# Management of Dyslipidemia 2015

## Principles of Prevention in Primary Care Practice


Jorge Plutzky, MD

Director, Preventive Cardiology

Cardiovascular Division

Brigham and Women's Hospital

Harvard Medical School

Boston, Massachusetts

jplutzky@partners.org


BRIGHAM AND WOMEN'S HOSPITAL

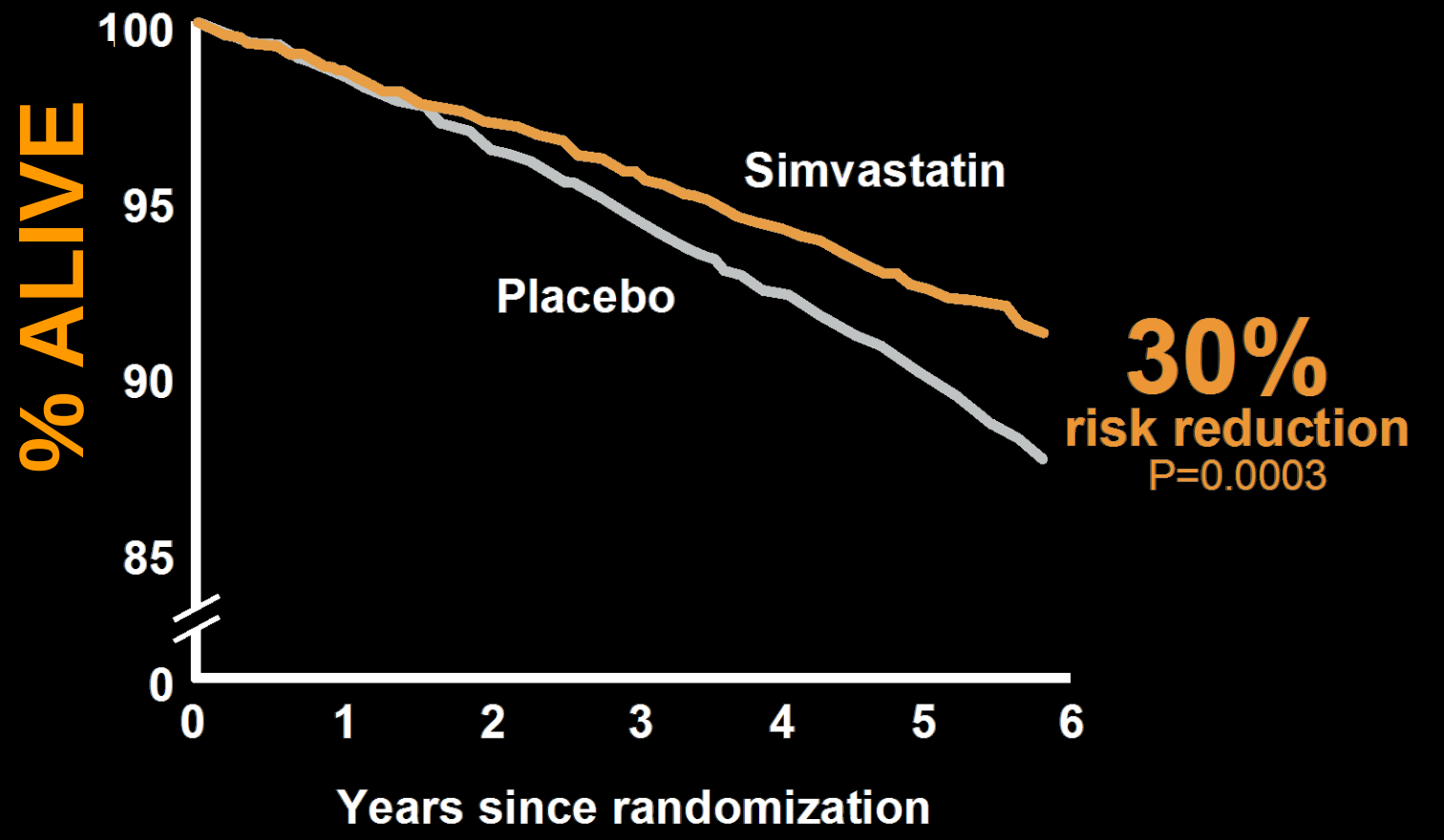
Harvard Medical School

# Statin Era: CV Risk Reduction Across A Spectrum of Risk


| | 4S | LIPID | CARE | WOS | AFCAPS |
|---|---|---|---|---|---|
| CHO / LDL | High | Mod. | Av. | High | Av. |
| | 188 | 150 | 139 | 192 | 150 |
| 1° Endpt CAD (Benefit) | + | + | + | - | - |
| | + | + | + | + | + |

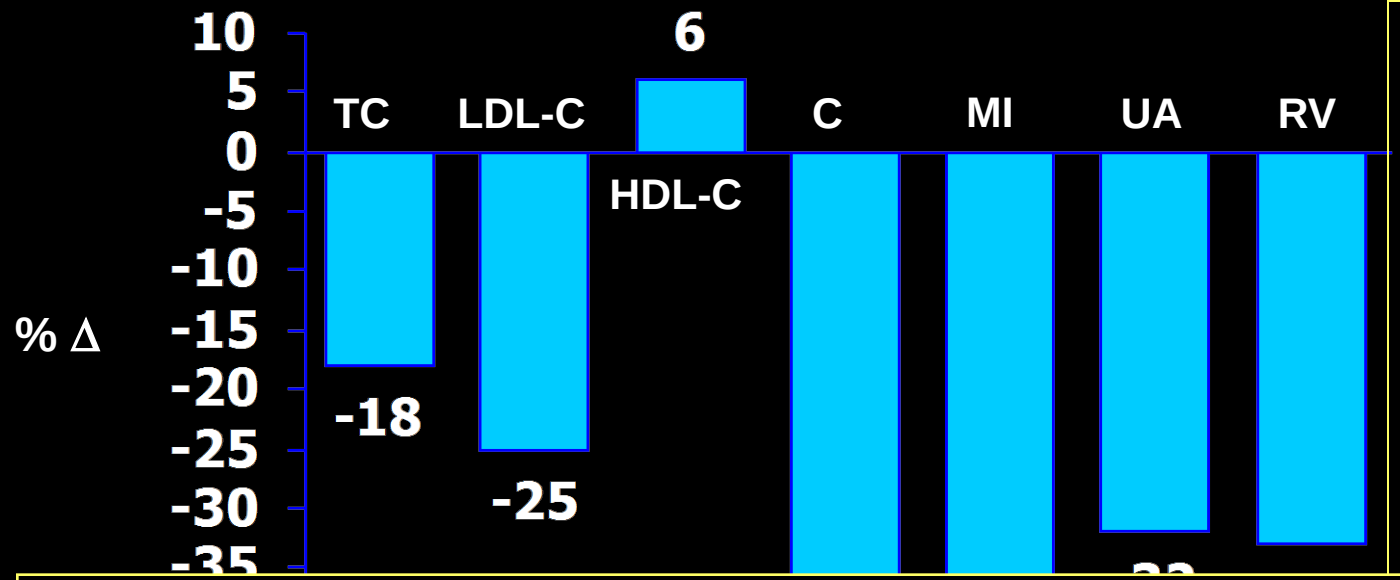
Secondary prevention | Primary prevention

# 4S: Total Mortality/Overall Survival




Adapted from Scandinavian Simvastatin Survival Study Group *Lancet* 1994;344:1383-1389.

# AFCAPS: LDL-Lowering in PEOPLE With No HX OF CAD and Average Cholesterol Levels




**Subjects: 6,605**

**85% men, 45-73 yr**

**15% women, 55-73 yr**

**Baseline lipids:**

**TC: 221 mg/dL**

**LDL-C: 150 mg/dL**

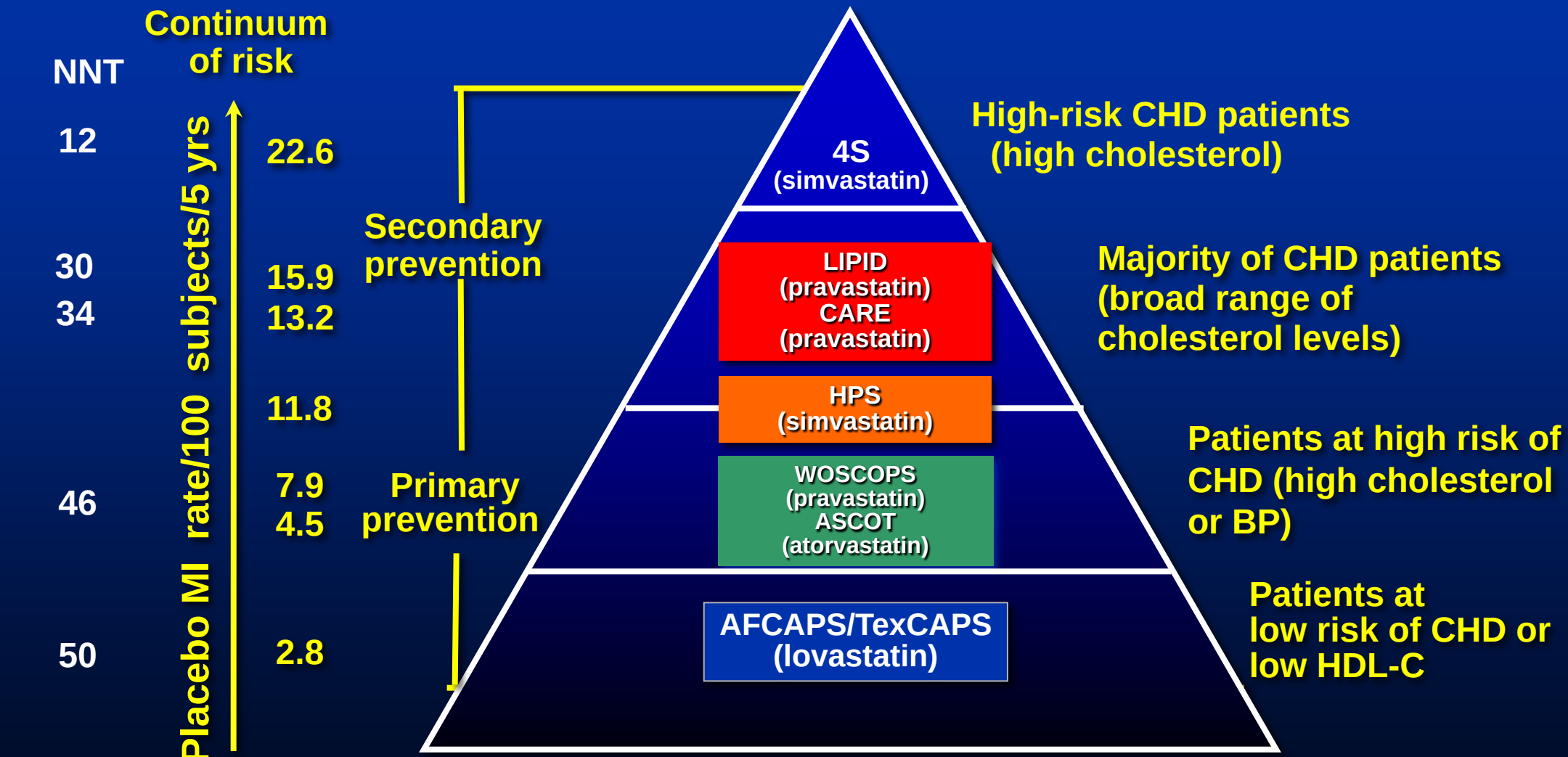
**HDL-C: men, 36 mg/dL**

**70% of AFCAPS subjects untreated under ATPII**

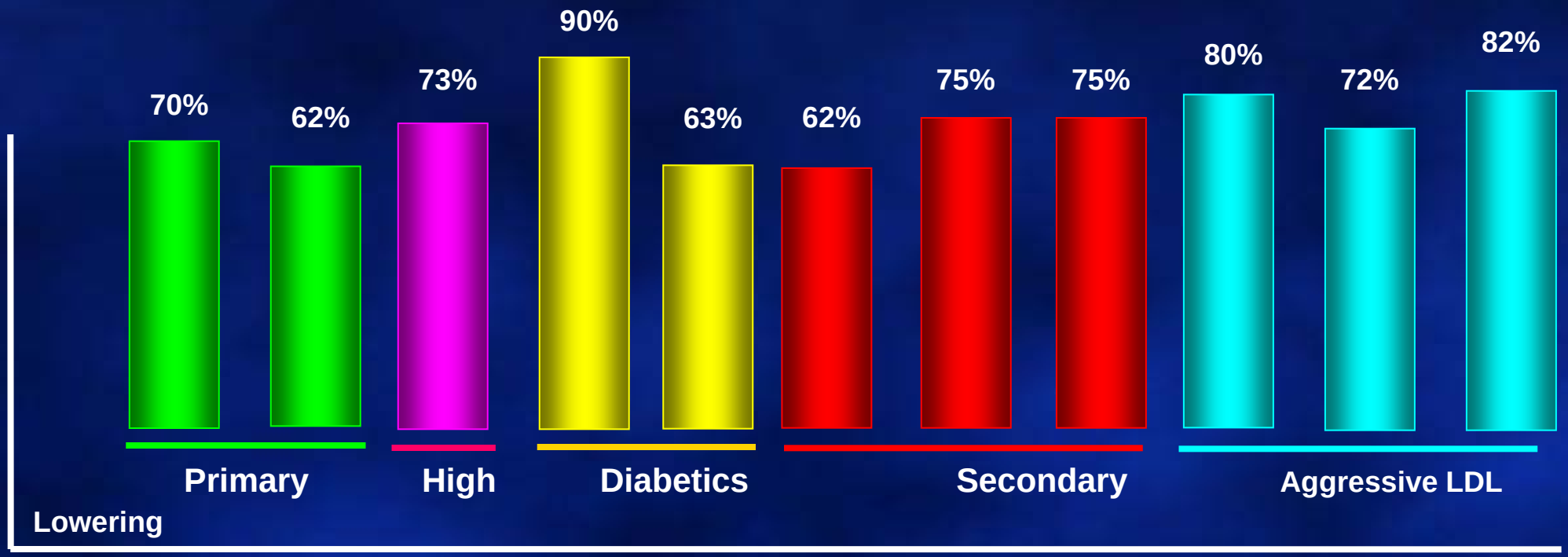
MI=fatal/nonfatal myocardial infarction; UA=unstable angina; RV=revascularizations.

