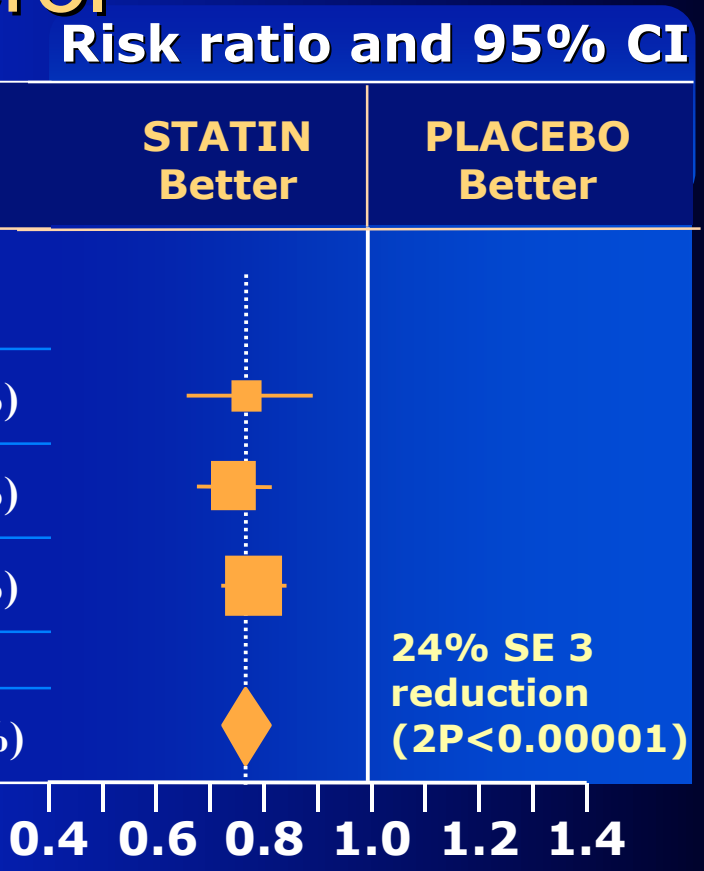
Simvastatin: Major Vascular Events by Year



Benefit/1000 (SE)	5 (3)	20 (4)	35 (5)	46 (5)	54 (7)	60 (18)

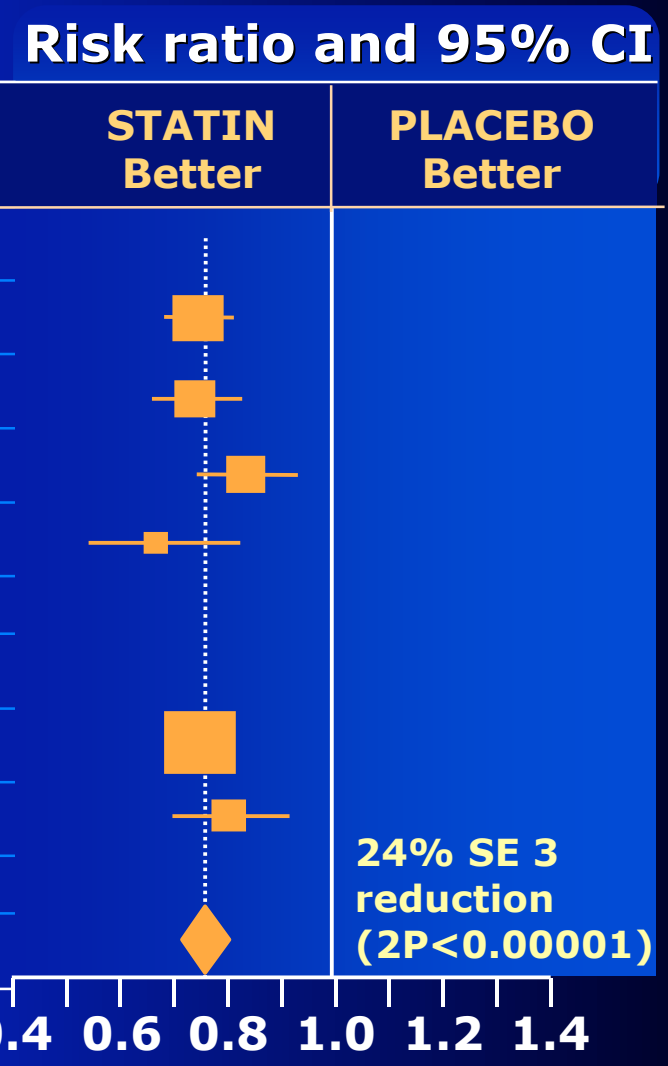
HPS: Major Vascular Events by LDL Cholesterol

Lipid Levels at Entry	Simvastatin (10,269)	Placebo (10,267)
LDL cholesterol (mg/dl)		
< 100	282 (16.4%)	358 (21.0%)
≥ 100 < 130	668 (18.9%)	871 (24.7%)
≥ 130	1083 (21.6%)	1356 (26.9%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)



Simvastatin: Major Vascular Events by Age and Sex

Baseline Feature	Simvastatin (10,269)	Placebo (10,267)
Age		
< 65	831 (16.9%)	1091 (22.1%)
65–69	512 (20.9%)	665 (27.2%)
70–74	548 (23.8%)	620 (27.7%)
≥ 75	142 (23.1%)	209 (32.3%)
Sex		
Male	1666 (21.6%)	2135 (27.6%)
Female	367 (14.4%)	450 (17.7%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)



Heart Protection Study Collaborative Group. *Lancet* 2002;360:7–22.

The CHD Risk of HPS and ATP III CHD and CHD Risk Equivalent Patients

Based on risk of CHD death or nonfatal MI

HPS (5-yr risk)

All Patients
25%

LDL-C ≥130
27%

LDL-C 100–129
25%

LDL-C <100
21%

ATP III CHD and Risk Equivalents (10-yr risk)

Acute MI	26–51%
Revascularization	25–30%
Stable angina	20%
Unstable angina	20–26%
PAD	20–29%*
CVA	14–20%*
Diabetes	15–25%*
10-yr estimated risk	>20%

***CHD death only**

www.hpsinfo.org | www.nhlbi.nih.gov/guidelines/cholesterol

Heart Protection Study Conclusions

- Patients at high risk for recurrent events benefit from treatment with simvastatin even with low baseline LDL levels
- Relative risk reduction remains relatively constant across LDL levels
- Absolute risk reduction depends on baseline risk rather than on baseline LDL alone

Case #2

- CD is a 72 y/o female pt with known CHD who presents for a follow-up visit
- PMH : NSTEMI 2001, s/p stent placement RCA
- Current Meds: Pravastatin 40 mg po qd, Toprol XL 200 mg po qd, ASA 81 mg po qd, Lisinopril 20 mg po qd
- Lipid Profile LDL 104, HDL 44, TG 170
- ? Changes in Rx

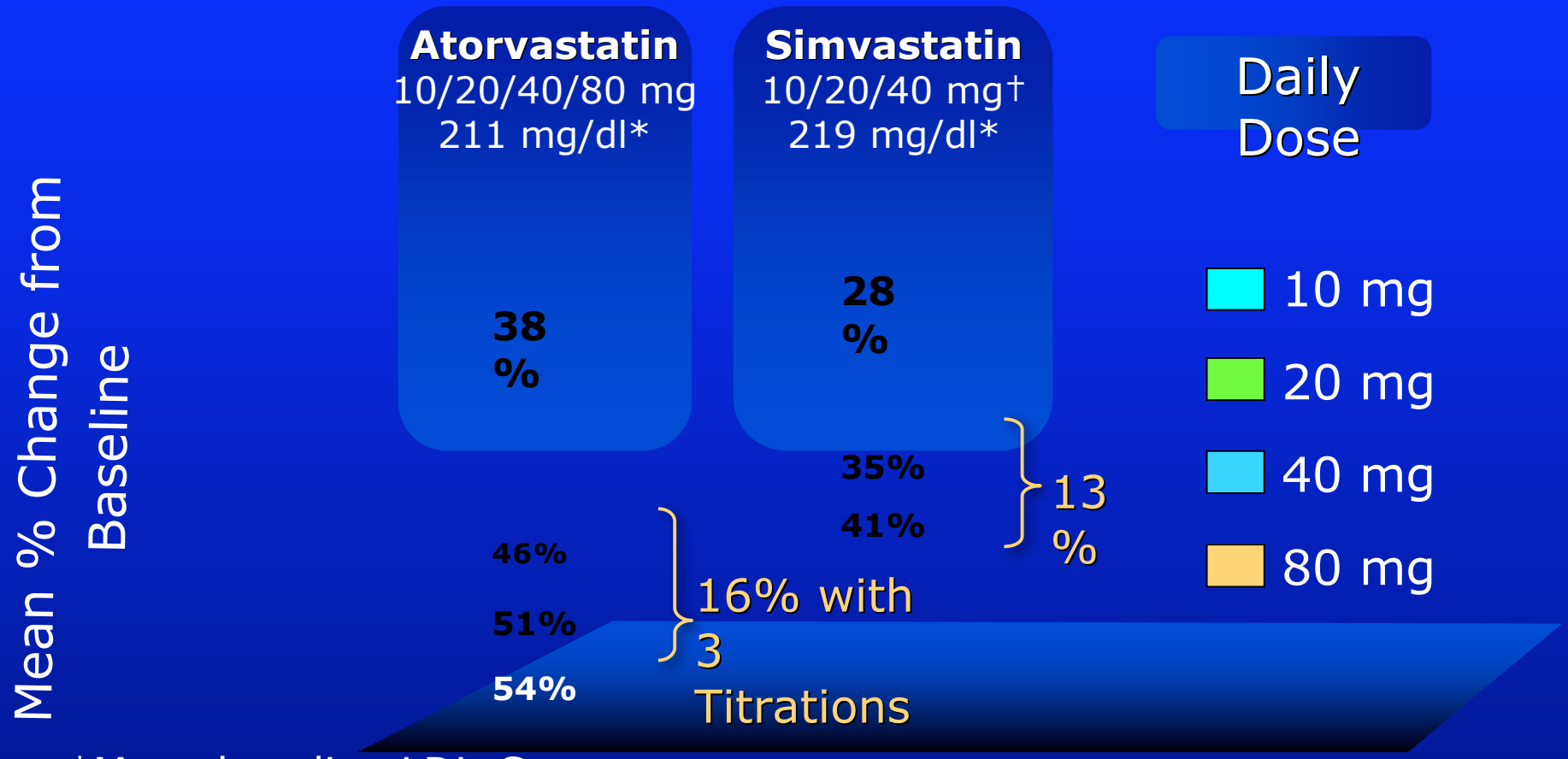
Is a Statin a Statin a Statin….?