Downs JR et al. *JAMA.* 1998;279:1615-1622.

# The Statin Decade – Benefit across full Spectrum of CAD



# “Residual risk”: Major CV Events Statin Arm, Clinical Trials




| Trial | WOSCOP | AFCAPS/ TexCAPS | HPS | ASPEN | CARDS | 4S | LIPID | CARE | TNT Total | TNT Met S | TNT Diabetes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 6.595 | 6.505 | 20.536 | 2.410 | 2.838 | 4.444 | 9.014 | 4.159 | 10.001 | 5.584 | 1.501 |
| ΔLDL-C | -26% | -27% | -29% | -29% | -40% | -36% | -25% | -28% | -21% | -24% | -20% |

# Is Lower Better (LDL)?

65 yo post-MI

Atorva 80 mg

LDL 105

# New Cholesterol ~~Guidelines~~ Scientific Statement


## New Approaches to Cholesterol Management

# Cholesterol Treatment to Reduce Atherosclerotic Risk
## Attempt to Identify 4 Statin Groups

1. Does the patient have a history of heart disease or stroke? Are they using secondary prevention?

2. Is LDL > 190 mg/dL?
3. Does patient have diabetes, 40-75 years old, with LDL of 70-189 mg/dL?
4. Does patient have global 10-year risk score $\geq$ 7.5% for primary prevention of risk assessment?

# Conceptual Changes In Guidelines

- **Don't treat to specific targets*:** Treating to targets results in under- and overtreatment*; use appropriate-intensity treatment
- LDL-C reduction of 50% are "high-intensity" statins, and "moderate-intensity" lower LDL-C by 30%-49%
- First 2 groups: recommend using high-intensity; second 2 groups use moderate-intensity

* Specific LDL targets of 100 and 70 were part of ATP III 2004 update and ACC/AHA guidelines for CHD patients in 2006

*Non-statin therapies to achieve an LDL goal not recommended*

# High-, Moderate-, and Low-Intensity Statin Therapy

**High-Intensity Statin Therapy**
Lowers LDL-C, on average, by approximately ≥ 50%

- **Atorvastatin (40)-80 mg**
- **Rosuvastatin 20** *(40)* **mg**

**Moderate-Intensity Statin Therapy**
Lowers LDL-C, on average, by approximately 30% to < 50%

- **Atorvastatin 10** *(20)* **mg**
- **Rosuvastatin** (*5*) **10 mg**
- **Simvastatin 20-40 mg‡**
- **Pravastatin 40** *(80)* **mg**
- **Lovastatin 40 mg**
- *Fluvastatin XL 80 mg*
- **Fluvastatin 40 mg bid**
- *Pitavastatin 2-4 mg*

# Major Recommendations for Statin Therapy for ASCVD Prevention

- For secondary prevention or LDL > 190 mg/dL, give high-intensity statin *unless* age > 75 years old or intolerant; then use moderate-intensity statin
- For diabetes (type 1 or 2, age 40-75) use moderate-intensity statin *unless* 10-year risk > 7.5%; then use high-intensity statin
- For primary prevention age 40-75 years, use moderate- to high-intensity statin if 10-year risk is > 7.5%

# Conceptual Changes In Guidelines

- **Don't treat to specific targets***

Rationale for not including lower LDL targets?

Not same drug titrated to different LDL targets.

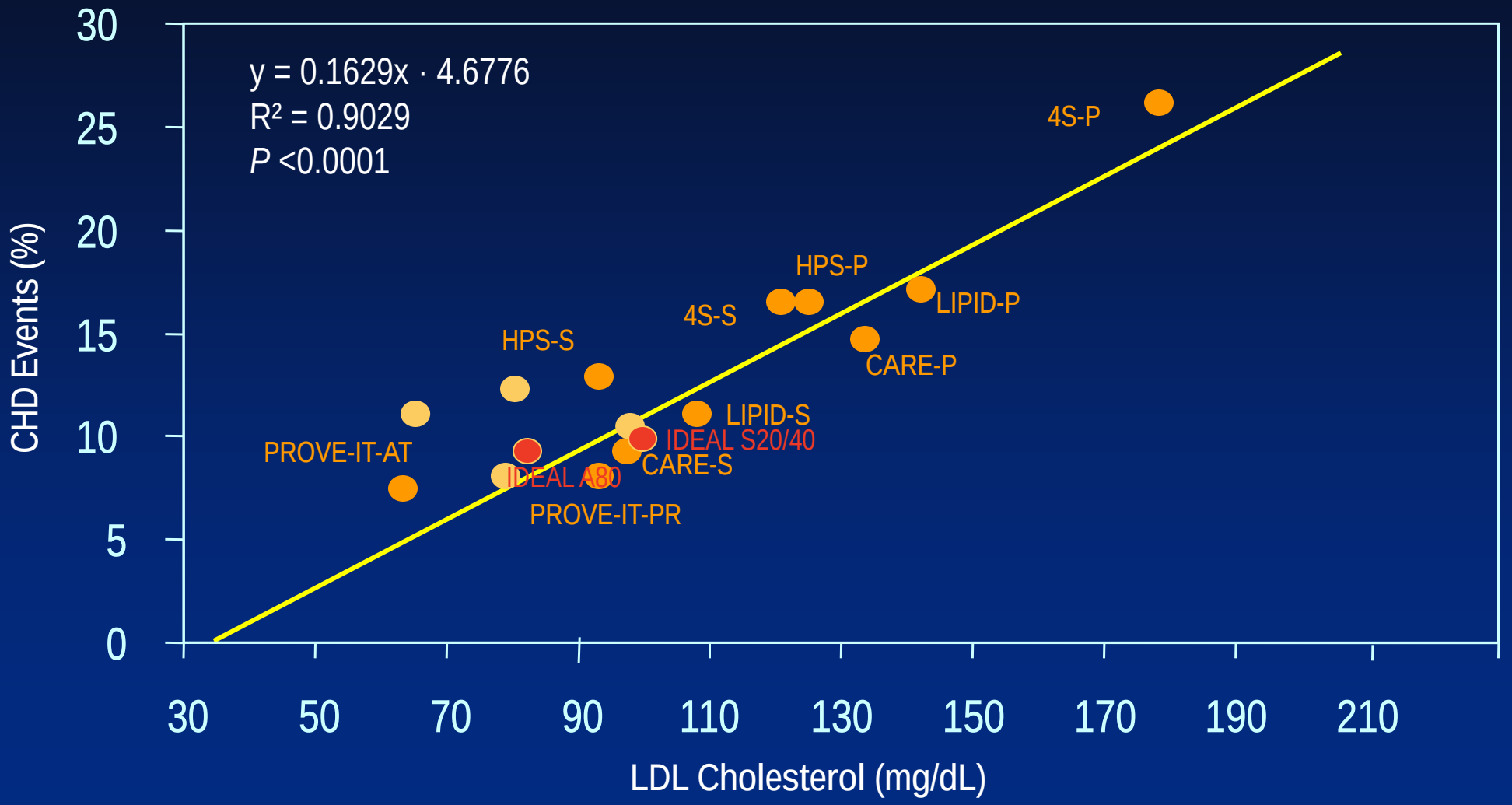
No RCT data for non-statin drugs.

- First 2 groups: recommend using high-intensity; second 2 groups use moderate-intensity

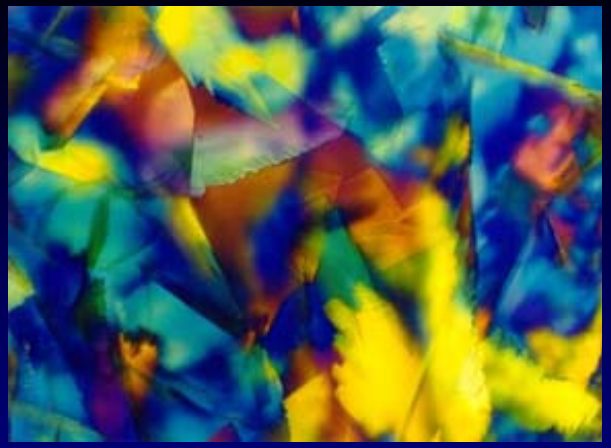
* Specific LDL targets of 100 and 70 were part of ATP III 2004 update and ACC/AHA guidelines for CHD patients in 2006

*Non-statin therapies to achieve an LDL goal not recommended*

# CHD Events Are Reduced Proportional to LDL-C Lowering w/ Statins




Updated from O' Keefe J et al. *J Am Coll Cardiol*. 2004;43:2142-46.