The LDL-C–Lowering Efficacy of the Currently Available Statins

Daily Dose	Atorva	Fluva	Lova	Prava	Simva
10 mg	–39%			–22%	–30%
20 mg	–43%	–22%	–27%	–32%	–38%
40 mg	–50%	–25%	–32%	–34%	–41%
80 mg	–60%	–36%	–42%		–47%

Physician's Desk Reference. 55th ed. Montvale, NJ: Medical Economics, 2001.

Majority of LDL-C Lowering Occurs at the Lowest Statin Dose



*Mean baseline LDL-C.

†At the time of this study, the maximum dose for simvastatin was 40 mg.

Adapted from Jones P et al. *Am J Cardiol* 1998;81:582-587.

Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)

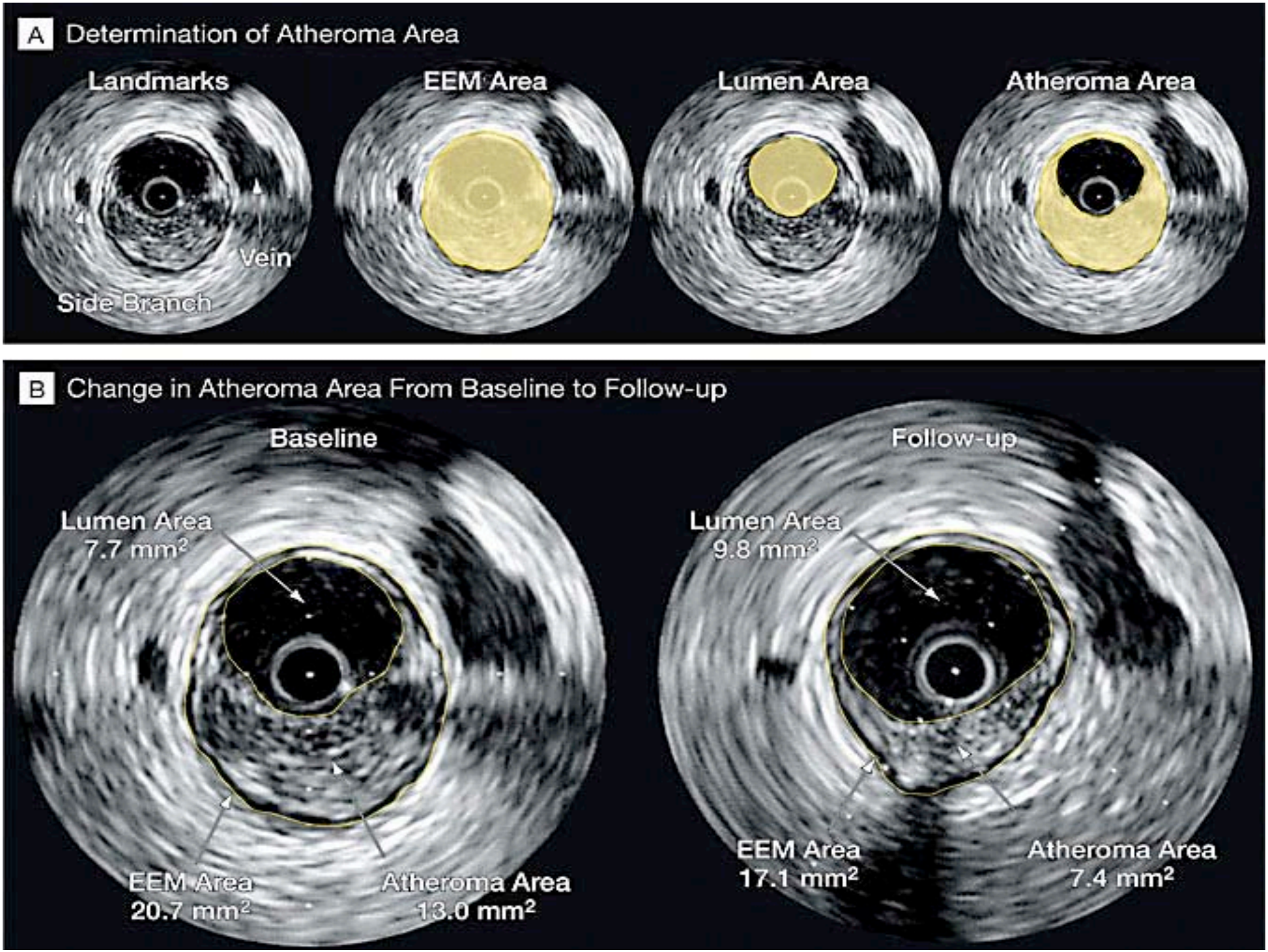
- 654 patients with stable CHD randomized to Atorvastatin 80 mg/day vs. Pravastatin 40 mg po qd
- 18 month f/u
- Primary endpoint—progression of atherosclerosis by endovascular ultrasound

REVERSAL—cholesterol results

Table 2. Final Laboratory Results (n = 502)

Characteristic	Type of Lipid-Lowering Regimen: Moderate; 40 mg of Pravastatin (n = 249) Final Mean (SD)	Moderate; 40 mg of Pravastatin (n = 249) Change From Baseline, %	Intensive; 80 mg of Atorvastatin (n = 253) Final Mean (SD)	Intensive; 80 mg of Atorvastatin (n = 253) Change From Baseline (%)	*P* Value*
Cholesterol, mg/dL					
Total	187.5 (32.2)	−18.4	151.3 (38.9)	−34.1	<.001
Low-density lipoprotein	110.4 (25.8)	−25.2	78.9 (30.2)	−46.3	<.001
High-density lipoprotein	44.6 (11.3)	5.6	43.1 (11.3)	2.9	.06
Triglycerides, mg/dL	165.8 (92.1)	−6.8	148.4 (94.9)	−20.0	<.001
Apolipoprotein B 100, mg/dL	118.1 (24.0)	−22.0	91.8 (27.9)	−39.1	<.001
C-reactive protein, mg/L	2.9 (3.0)	−5.2	1.8 (3.7)	−36.4	<.001

SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
*Analysis of variance was used to analyze lipid parameters and log-transformed C-reactive protein data.


A Determination of Atheroma Area
Landmarks
EEM Area
Lumen Area
Atheroma Area
Vein
Side Branch
B Change in Atheroma Area From Baseline to Follow-up
Baseline
Lumen Area
7.7 mm²
EEM Area
20.7 mm²
Atheroma Area
13.0 mm²
Follow-up
Lumen Area
9.8 mm²
EEM Area
17.1 mm²
Atheroma Area
7.4 mm²

REVERSAL Results

- Atheroma volume *increased* 2.7% in the pravastatin group (P=0.001)
- Atheroma volume *remained unchanged* in the atorvastatin group (-0.4% decrease from baseline, p=0.98 NS)

REVERSAL Conclusions

- High dose atorvastatin was superior to medium dose pravastatin in preventing progression of atheroma
- high dose atorvastatin was well tolerated
- Benefit of high dose atorvastatin on clinical endpoints –MI, death, recurrent angina, need for revascularization is not known

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)

- Randomized controlled trial of Pravastatin 40 mg vs. Atorvastatin 80 mg in patients with an acute coronary syndromes (STEMI, NSTEMI, Unstable Angina)
- 18-36 month follow-up
- Primary endpoint: composite of death,MI, unstable angina, revascularization and stroke

PROVE-IT (continued

- Eligibility: age>18, ACS within past 10 days
- PCI completed (if planned)
- Cholesterol <240, or <200 if on statin
- Exclusion criteria:
  - PCI in past 6 months
  - planned CABG or CABG in past 2 months
  - Liver disease or Cr >2.0

PROVE-IT Patient characteristics

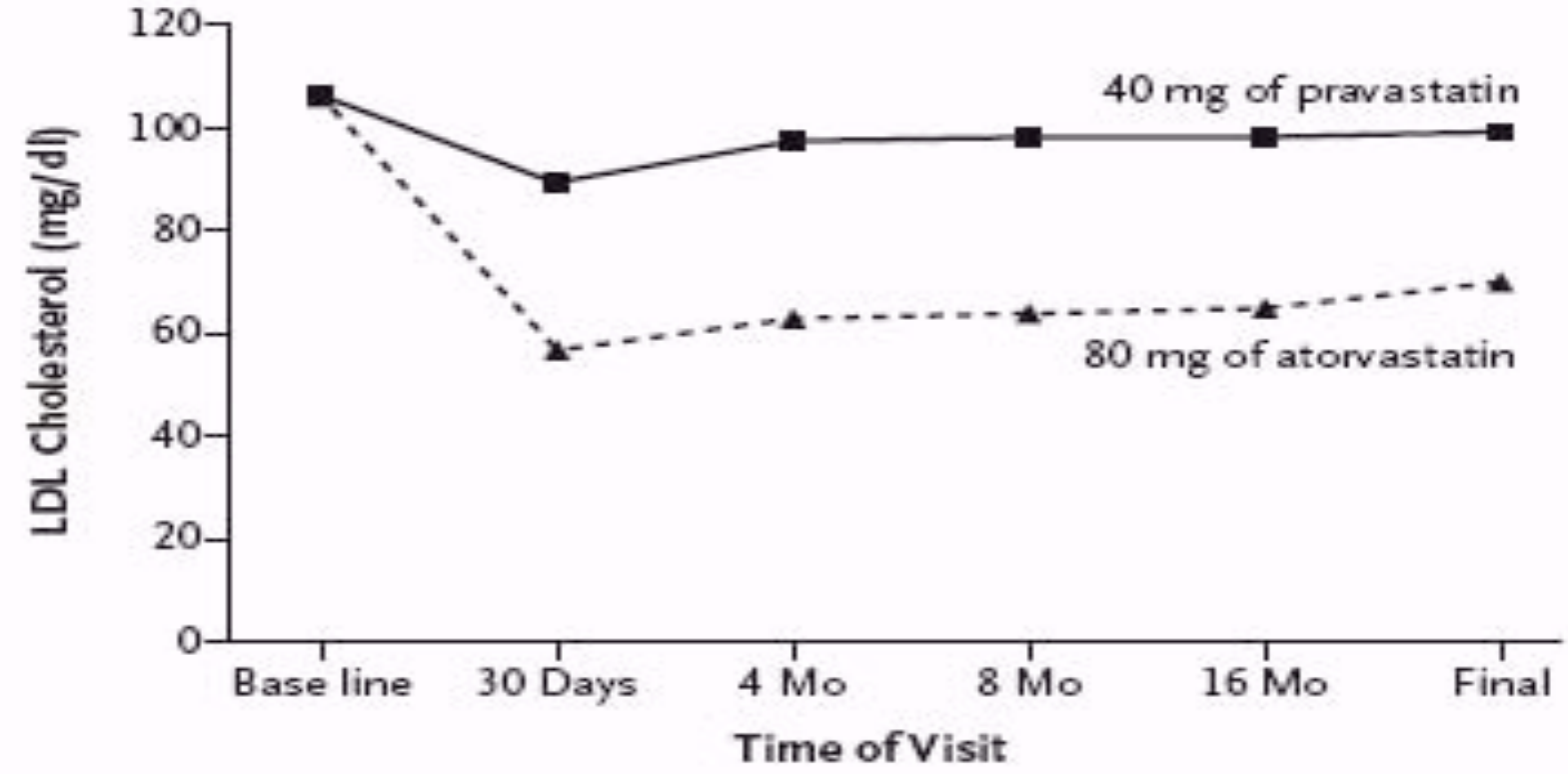
- Age: 58 (mean)
- Gender 78% men
- DM 18%
- HTN 50%
- Smoking 37%
- PCI 69% (for index event)

PROVE IT patient characteristics (Cont.)

- On statin therapy 25%
- Baseline LDL 106 mg/dl
  - Interquartile range 87-128
- Baseline HDL 38 mg/dl

LDL levels on treatment (mg/dl)

	Pre	***Post***
Atorvastatin 80 mg	**106**	**62**
Pravastatin 40 mg	**106**	**95**



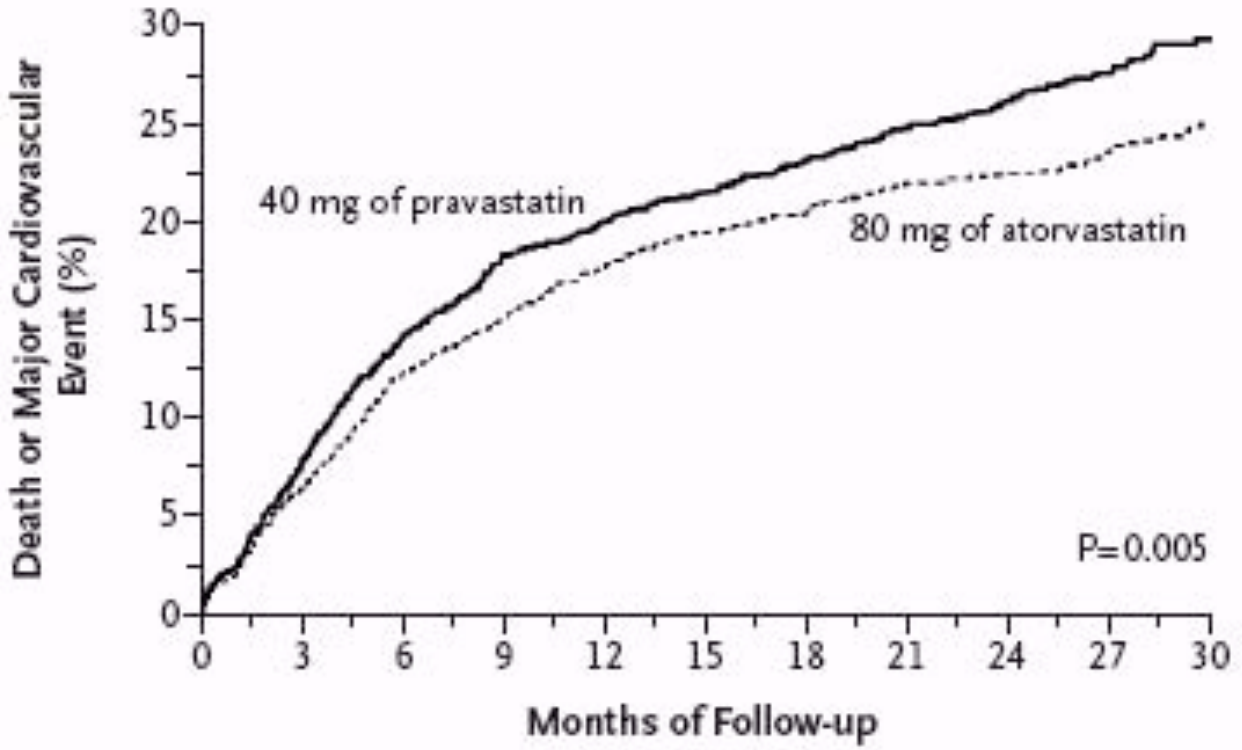
No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Figure 1. Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study.

To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

PROVE-IT Results

- 16 percent relative reduction in primary endpoint at 2 years (death ,MI, revascularization, or unstable angina)
  - 26.3% in the pravastatin group vs.
  - 22.4% in the atorvastatin group
- Revascularization (16.3% vs. 18.8%) and unstable angina (3.8% vs. 5.15%) were the only *individual* endpoints to achieve statistical significance



No. at Risk						
Pravastatin	2063	1688	1536	1423	810	138
Atorvastatin	2099	1736	1591	1485	842	133

Figure 2. Kaplan–Meier Estimates of the Incidence of the Primary End Point of Death from Any Cause or a Major Cardiovascular Event.

Intensive lipid lowering with the 80-mg dose of atorvastatin, as compared with moderate lipid lowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death or a major cardiovascular event by 16 percent.

Censoring Time	Hazard Ratio (95% CI)	Risk Reduction	Event Rates	
			Atorvastatin	Pravastatin
		percent		
30 Days		17	1.9	2.2
90 Days		18	6.3	7.7
180 Days		14	12.2	14.1
End of follow-up		16	22.4	26.3

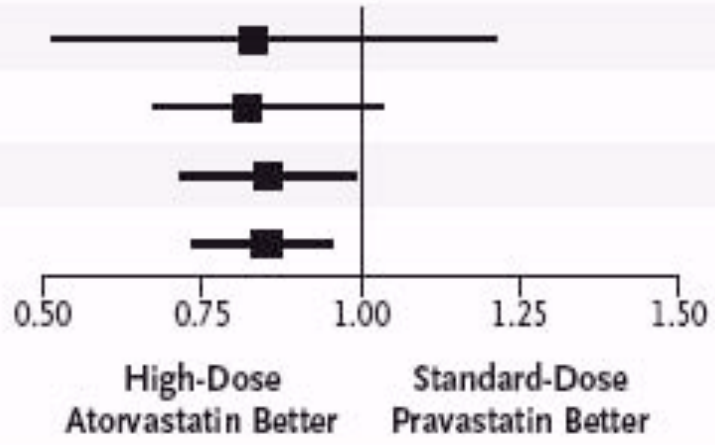
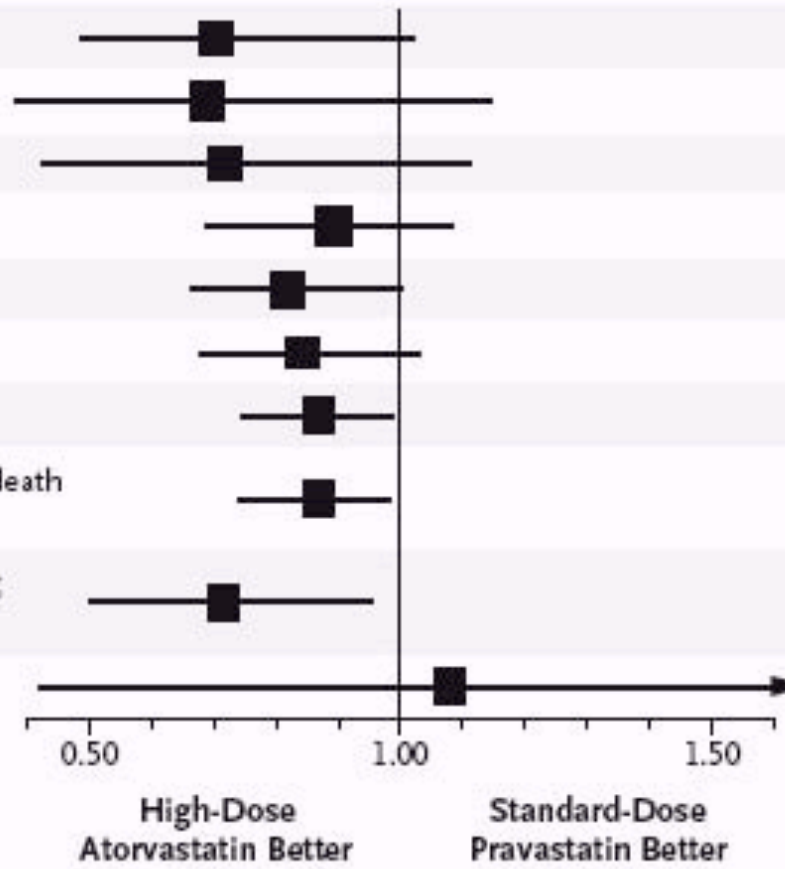