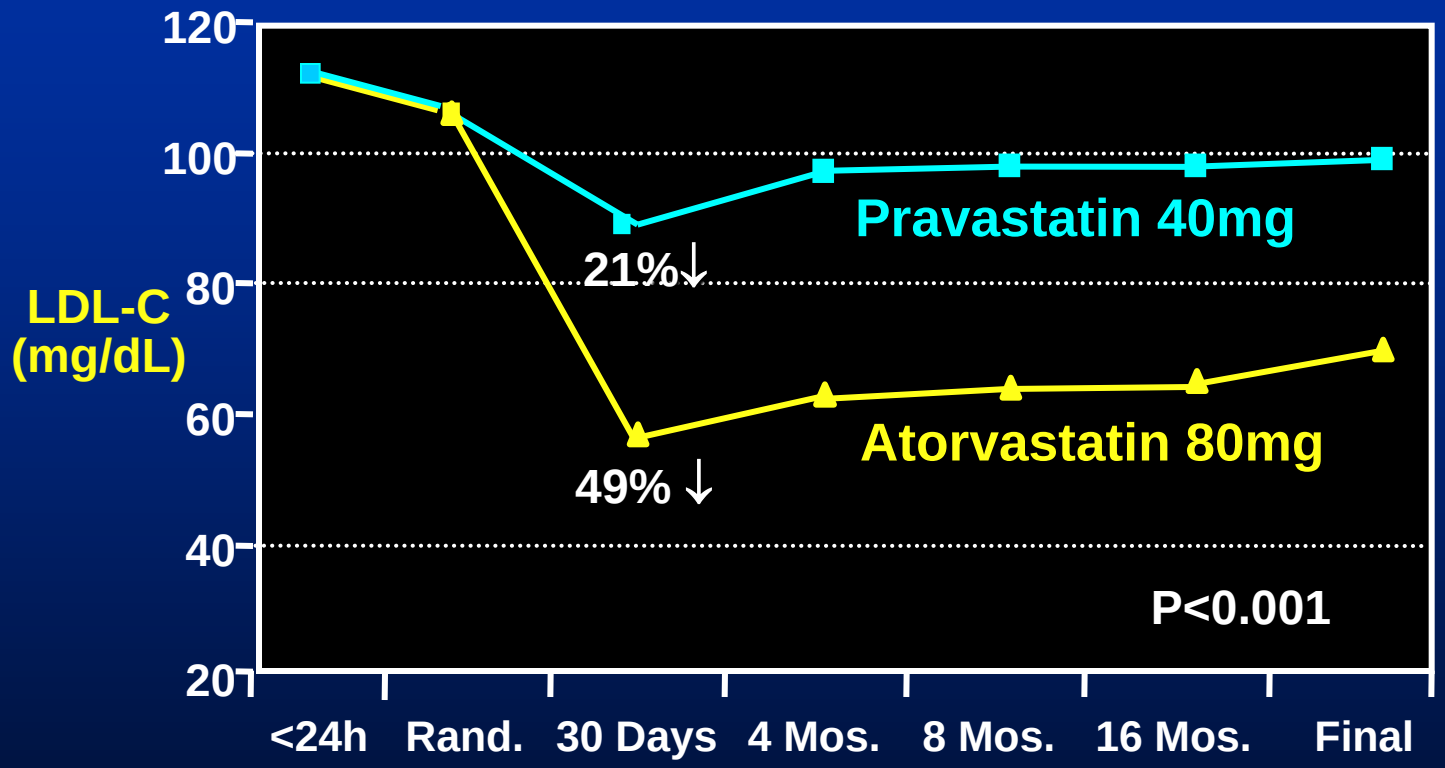
# New Questions, New Issues

**Is even lower LDL better**

**In high risk population:**

**acute coronary syndrome?**

# PROVE-IT: Changes from Post-ACS Baseline LDL-C




**Median LDL-C (Q1, Q3)**

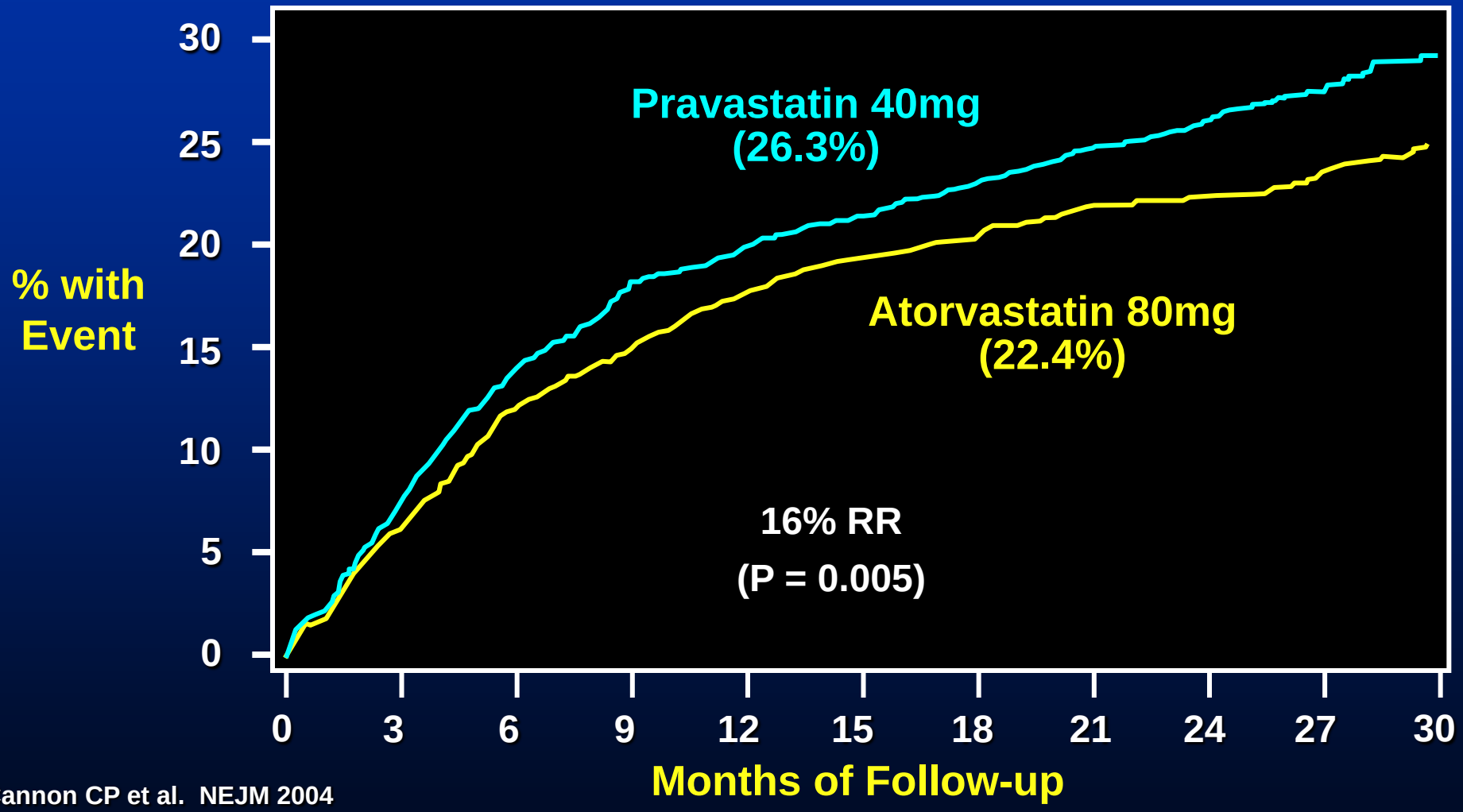
**95 (79, 113)**

**62 (50, 79)**

**Note: Changes in LDL-C may differ from prior trials:**

- **25% of patients on statins prior to ACS event**
- **ACS response lowers LDL-C from true baseline**

# All-Cause Death or Major CV Events in All Randomized Subjects




Cannon CP et al. NEJM 2004

# Study Design

IMPROVE-IT

*3.2mM
**2.6mM

N=18,144

tatin

r to detect
fference

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

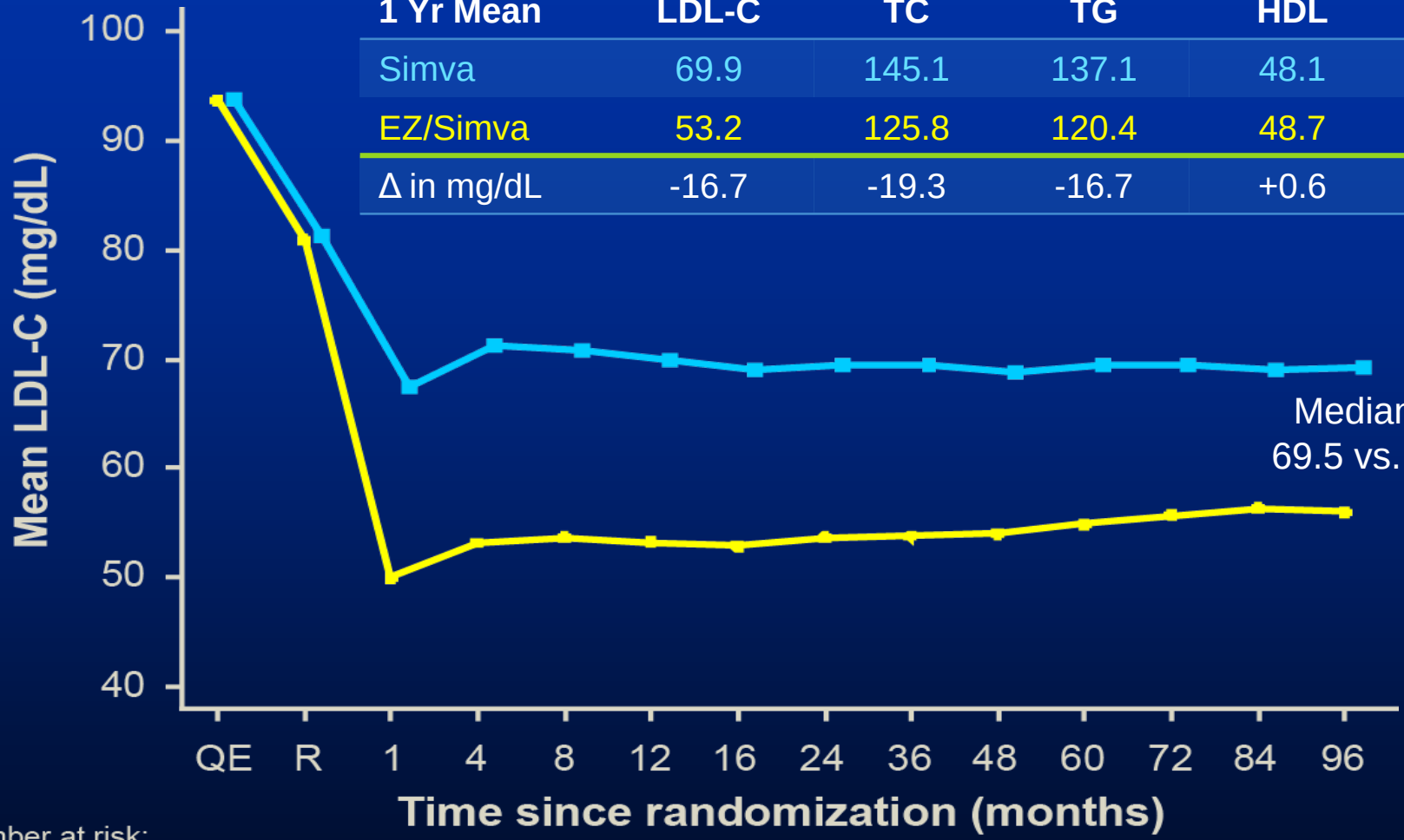
Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

Cannon CP AHJ 2008;156:826-32

# LDL-C and Lipid Changes

IMPROVE-IT

| 1 Yr Mean | LDL-C | TC | TG | HDL | hsCRP |
|---|---|---|---|---|---|
| Simva | 69.9 | 145.1 | 137.1 | 48.1 | 3.8 |
| EZ/Simva | 53.2 | 125.8 | 120.4 | 48.7 | 3.3 |
| Δ in mg/dL | -16.7 | -19.3 | -16.7 | +0.6 | -0.5 |



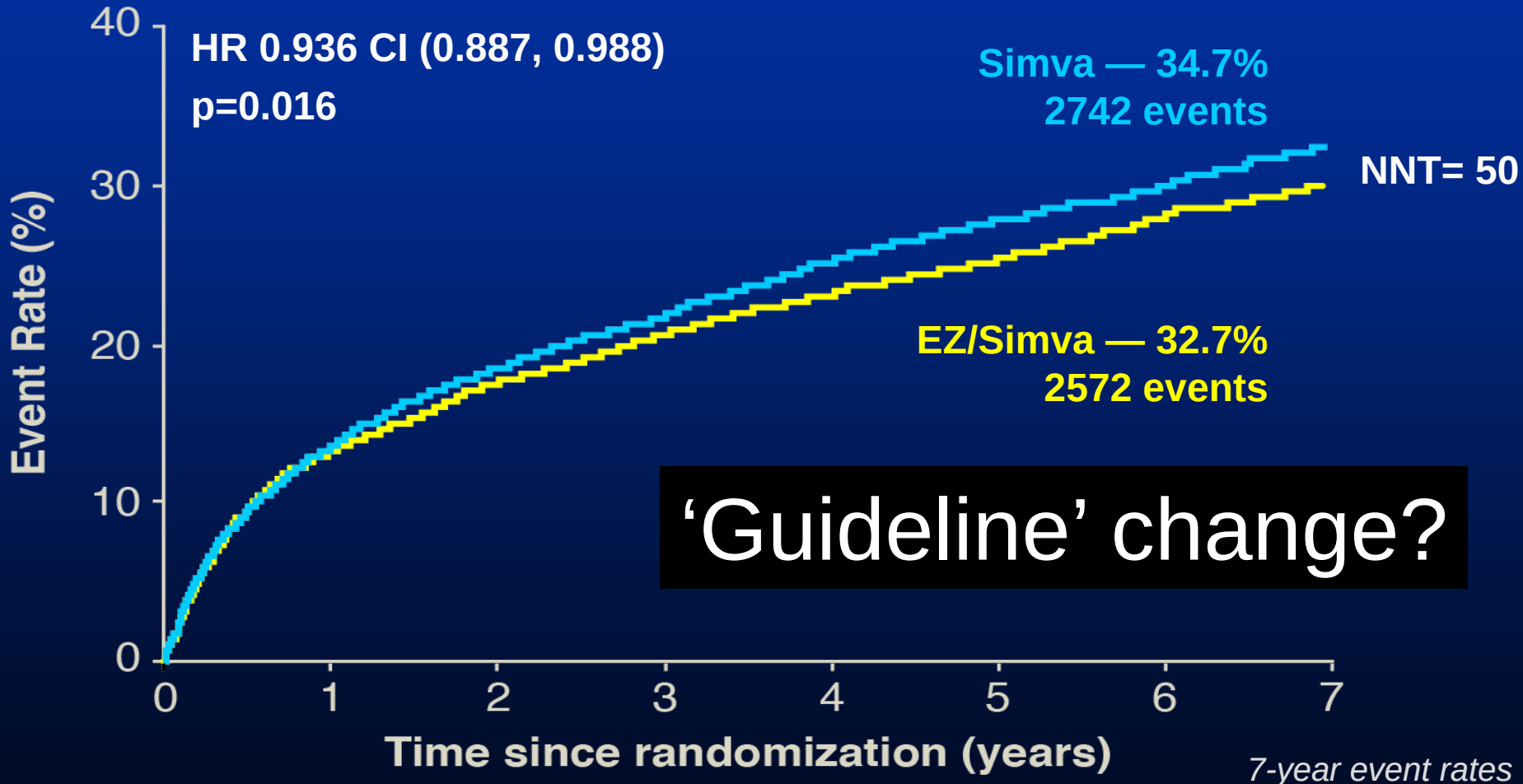

Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EZ/Simva | 8990 | 8889 | 8230 | 7701 | 7264 | 6864 | 6583 | 6256 | 5734 | 5354 | 4508 | 3484 | 2608 | 1078 |
| Simva | 9009 | 8921 | 8306 | 7843 | 7289 | 6939 | 6607 | 6192 | 5684 | 5267 | 4395 | 3387 | 2569 | 1068 |

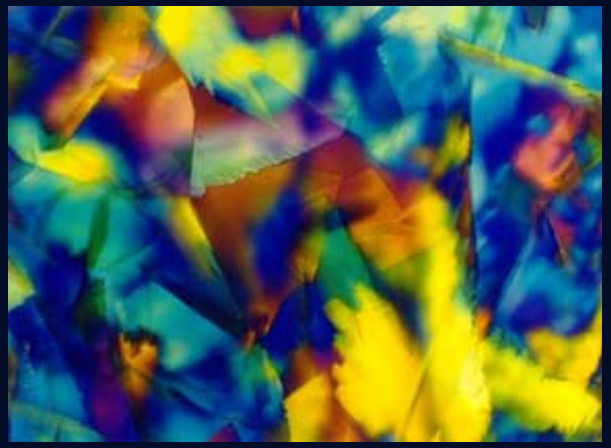
# Primary Endpoint — ITT

*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*




‘Guideline’ change?

*7-year event rates*



# New Questions, New Issues

Other ways to address

risk in the post-statin era?