Figure 3. Hazard Ratio for the the Primary End Point of Death from Any Cause or a Major Cardiovascular Event at 30, 90, and 180 Days and at the End of Follow-up in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group.

Event rates are Kaplan–Meier estimates censored at the time points indicated with the use of the average duration of follow-up (two years). CI denotes confidence interval.



End Point	Risk Reduction	2-Yr Event Rates	
		Atorvastatin	Pravastatin
	percent		
Death from any cause	28	2.2	3.2
Death from CHD	30	1.1	1.4
Death from other causes	27	1.2	1.8
MI	13	6.6	7.4
Death or MI	18	8.3	10.0
Death from CHD or MI	16	7.2	8.3
Revascularization	14	16.3	18.8
MI, revascularization, or death from CHD	14	19.7	22.3
Unstable angina requiring hospitalization	29	3.8	5.1
Stroke	−9	1.0	1.0

Figure 4. Estimates of the Hazard Ratio for the Secondary End Points and the Individual Components of the Primary End Point in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group.

CI denotes confidence interval, CHD coronary heart disease, and MI myocardial infarction. Revascularization was performed at least 30 days after randomization.

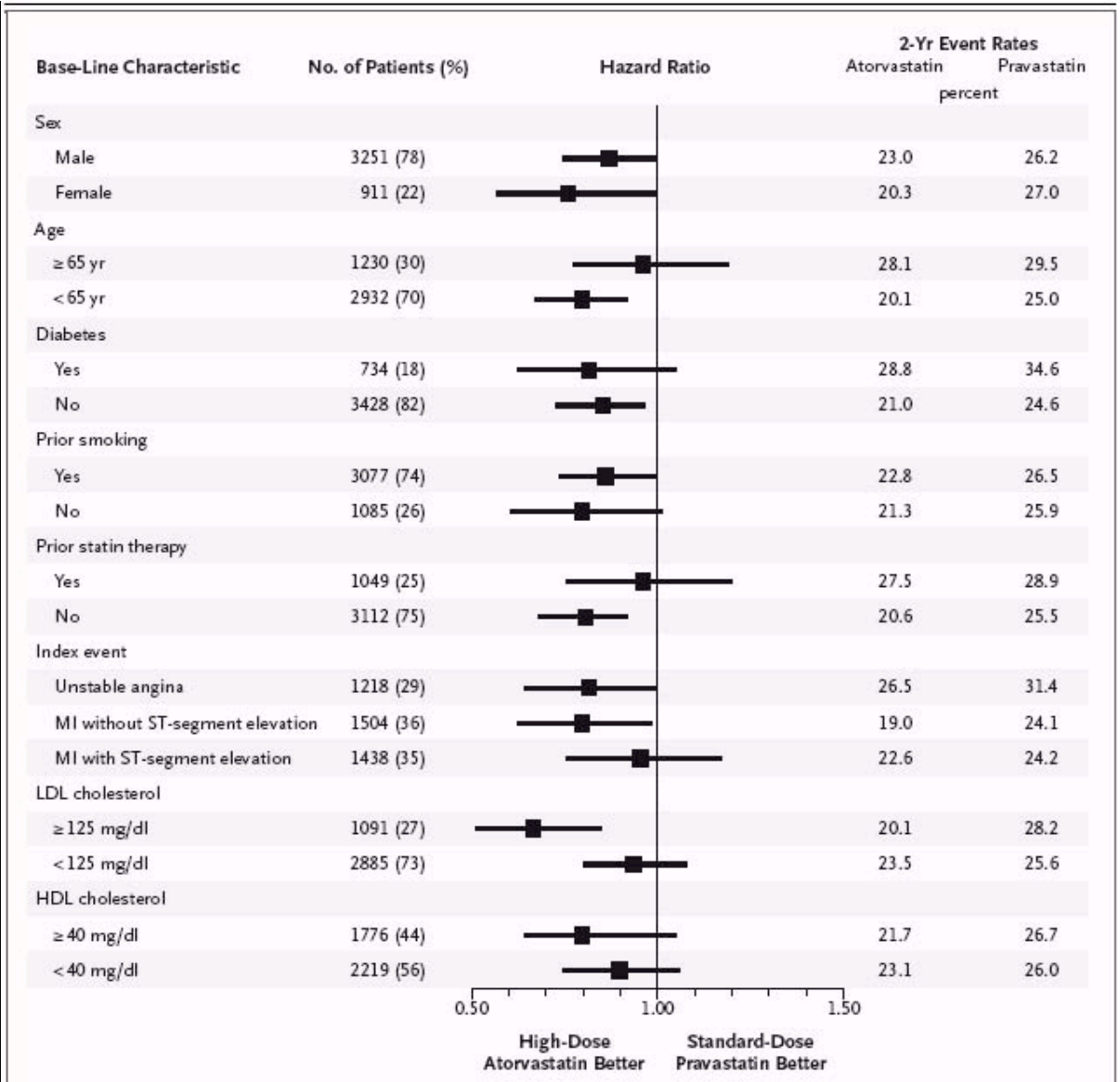


Figure 5. Two-Year Event Rates and Estimates of the Hazard Ratio for the Primary End Point in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group, According to Base-Line Characteristics.

A test for interaction was significant only for a base-line low-density lipoprotein (LDL) value of at least 125 mg per deciliter, as compared with a value of less than 125 mg per deciliter ($P=0.02$). LDL cholesterol was measured at base line in a total of 3976 patients, and high-density lipoprotein (HDL) cholesterol was measured in 3995. Two patients did not have information regarding the electrocardiographic type of acute coronary syndrome, and one patient had missing information regarding prior statin use. MI denotes myocardial infarction.

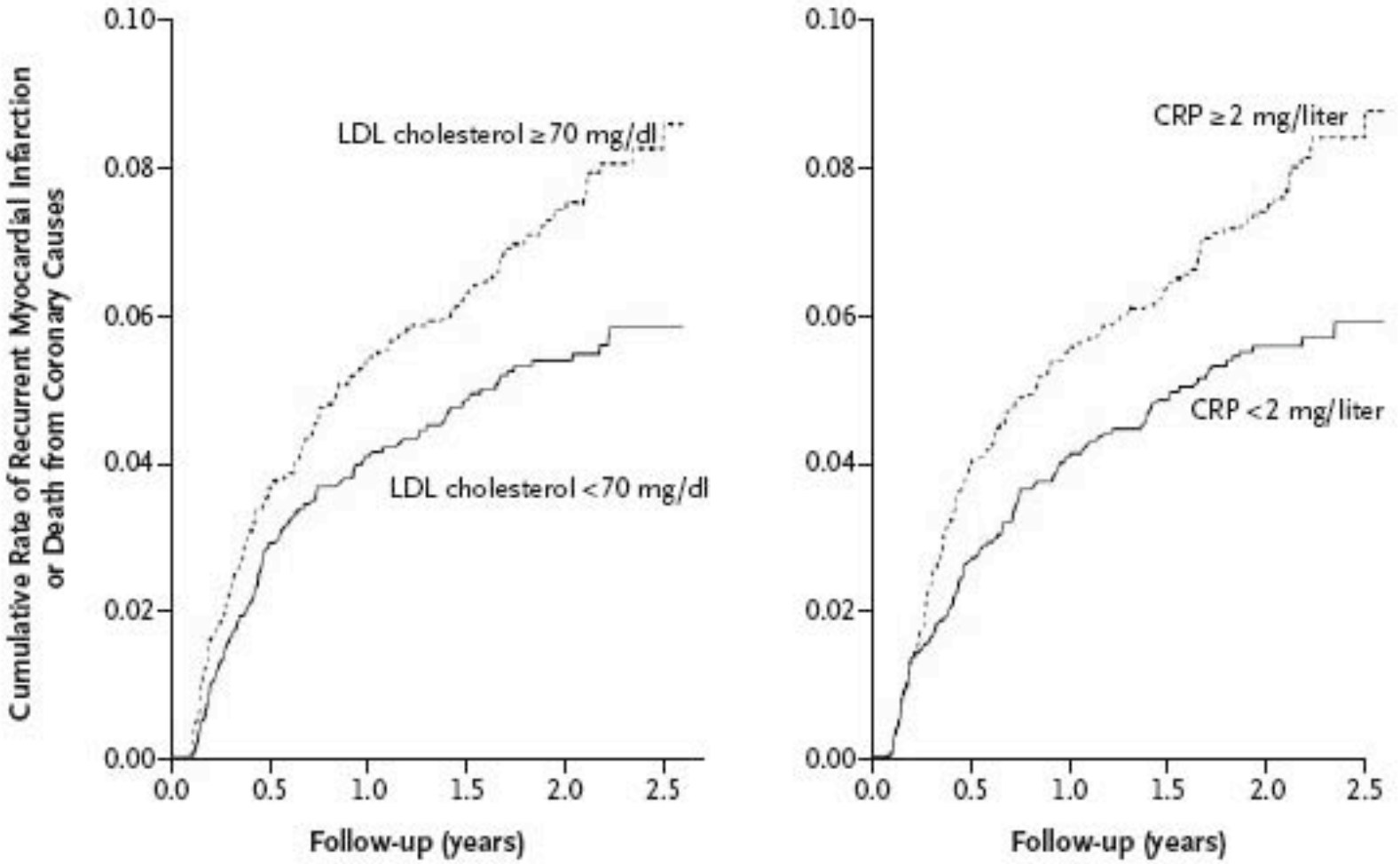


Figure 2. Cumulative Incidence of Recurrent Myocardial Infarction or Death from Coronary Causes, According to Whether the Achieved LDL Cholesterol or CRP Levels Were above or below the Median.

The approximate median value of LDL cholesterol was 70 mg per deciliter (1.8 mmol per liter), and the median value of CRP was 2 mg per liter. The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.

REVERSAL, PROVE –IT Summary

- In patients with an *ACS*, aggressive lipid lowering results in reduction in clinically important endpoints (PROVE-IT)
- In patients with *stable* CHD, aggressive lipid lowering appears to halt progression of atheroma, but the effect on clinical endpoints is not known (REVERSAL)
- Patients who achieved an LDL of <70 mg/dl had a decrease in recurrent MI or cardiac death compared to those patients with a post-treatment LDL >70 mg/dl (PROVE-IT)

A to Z trial

- 4500 patients with ACS randomized to simvastatin 40 mg for one month then 80 mg vs placebo for 4 months then simvastatin 20 mg
- 6 to 24 month f/u
- Endpoint: composite of cardiac death, MI, readmission for ACS, stroke

A to Z trial results

- LDL
  - 122 mg/dl in placebo group
  - 77 mg/dl on 20 mg simvastatin
  - 68 mg/dl on 40 mg simvastatin
  - 63 mg/dl on 80 mg simvastatin

  - Endpoint reached in 16.7% in placebo/simvastatin 20 group vs 14.4% in simvastatin 40/80 group (NS)
  - 32% dropout rate

*JAMA 2004 292:1307-1316

Ongoing Clinical Trials

- SEARCH—Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine,
  - 80 mg simvastatin vs. 20 mg simvastatin
  - Report due ~ 2005
- IDEAL: Incremental Decrease in Events through Aggressive Lipid Lowering
  - Atorvastatin 80 vs Simvastatin 40/20
- TNT—Treating to New Targets
  - 10 mg atorvastatin vs. 80 mg atorvastatin

Case #3

An inquisitive, well educated, 66 y/o recently retired patient emails you after reading in the paper about hsCRP . She is in excellent health, has well controlled hypertension. She has no other cardiac risk factors except her age, and has an LDL of 120, HDL 50, and normal triglycerides

She wants to know if she should have her hsCRP checked and whether she should be on a statin if it is elevated?

C-Reactive Protein

- Hepatically derived pentraxin five 23kDa subunits
- Marker and mediator of atherosclerosis
- Associated with increased risk for vascular events in numerous epidemiological studies
- Increases with infection , trauma, hospitalization

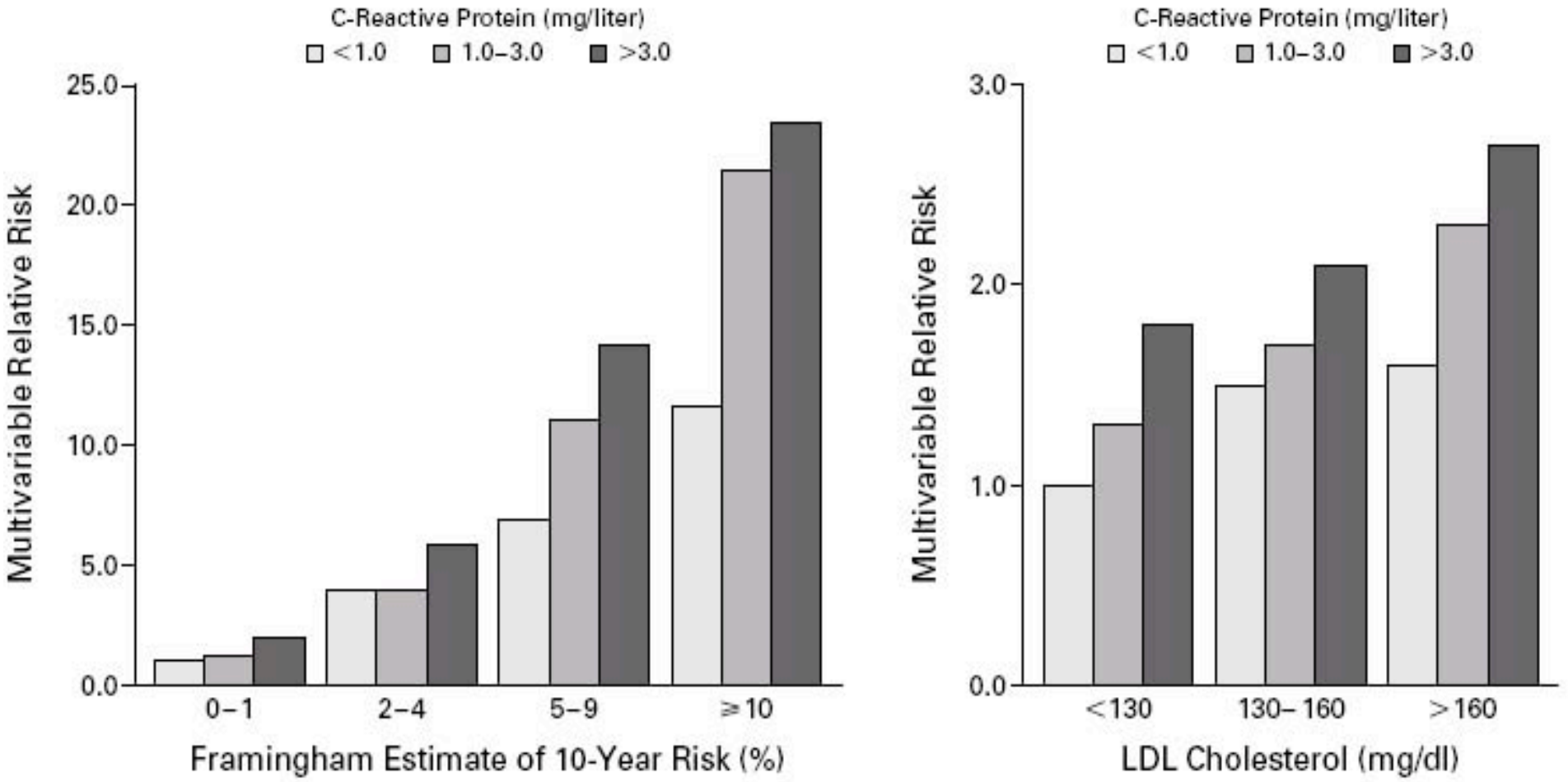


Figure 4. Multivariable-Adjusted Relative Risks of Cardiovascular Disease According to Levels of C-Reactive Protein and the Estimated 10-Year Risk Based on the Framingham Risk Score as Currently Defined by the National Cholesterol Education Program and According to Levels of C-Reactive Protein and Categories of LDL Cholesterol.

To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

HsCRP and Statin Treatment: AFCAPS Data

Subgroup	**Event Rate %** Statin	Placebo	**Relative Risk Reduction**%	**Number Needed to Treat (NNT)**
Chol/HDL<median CRP< median	**2.4**	**2.5**	0.1%	**983**
Chol/HDL<median CRP>median	**2.5**	**5.0**	53%	**43**
Chol/HDL>median CRP<median	**2.1**	**5.0**	58%	**35**
Chol/HDL>median CRP>median	**4.1**	**5.7**	28%	**62**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

C-Reactive Protein Levels and Outcomes after Statin Therapy

Paul M Ridker, M.D., Christopher P. Cannon, M.D., David Morrow, M.D., Nader Rifai, Ph.D., Lynda M. Rose, M.S., Carolyn H. McCabe, B.S., Marc A. Pfeffer, M.D., Ph.D., and Eugene Braunwald, M.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigators

ABSTRACT

Table 1. Key Findings in Two New Trials of Statin Drugs.*

Variable	REVERSAL	PROVE-IT
Clinical indication for therapy	Stable coronary disease	Acute coronary syndromes
Length of follow-up (mo)	18	24
LDL cholesterol†	150	106‡
Base-line (mg/dl)		
Atorvastatin group (mg/dl)	79	62
Percent decrease	46	42
Pravastatin group (mg/dl)	110	95
Percent decrease	26	10
High-sensitivity CRP		
Base-line (mg/liter)	2.9	12.3
Atorvastatin group (mg/liter)	1.8	1.3
Percent decrease	36	89
Pravastatin group (mg/liter)	2.9	2.1
Percent decrease	5	83

* REVERSAL denotes Reversing Atherosclerosis with Aggressive Lipid Lowering trial, PROVE-IT Pravastatin or Atorvastatin Evaluation and Infection Therapy trial, LDL low-density lipoprotein, and CRP C-reactive protein.
† To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
‡ One fourth of the patients were taking a statin drug at the time of enrollment.