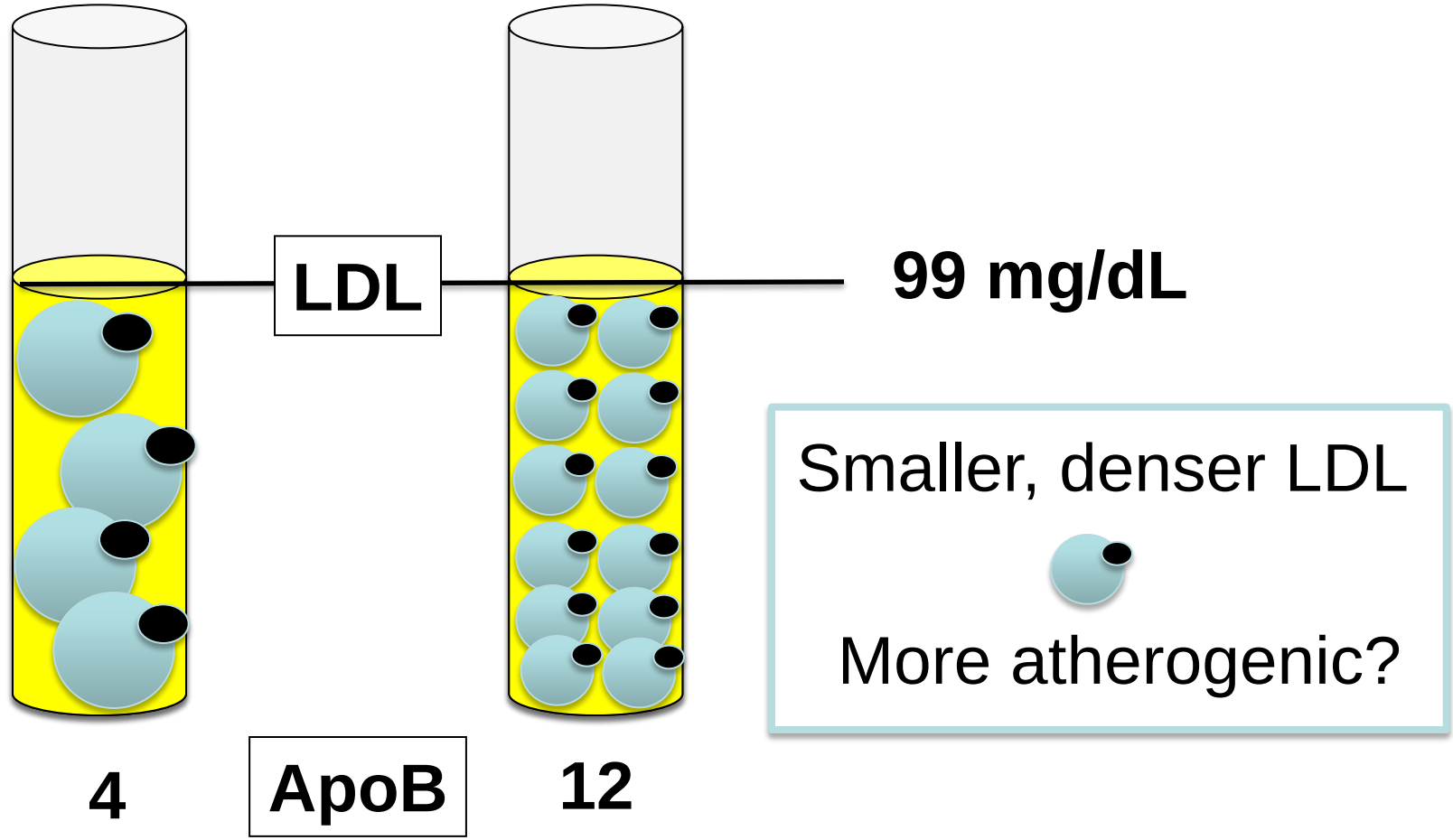
Better risk predictors?

# Apolipoprotein B

- THE risk molecule?

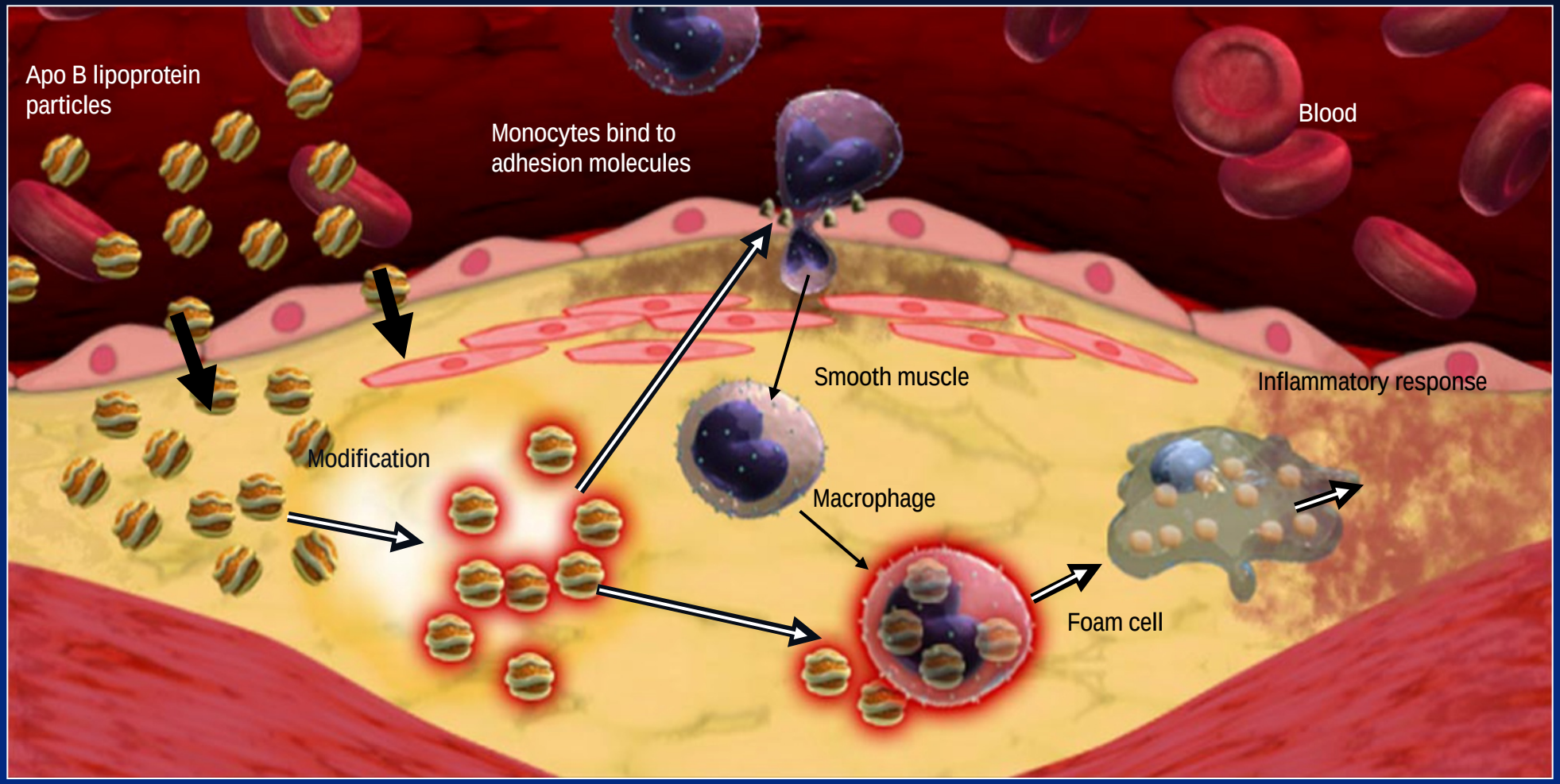
- One apo B molecule/particle
- Measure of particle number:
  Most atherogenic parameter?
- Highly correlated with non-HDL cholesterol
  - 0.95 when TG < 300 mg/dl
  - 0.80 when TG higher

# LDL Levels vs Apo B (particle number, non-HDL)



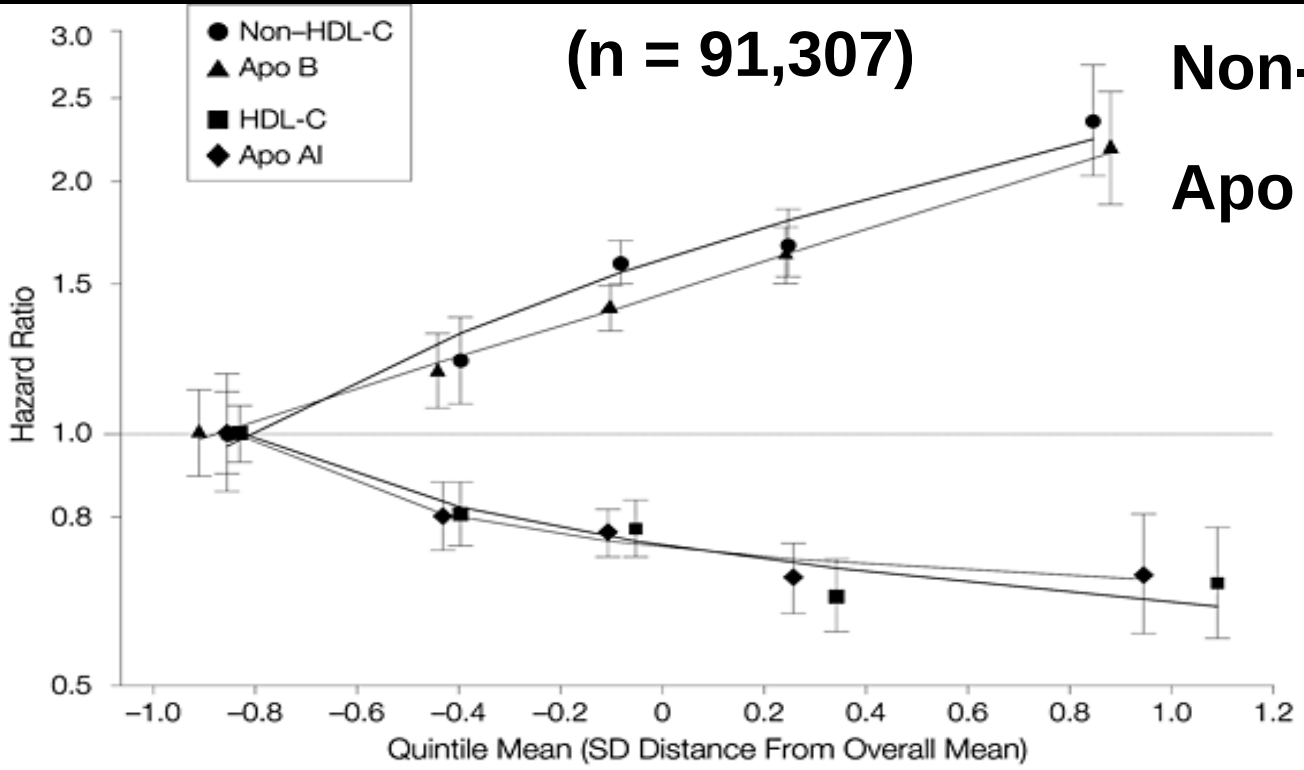
# Higher Plasma Apo B Lipoprotein Levels Promote Atherosclerosis

*Rationale for therapeutic Apo B lowering:* *Broader targeting of risk molecules*
*Decreased retention, inflammatory response to retention*




Tabas I et al. *Circulation.* 2007;116:1832-1844.
Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 1995;15:551-561.
Williams KJ et al. A ATVB . 2005;25:1536-1540
Hoshiga M et al. *Circ Res.* 1995;77:1129-1135

# CHD Risk Based on Lipids and Apolipoproteins




| Quintile | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Mean usual level, mg/dL | | | | | |
| Non–HDL-C | 125 | 145 | 159 | 173 | 198 |
| Apo B | 85 | 99 | 108 | 118 | 137 |
| HDL-C | 37 | 44 | 49 | 55 | 66 |
| Apo AI | 126 | 139 | 148 | 158 | 178 |

**Non-HDL**

**Apo B**

**HDL**

**Apo A1**

**ERF Collaboration, *JAMA* 302:1993, 2009**

# Cholesterol, Trig

**Non-HDL Target:**

30 points above the LDL target

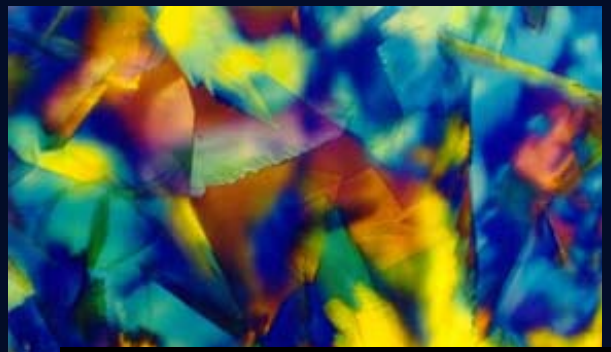
**Therapeutic intervention?**

Intensify statin

Add 2nd LDL agent

Add fibrate


Non-HDL-C = Total cholesterol – HDL-C



Elevated non-HDL (30 points above target LDL):

LDL < 70, non-HDL < 100

LDL < 100, non-HDL < 130

More potent statin
Second agent on LDL: ezetimibe, BAS, niacin
Treat triglycerides: fibrate, fish oil
Lifestyle

# Treat to Target LDL? Lower LDL Levels?

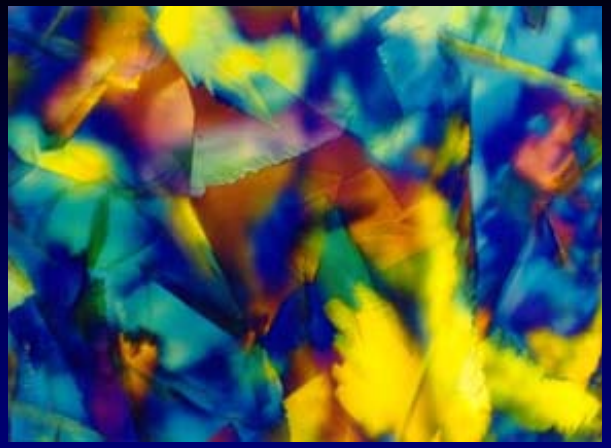
Evidence now exists for lower LDL levels in patients with significant CV risk. OK to use targets.

Estimate risk:

AHA/ACC Risk calculator, Reynolds Risk Score, F-ham

LDL Options:

- Higher dose, more potent statin
- Ezetimibe – additional 15 - 20%
- Bile Acid Resins: Colesevelam
- Not if hyperTG
- Modest glucose-lowering effect



# New Questions, New Issues

Statin Intolerance

# Statin Intolerance

Increased LFTs → Up to 3x ULN

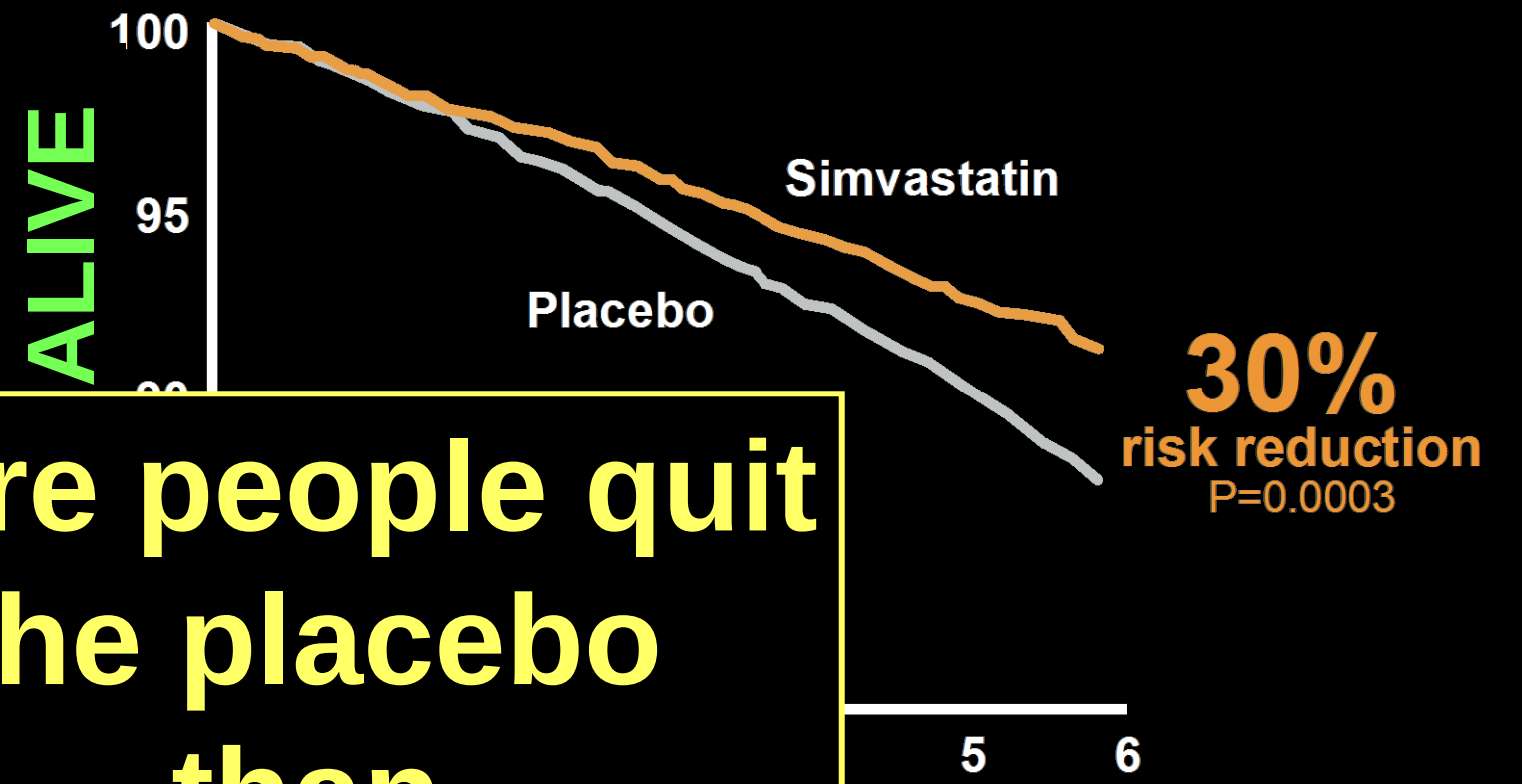
Increased CKs → Up to 10x ULN

Myalgias → With or without CK changes

**Clinical trials: ~5 % subjects**

**Clinical experience: Higher? 10%?**

# 4S: Total Mortality/Overall Survival




**More people quit the placebo than quit the Statin**

04;344:1383-1389.

# PROVE-IT:
# Atorva 80 vs Prava 40 mg in ACS

## Liver and Muscle Effects

| | Atorvastatin 80mg | Pravastatin 40mg | P-value |
|---|---|---|---|
| ALT ≥ 3 UL | 3.3% | 1.1% | 0.05 |
| CK > 3x ULN | 1.5% | 1.1% | 0.24 |
| DC for Myalgias | 3.3% | 2.7% | 0.23 |

# Statin Discontinuation after Adverse Reaction

Patients who were treated with a statin over the subsequent 12 mo (*n* = 30 412)

Patients who were treated with the same statin (*n* = 8741)
- Patients who were taking a statin 12 mo after the original discontinuation: 8554
  - Patients who were taking the same statin 12 mo after the original discontinuation: 5529
  - Patients who were taking the original statin at the same or a higher dose: 3658
- Patients who were not taking a statin 12 mo after the original discontinuation: 187

Patients who were treated with a different statin (*n* = 21 671)
- Patients who were taking a statin 12 mo after the original discontinuation: 21 253
- Patients who were not taking a statin 12 mo after the original discontinuation: 418

**98.0**% of patients who restarted statins were on a statin at 12 months

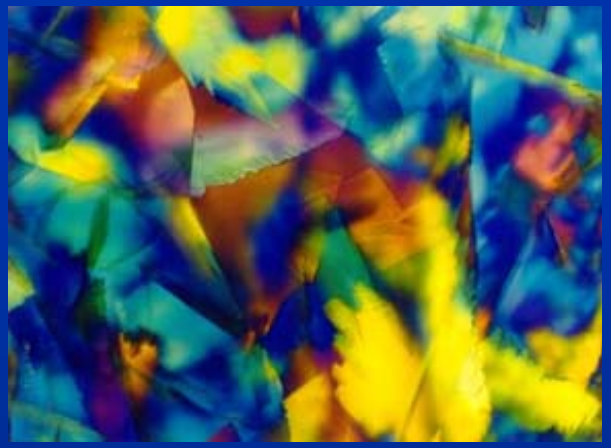
Zhang H, et al (2013). Annals of Internal Medicine; 158(7):526-34

A new (often non-generic) statin at the lowest conceivable dose (half, QOD)

+ pep talk…

## What do we do about the patient with ‘statin intolerance’?

- It may not be the statin.
- It may be dose related.
- It may be statin specific



# New Questions, New Issues

**Is a statin going to give my patient diabetes?**

**Small risk for increased incidence of T2D all statins.**

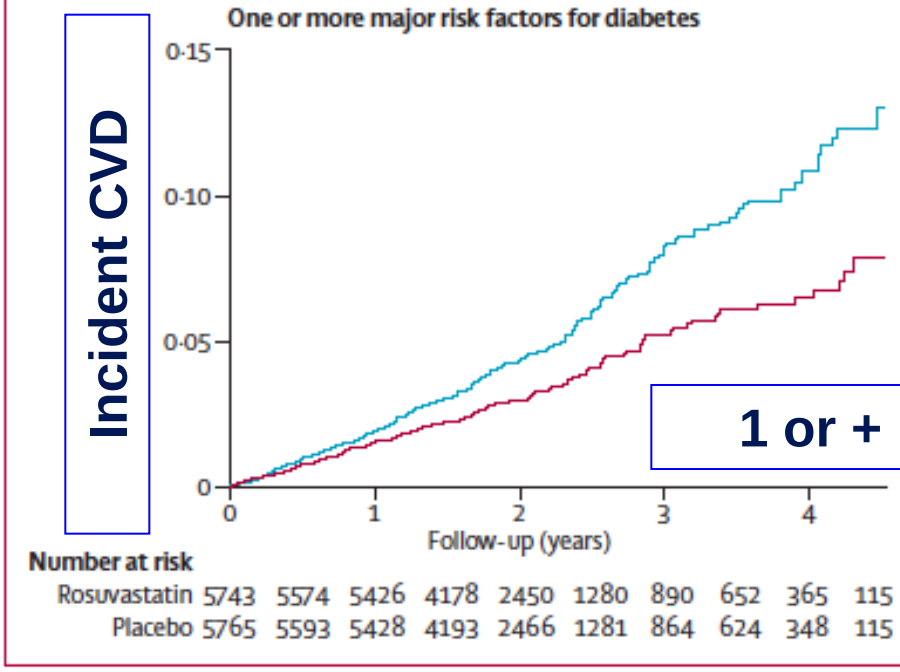
**Increased risk if T2D risk factors?**

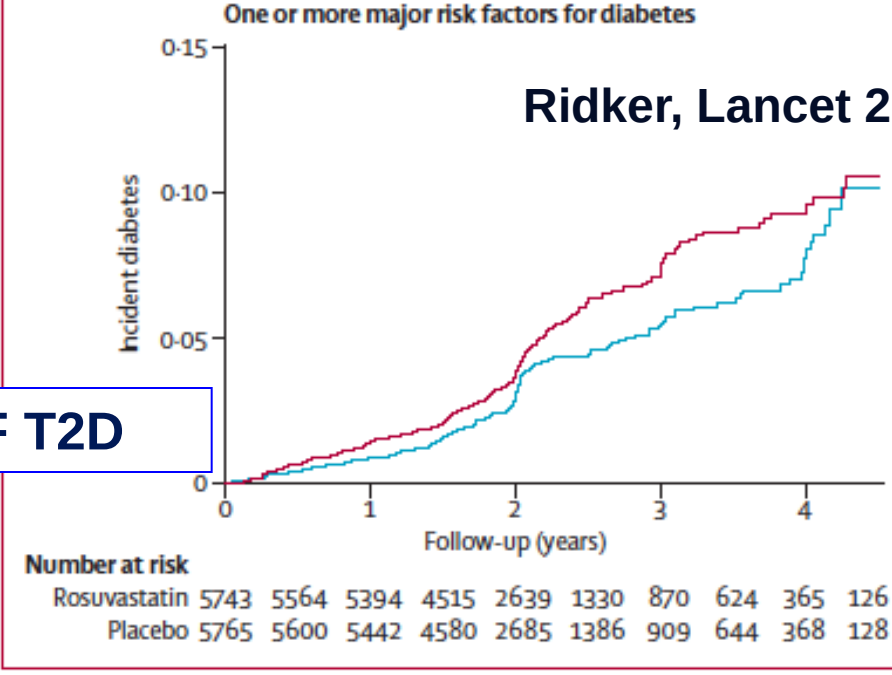
**Any increase in diabetes offset by decreased CV events.**

**Use appropriately.**

Incident CVD

1 or + RF T2D




Ridker, Lancet 2013

# Case

64 yo man, T2D, 3V CAD, CABG 2009

Meds: atorva 80, ASA, lisinopril/HCTZ, metoprolol

Lipid profile:

LDL 68, HDL 34, TG 380

# Statin Intolerance

Increased LFTs → Up to 3x ULN

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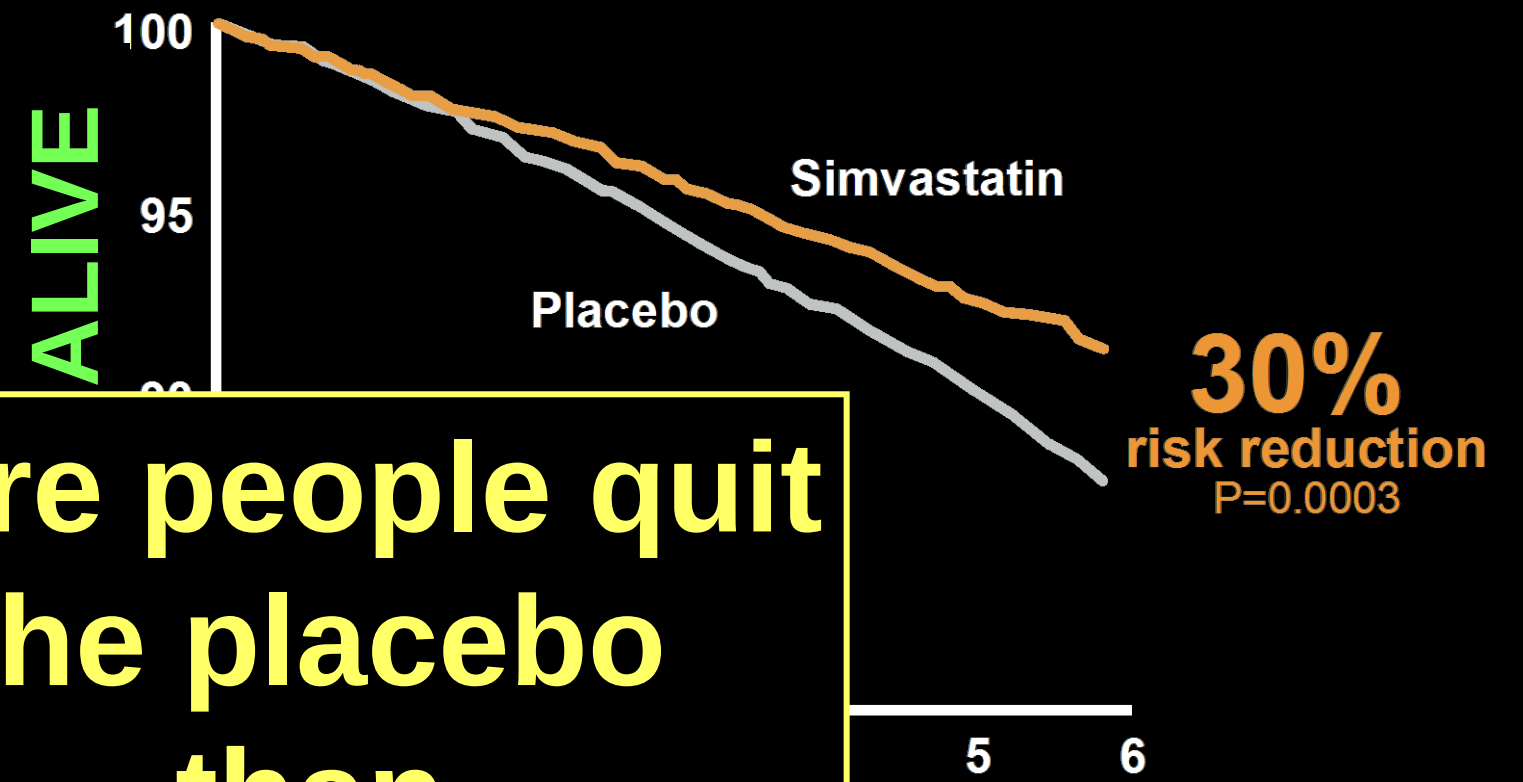


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# What about triglycerides?