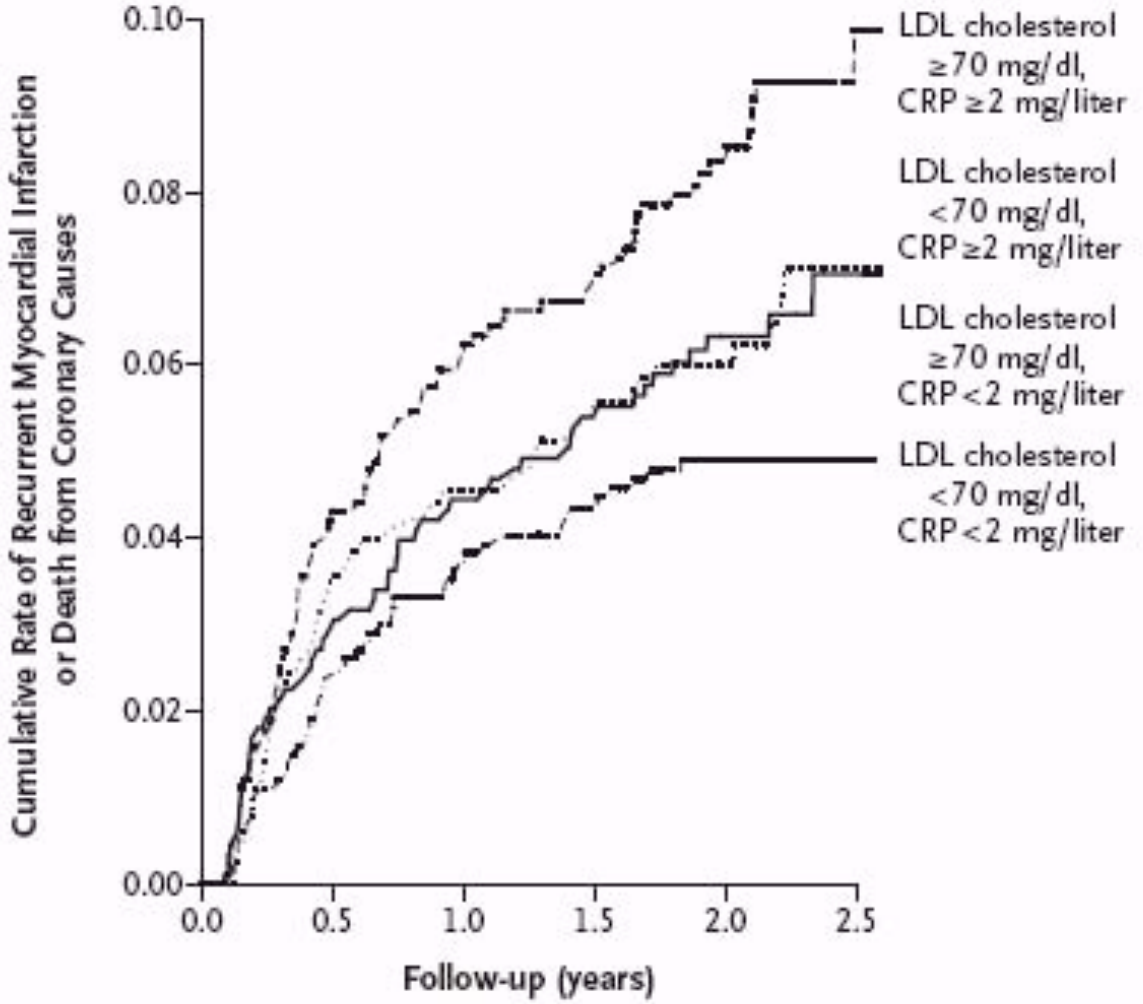


Figure 3. Cumulative Incidence of Recurrent Myocardial Infarction or Death from Coronary Causes, According to the Achieved Levels of Both LDL Cholesterol and CRP.

The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.

Table 2. Age-Adjusted Rates of Recurrent Myocardial Infarction or Death from Coronary Causes, According to the LDL Cholesterol and CRP Level Achieved by Statin Therapy.

Subgroup*	No. of Patients	No. of Person-Yr	No. of Recurrent Events	Age-Adusted Event Rate/100 Person-yr	P Value†
Prespecified analysis					
LDL cholesterol ≥70 mg/dl	1985	3850.7	148	4.0	0.008
LDL cholesterol <70 mg/dl	1760	3511.5	95	2.7	
CRP ≥2 mg/liter	1828	3559.3	139	3.9	0.006
CRP <2 mg/liter	1917	3802.9	104	2.8	
LDL ≥70 mg/dl, CRP ≥2 mg/liter	1086	2086.2	92	4.6	<0.001
LDL <70 mg/dl, CRP ≥2 mg/liter	742	1473.0	47	3.1	
LDL ≥70 mg/dl, CRP <2 mg/liter	899	1764.5	56	3.2	
LDL <70 mg/dl, CRP <2 mg/liter	1018	2038.4	48	2.4	
Post hoc analysis					
CRP ≥1 mg/liter	2699	5250.7	200	3.8	<0.001
CRP <1 mg/liter	1046	2111.5	43	2.1	
LDL ≥70 mg/dl, CRP ≥1 mg/liter	1536	2952.3	128	4.5	<0.001
LDL <70 mg/dl, CRP ≥1 mg/liter	1163	2298.4	72	3.1	
LDL ≥70 mg/dl, CRP <1 mg/liter	449	898.4	20	2.3	
LDL <70 mg/dl, CRP <1 mg/liter	597	1213.0	23	1.9	

* The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.

† P values are for the comparisons between two groups or among four groups.

AHA/CDC recommendations

"those patients at intermediate risk (e.g., 10% to 20% risk of coronary heart disease (CHD) over 10 years), in whom the physician may need additional information to guide considerations of further evaluation (e.g., imaging, exercise testing) or therapy (e.g., drug therapies with lipid-lowering, antiplatelet, or cardioprotective agents), may benefit from measurement of hs-CRP."

JUPITER Trial—ongoing

- **J**ustification for **U**se of Statins in **P**rimary Prevention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin
- 15,000 patients (M>55, W>65)
- hsCRP>2 mg/L, LDL < 130, TG<500
- No CHD history or CHD risk equivalents
- Randomized to placebo vs. rosuvastatin 20 mg

Role of hsCRP Testing

- Patients at high risk for recurrent events should be treated with a statin regardless of CRP level
- Primary prevention---*consider* treatment of patients with high CRP, “normal” LDL at intermediate risk (10-20%) for CHD

Case #4

- 54 y/o male pt s/p anterior MI in 1998, ex-smoker here for routine f/u visit
- Feels well, no angina, active, fit
- Meds: ASA, atenolol
- Lipid Profile HDL 28, LDL 95, TG 160
- Treatment recommendations?

Isolated Low HDL

- 11% of US men have isolated low HDL
- 30% of men have an HDL <40 mg/dl
- Each 1% drop in HDL is associated with a 2-3% increase in CHD risk

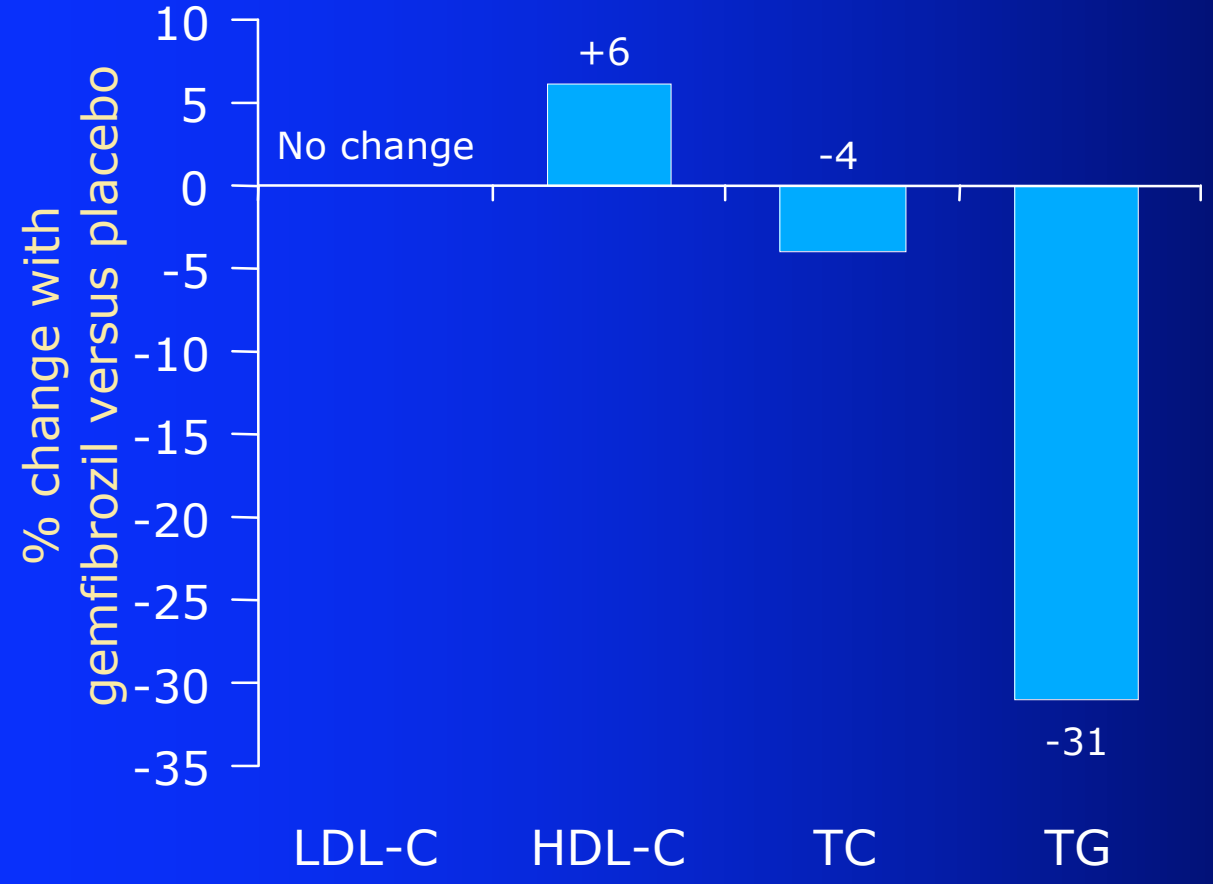
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)