64 yo man, T2D, 3V CAD, CABG 2009

Meds: atorva 80, ASA, lisinopril/HCTZ, metoprolol

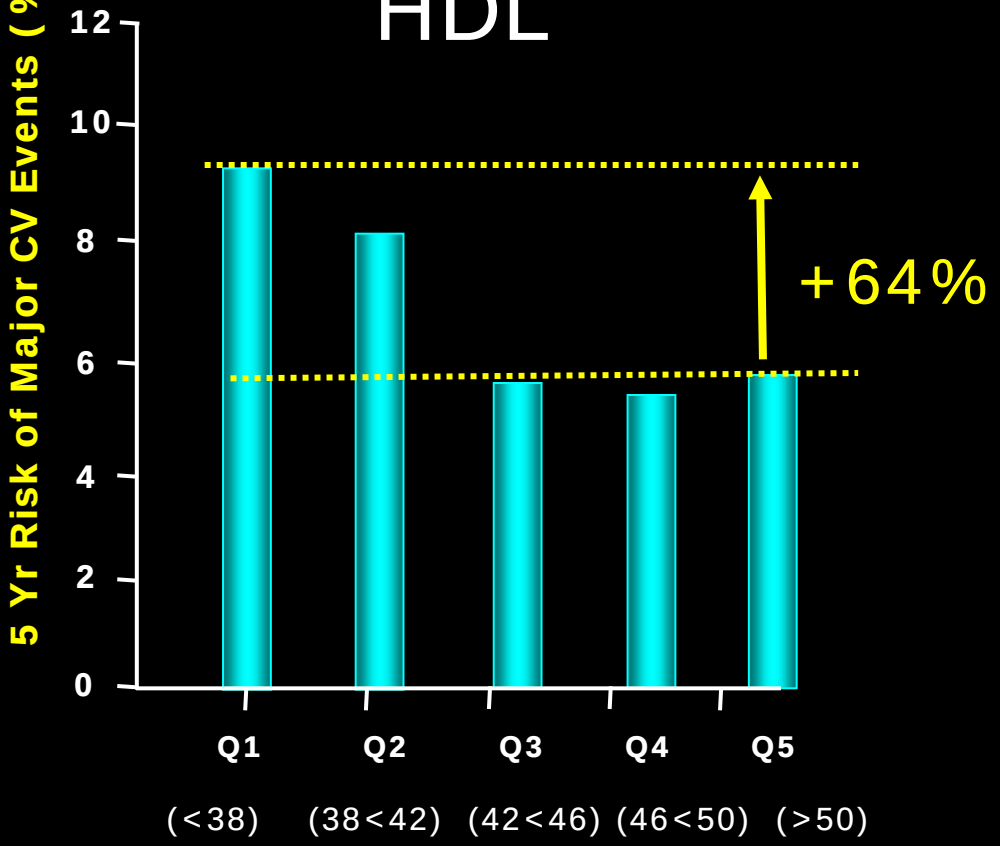
Lipid profile:

LDL 68, HDL 34, TG 380

# HDL & TG predict CV events, statin treated low LDL: TNT + PROVE-IT

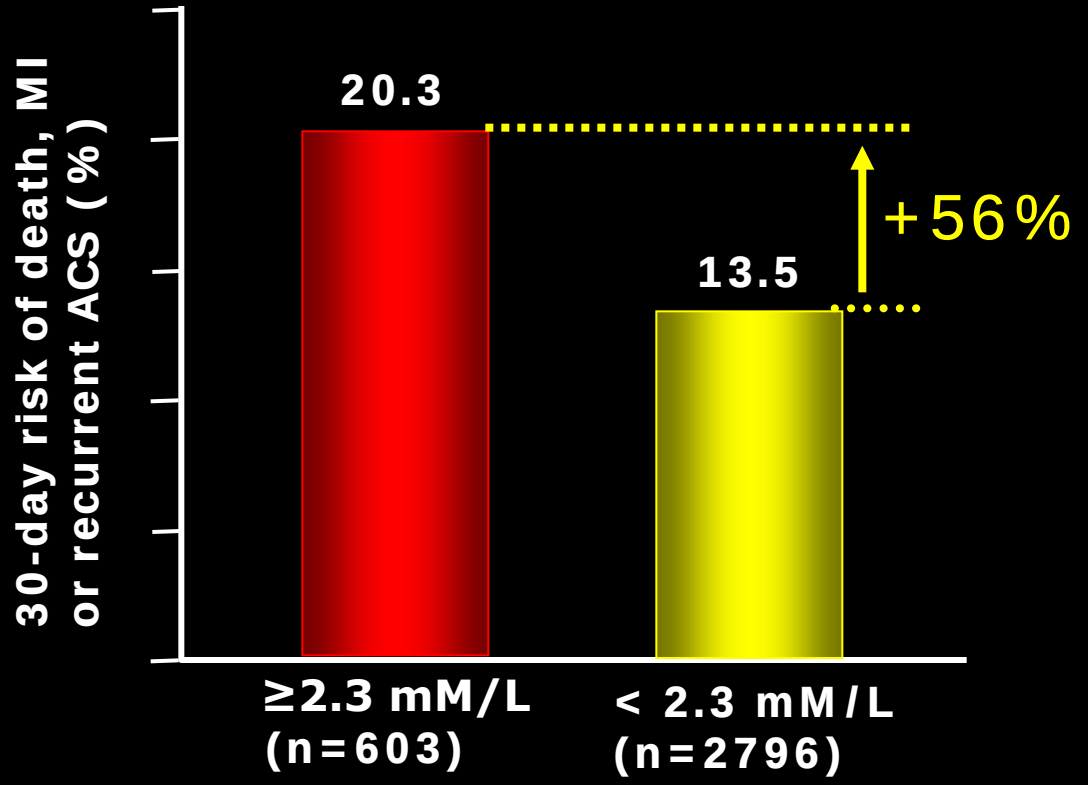
## On-Treatment, LDL-C < 70

### HDL




Barter P et al. NEJM 357:1301-10, 2007

### TG

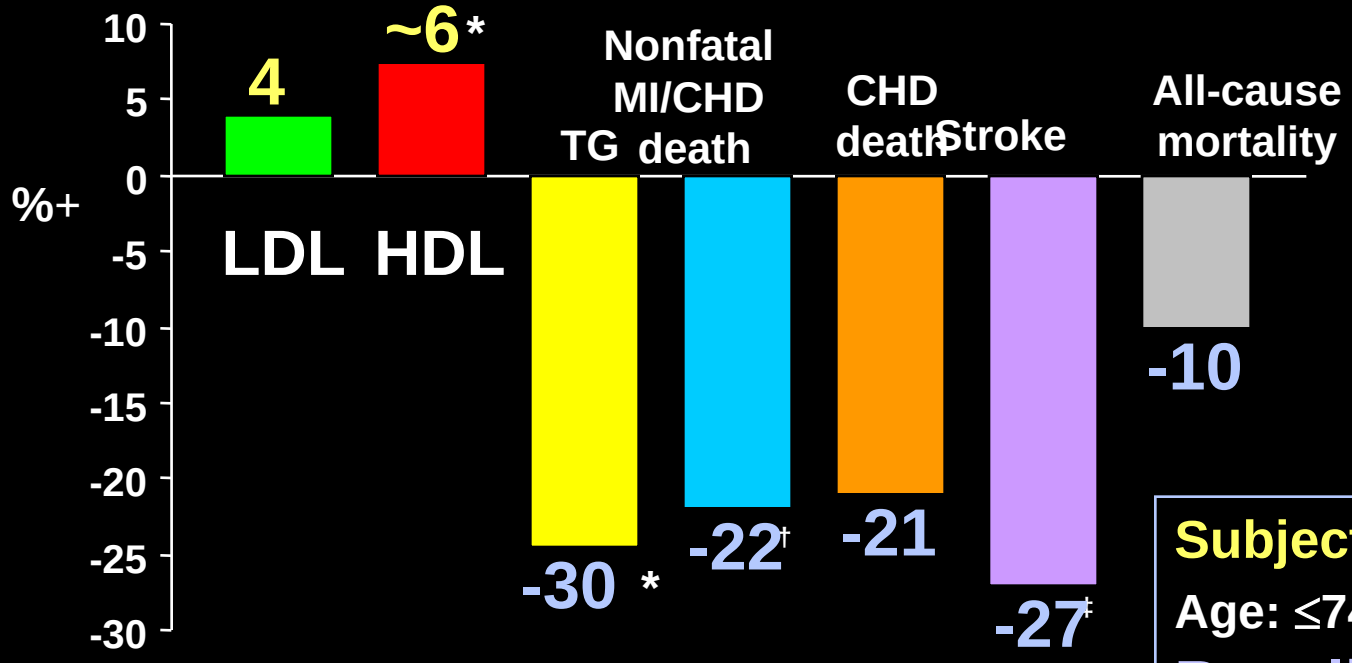



Miller et al. JACC, 51: 724-30, 2008

# Secondary Causes of Hypertriglyceridemia

- Nephrotic syndrome (Urine analysis)
- Thyroid abnormalities (TSH)
- Drugs (Thiazides, HRT, beta blockers, HIV rx)
- Diet (Excess carbs)
- Diabetes:
  - Inadequate control
  - Undiagnosed
- Alcohol
- Obesity

# VA-HIT:
# Fibrate Decreases CVD Events in CHD Patients With Low HDL-C



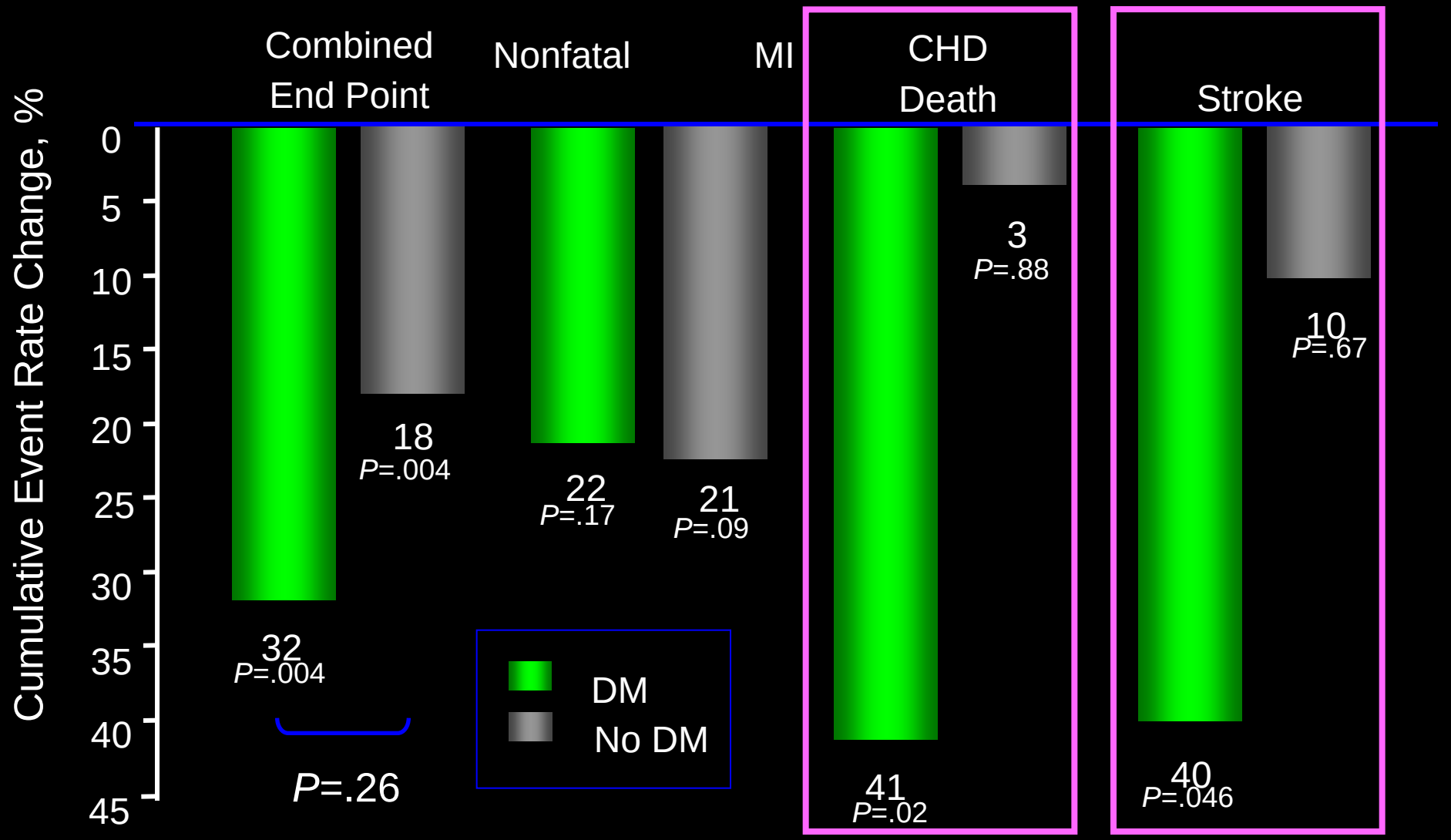

25% diabetes
50% insulin resistant

**Subjects: 2,531 men**
**Age: ≤74 (avg 64) yr**
**Baseline LDL-C: 111 mg/dL**
**Baseline HDL-C: 32 mg/dL**
**Baseline TG: 161 mg/dL**
**Duration: 7 yr**
**Intervention: Gemfibrozil 600 mg bid**

*$P$<0.01; †$P$=0.006; ‡$P$=0.05
P=placebo group; Rx=treated group.
HB Rubins et al NEJM 1999

# VA-HIT

## CVD Risk Reduction in Diabetics Compared With Nondiabetics




Rubins HB, et al. *Arch Intern Med*. 2002;162:2597-2604.