- Double-blind study
- Gemfibrozil (600 mg BID) versus placebo
- 2,531 men with CHD, LDL-C ≤ 140 mg/dL, and HDL-C ≤ 40 mg/dL
- Mean age: 64 y (76.5% aged > 60 y)
- Study duration: 7 y
- Median follow-up: 5.1 y
- Primary end point: nonfatal MI or coronary death

Rubins HB et al. *N Engl J Med* 1999;341:410–418

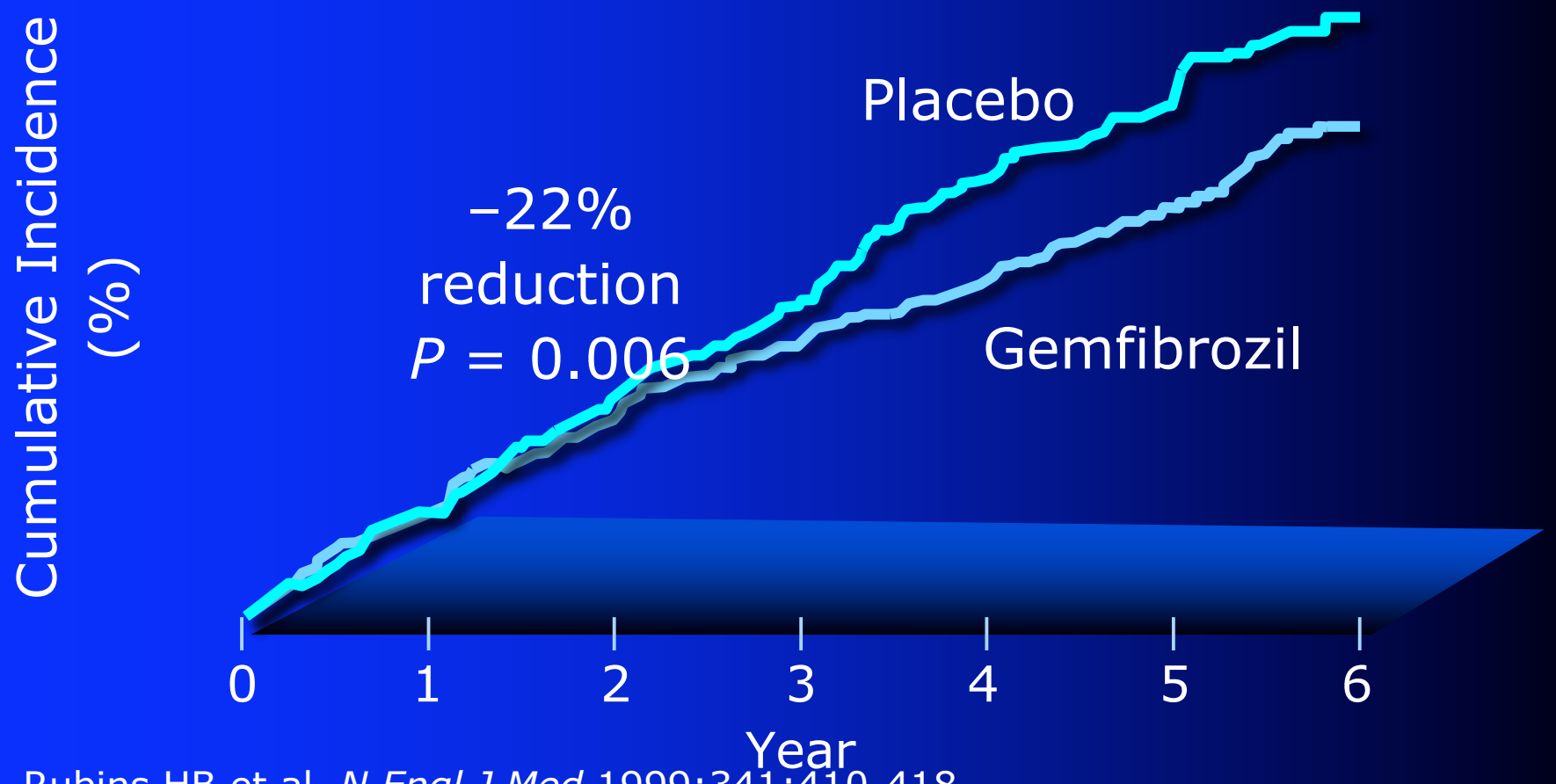
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)

Effects on Lipid Levels at 1 Year



Rubins HB et al. *N Engl J Med* 1999;341:410–418

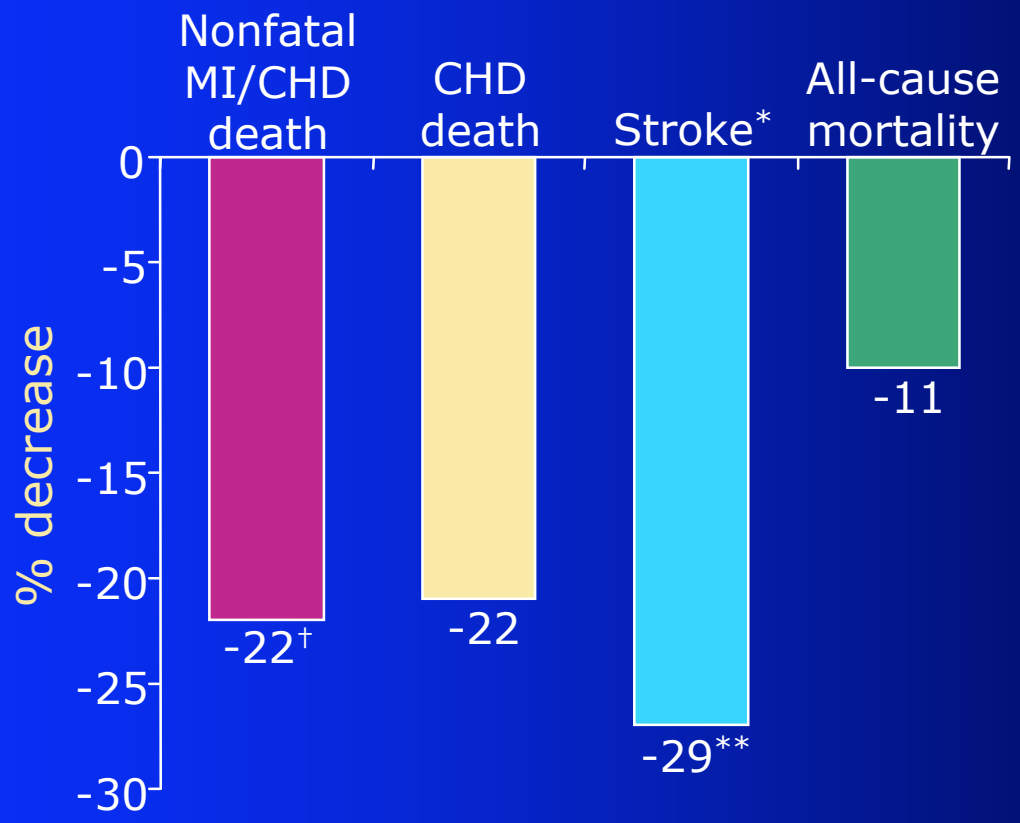
VA-HIT: Major Coronary Events in Gemfibrozil vs. Placebo Groups



Rubins HB et al. *N Engl J Med* 1999;341:410-418.

Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)

Effects of Fibrate on CVD Events in CHD Patients With Isolated Low HDL-C



Placebo/Treated: 275/219 118/93 88/64 220/198

*Investigator-designated

†*P* = 0.006; ***P** = 0.04

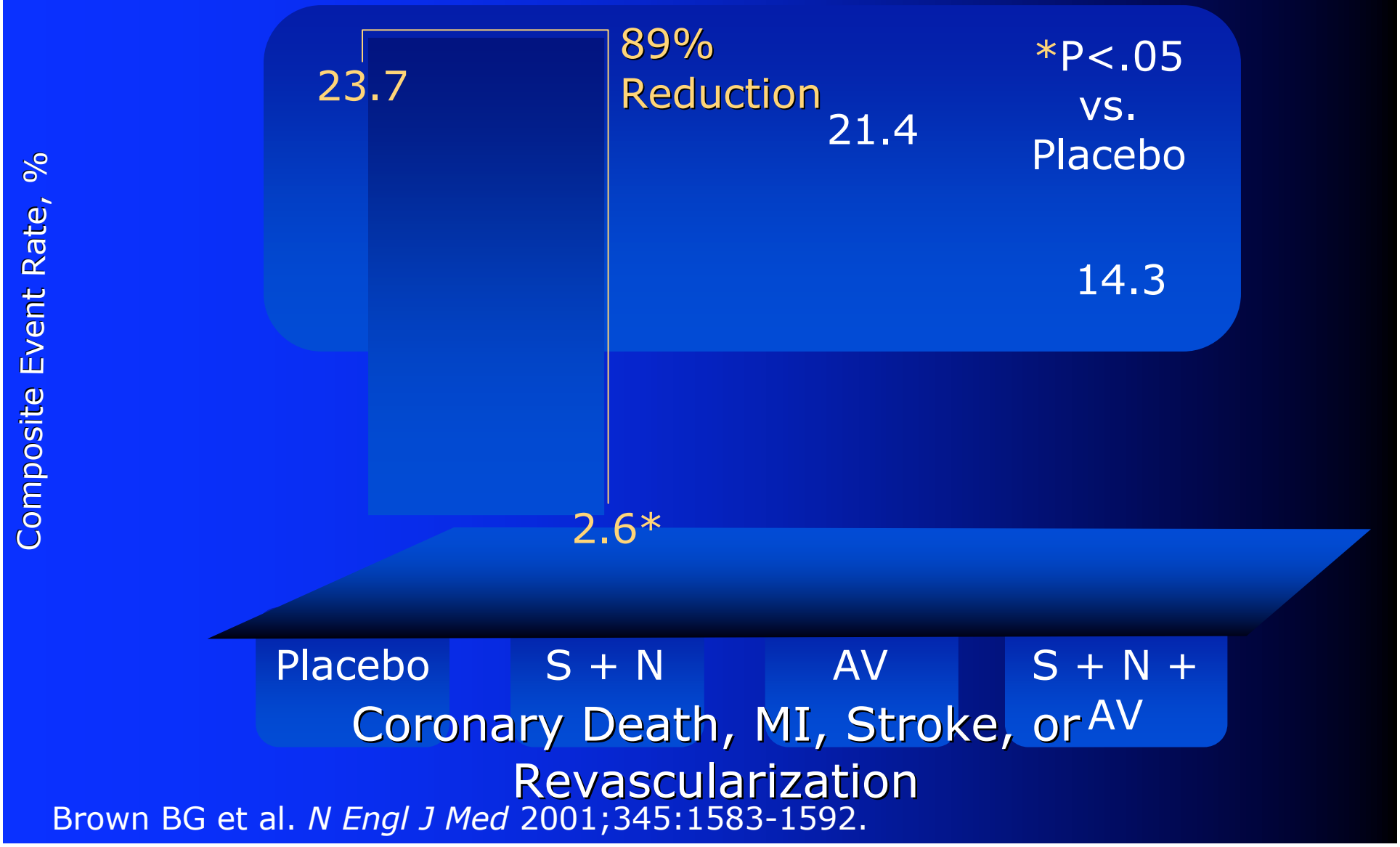
Rubins HB et al. *N Engl J Med* 1999;341:410–418

HDL-Atherosclerosis Treatment Study (HATS)

- RCT of 160 patients with baseline HDL<35, LDL <145
- Simvastatin 10-20 mg + Niacin 2-4 g vs. placebo
- Target LDL <90, HDL increase of > 5 mg/dl
- 3 year follow-up
- Endpoints-angiographic progression or MI, death, stroke, revascularization

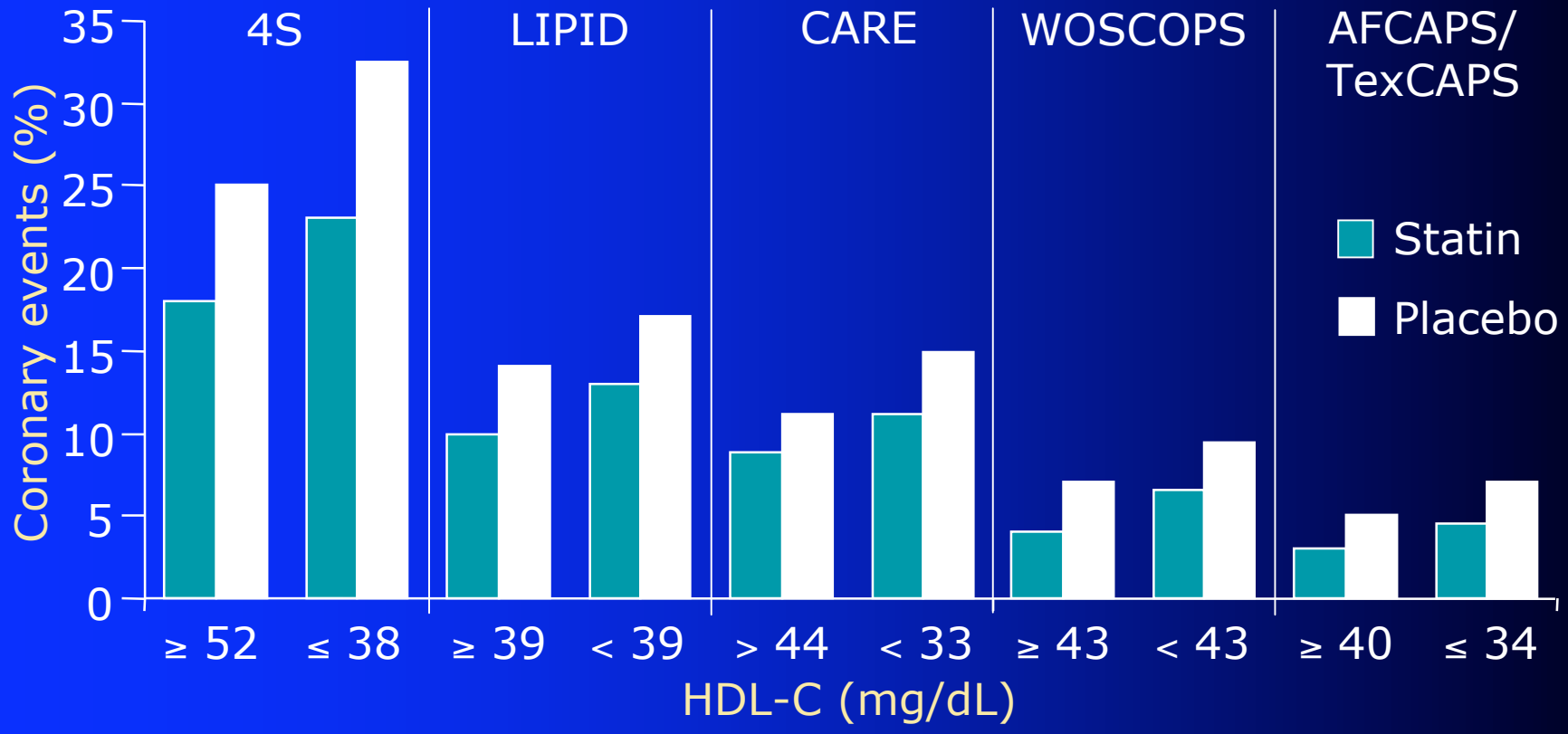
HDL-Atherosclerosis Treatment Study (HATS)

Niacin and Statin Outcome Trial



Brown BG et al. *N Engl J Med* 2001;345:1583-1592.

Comparison of Trials in Which Statin Therapy Ablated Coronary Risk Associated With Low HDL-C



Adapted from Ballantyne CM et al. *Circulation* 1999;99:736–743

Monthly Costs of Common Statins at Drugstore.com

Atorvastatin	10 mg	$62.99
	80mg	$94.99
Simvastatin	20 mg	$123.99
Pravastatin	40mg	$119.99
Lovastatin	40mg	$62.99
Rosuvastatin	5mg	$69.99
Niacin	2gm	$15

Cost- Effectiveness of Statins (per QALYs Gained)

10 yr CHD risk	Annual Statin Cost $	$1000	$500	$250	$125
35%		10,000	5000	2500	1250
25%		25000	12500	6250	3125
15%		50000	25000	12500	6250
10%		100000	50000	25000	12500
5%		200000	10000	50000	25000

PROVE-IT Safety and tolerability

- **Tolerability**: ~ 22% of patients discontinued treatment because of " *adverse events or patient preference or other reasons*"
- **LFT abnormalities-** ALT > 3x normal in 1.1% pravastatin patients vs. 3.1 % in the atorvastatin group (p <0.001)
- **Myalgias or CK elevations**: 2.7 % pravastatin vs. 3.3 % atorvastatin

Summary

- Patients at high risk for CHD appear to benefit from statin therapy even with baseline LDL levels <100
- The “optimal” target for lipid lowering is not yet known, but a target less than 70 mg/dl in very high risk populations is a reasonable goal
- Patients with low HDL benefit from treatment with gemfibrozil or statin-niacin combinations
- Biomarkers such as hsCRP may play a key role in identifying candidates for lipid lowering, but definitive studies have not yet been performed