# FIELD: Design

9795 patients, age 50-75 years, type 2 diabetes diagnosed after age 35 years, no clear indication for cholesterol-lowering therapy at baseline (total cholesterol 116-251 mg/dL, plus either total cholesterol to HDL ratio ≥4.0 or triglyceride >88.6 mg/dL

**Fenofibrate**
(200 mg daily)
n=4895

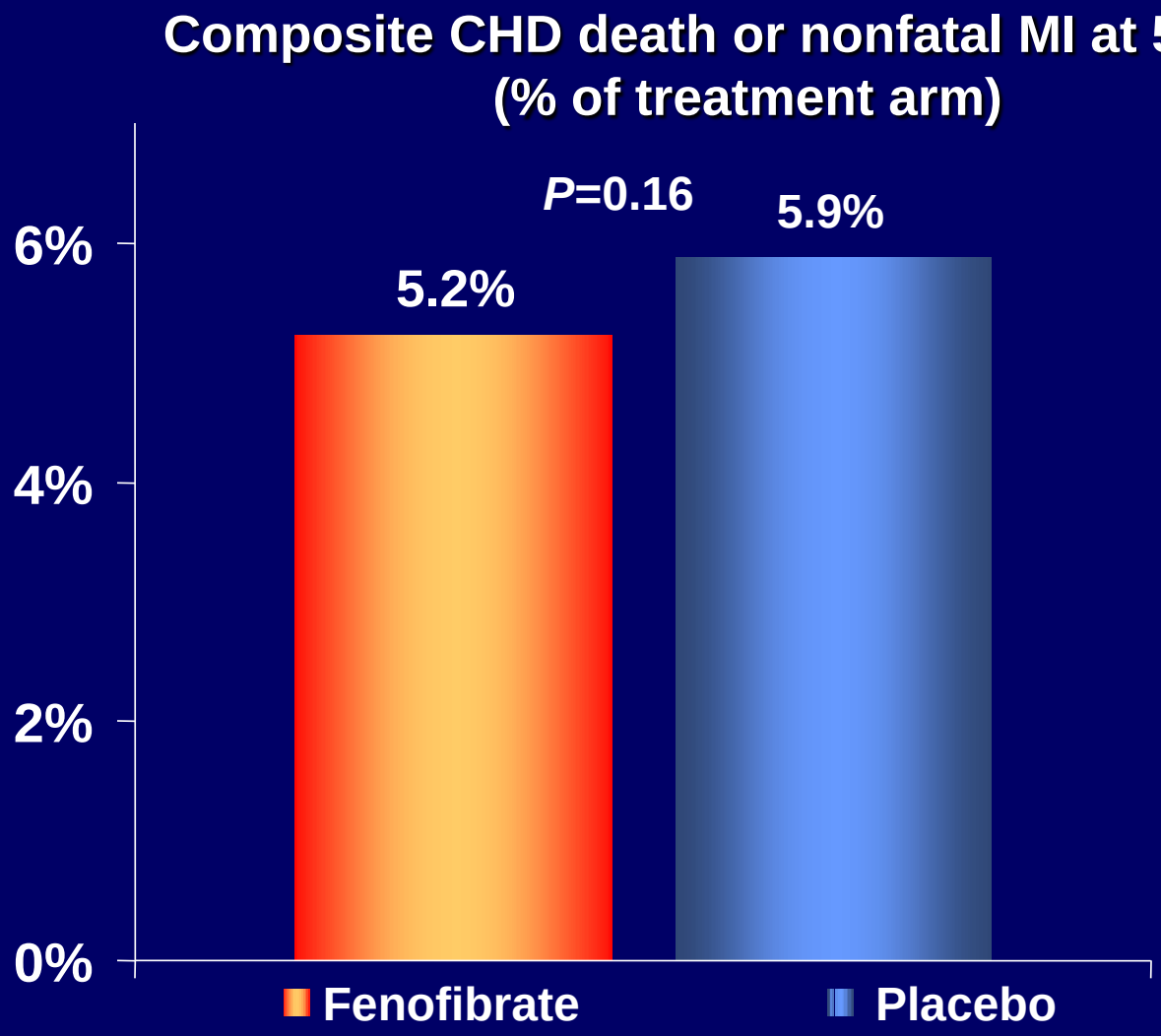
**Placebo**
N=4900

**Endpoints:**

- Primary – Composite of CHD death or nonfatal MI at 5 year follow-up
- Secondary – Composite of total CV events, CV mortality, total mortality, stroke, coronary revascularization and all revascularization at 5 year follow-up

**FIELD Study Investigators. *Cardiovasc Diabetol*. 2004;3:9-24.**

# FIELD: Primary Endpoint

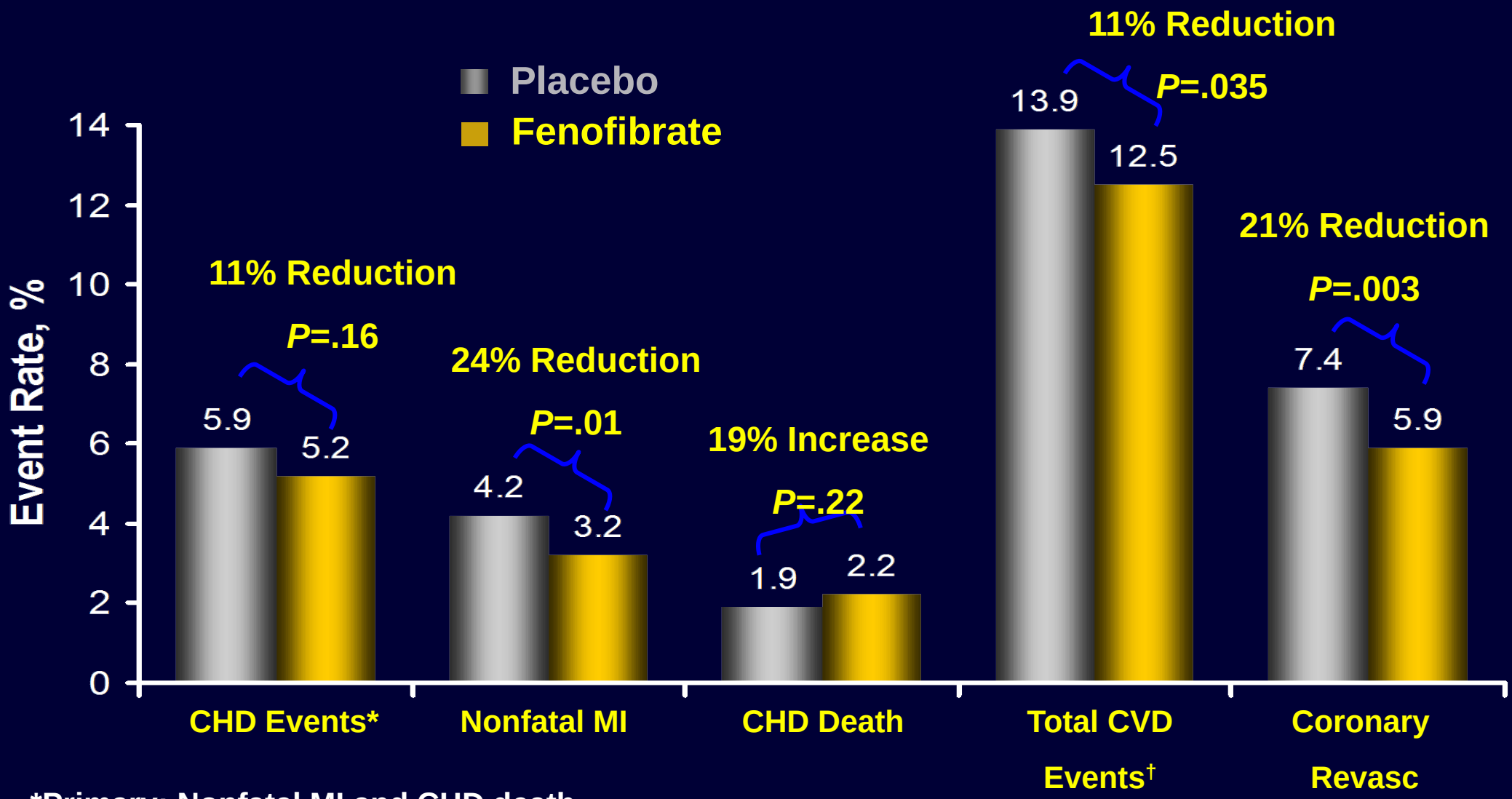



- The primary composite endpoint of CHD death or nonfatal MI was not significantly lower in the fenofibrate group compared to the placebo group.

Data from FIELD Study Investigators. *Lancet*. 2005;366:1849-1861.

# FIELD: Fenofibrate

## Primary and Secondary End Points

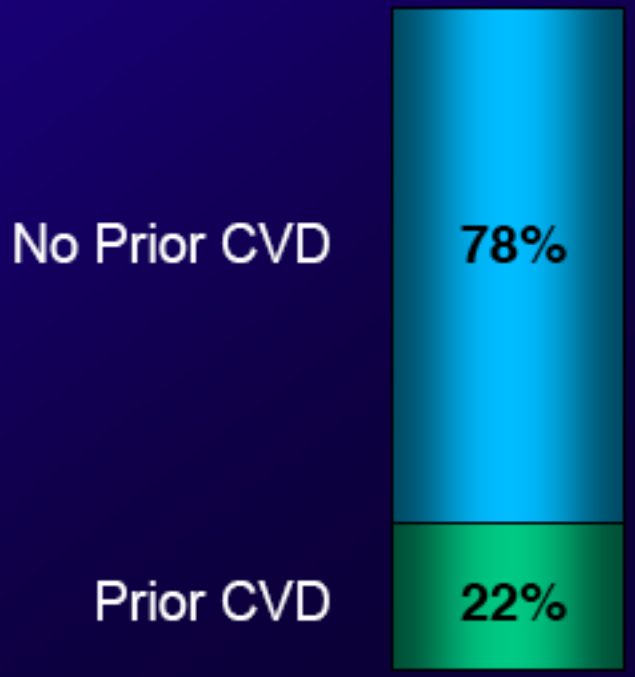


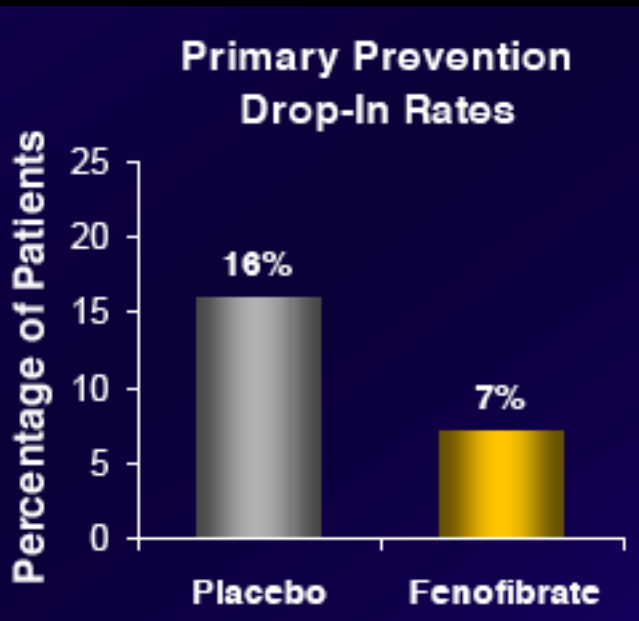

*Primary: Nonfatal MI and CHD death

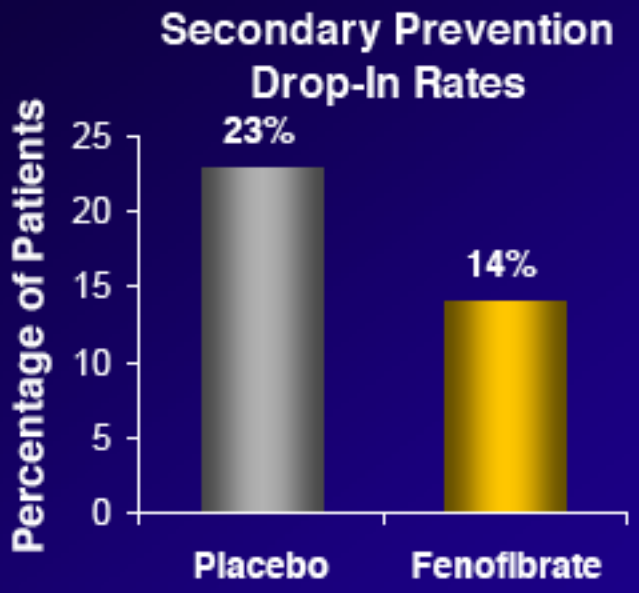
†Secondary: CHD events, stroke, CVD death, revasc

*Lancet.* 2005;366:1849

# Statin Drop In's in FIELD



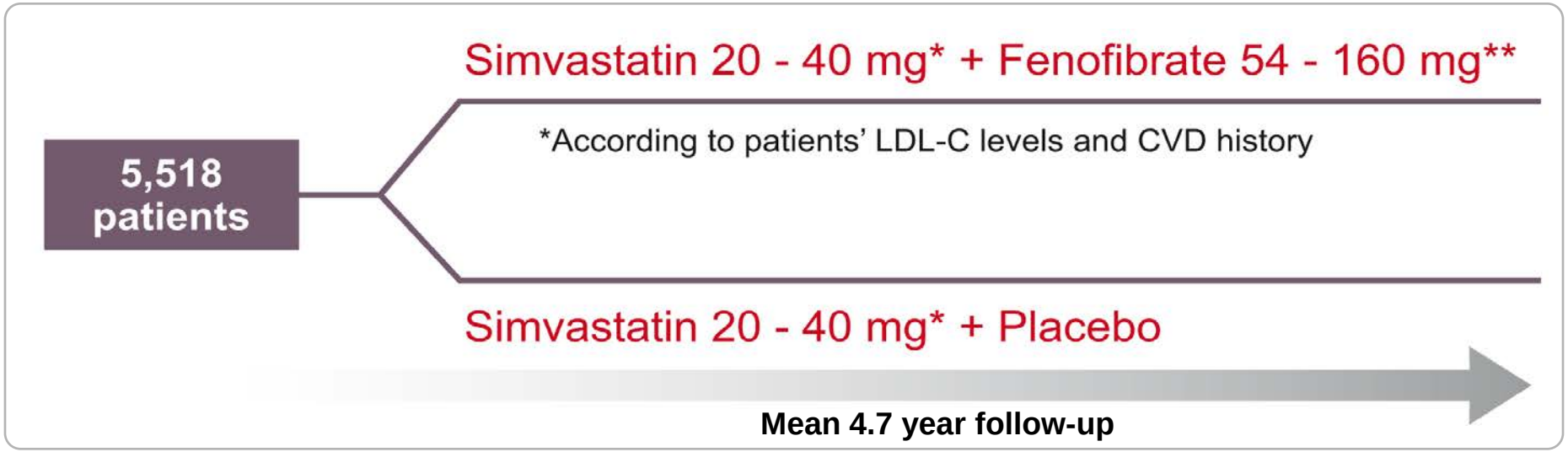




The FIELD Study Investigators. *Lancet* [Early Online Publication]. November 14, 2005.

# ACCORD - Lipid

Objective:

To test whether, in the context of good glycemic and LDL-C control, a strategy targeting triglycerides and HDL-C levels provides any additional macrovascular and/or microvascular benefits




*** 20 mg for primary prevention patients, 40 mg for secondary prevention patients**

**** 160 mg if baseline GFR ≥50 ml/min/1.73 $m^2$; 54 mg if baseline GFR between 30 and 50 ml/min/1.73 $m^2$**


Buse JB *et al. Am J Cardiol*. 2007;99(12A):21i-33i.

ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.

# Baseline characteristics: Lipids

| Baseline lipids | Simvastatin + Fenofibrate (n=2,765) | Simvastatin + Placebo (n=2,753) | Overall (n=5,518) |
|---|---|---|---|
| Mean total cholesterol | 175 (4.5) | 176 (4.5) | 175 (4.5) |
| Mean LDL-C | 100 (2.6) | 101 (2.6) | 101 (2.6) |
| Mean HDL-C | 38 (1.0) | 38 (1.0) | 38 (1.0) |
| Median triglycerides | 164 (1.9) | 160 (1.8) | 162 (1.8) |

**Data presented as mg/dL (mmol/L)**

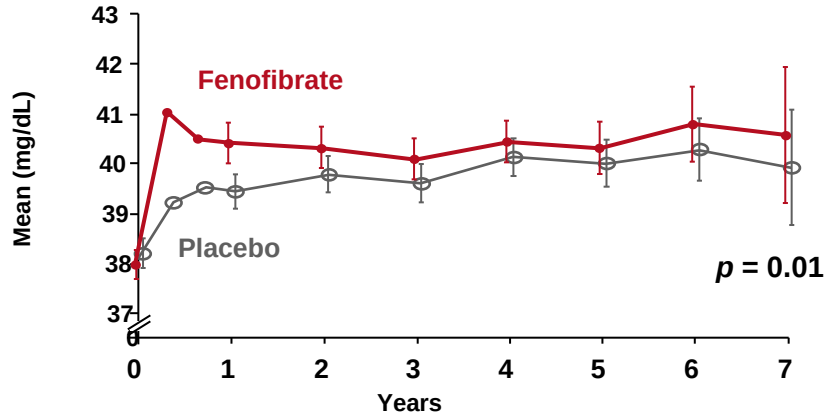
**ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.**

# ACCORD Lipid:
## Changes in HDL-C and triglycerides during the study

**Increase in HDL-C was significantly greater in the combination arm**

**Reduction in triglycerides was significantly greater in the combination arm**

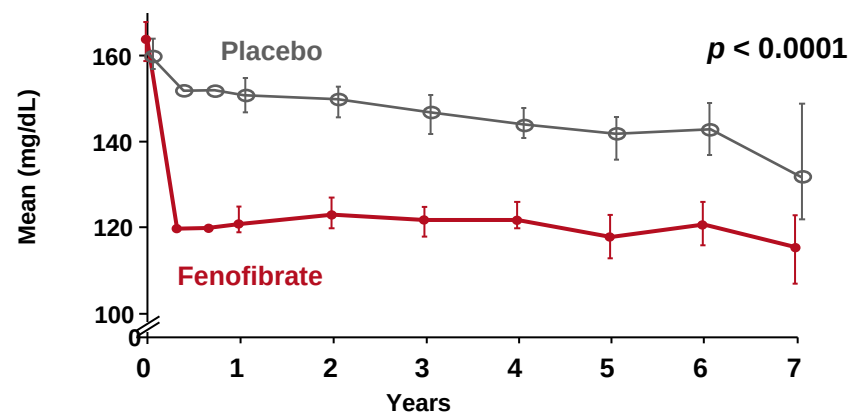
### Change in mean HDL-C




No. of Patients

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fenofibrate | 2747 | 2593 | 2505 | 2417 | 2361 | 1477 | 796 | 248 |
| Placebo | 2735 | 2591 | 2484 | 2375 | 2361 | 1480 | 801 | 243 |

### Change in mean triglycerides



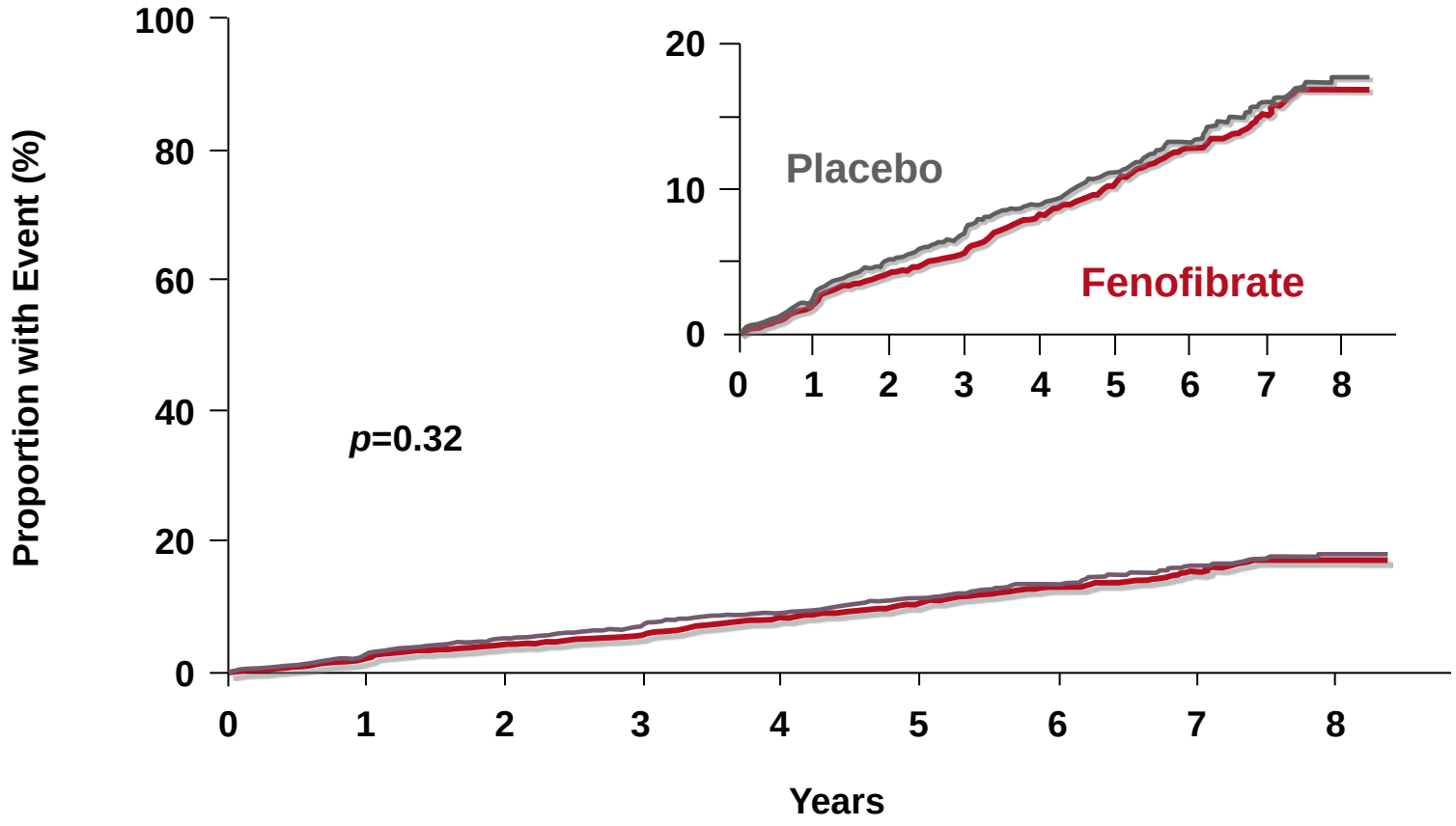

No. of Patients

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fenofibrate | 2747 | 2593 | 2505 | 2417 | 2361 | 1478 | 796 | 248 |
| Placebo | 2735 | 2591 | 2484 | 2375 | 2361 | 1480 | 801 | 243 |

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

# ACCORD Lipid primary macrovascular outcome

## (CV death + nonfatal MI + nonfatal stroke)



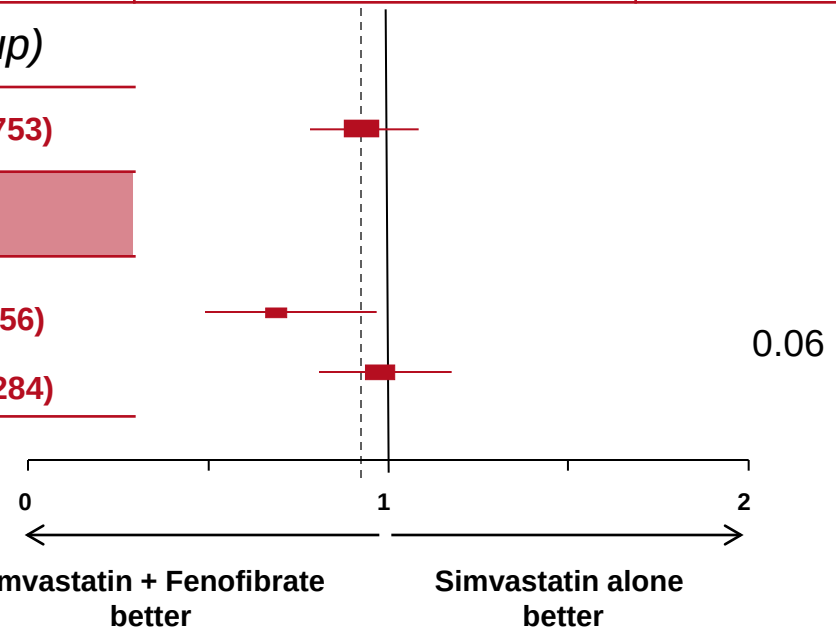

| No. At Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fenofibrate | 2765 | 2644 | 2565 | 2485 | 19811160 | 412 | 249 | 137 |
| Placebo | 2753 | 2634 | 2528 | 2442 | 19791161 | 395 | 245 | 131 |

ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.

# ACCORD Lipid

## 31% reduction in events in patients with atherogenic dyslipidemia

| Subgroup | Simvastatin + Fenofibrate | Simvastatin + Placebo | Hazard ratio (95% CI) | *p* value for interaction |
|---|---|---|---|---|
| | *% of event (no. in group)* | | | |
| **Overall** | **10.5 (2765)** | **11.3 (2753)** | | |
| **Triglyceride – HDL-C combination** | | | | |
| TG ≥204 mg/dL + HDL-C ≤34 mg/dL | **12.4 (485)** | **17.3 (456)** | | 0.06 |
| All others | **10.1 (2264)** | **10.1 (2284)** | | |



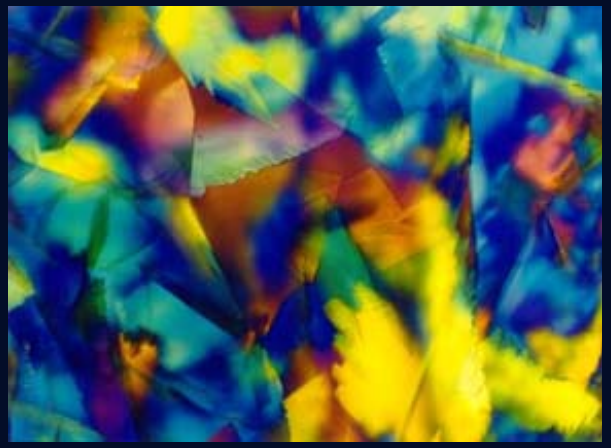

- **20 patients with type 2 diabetes and atherogenic dyslipidemia needed to be treated for 5 years to prevent one CV event**

ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.

# ACCORD Lipid

## Comparison of subgroup results with those from prior landmark trials with fibrates

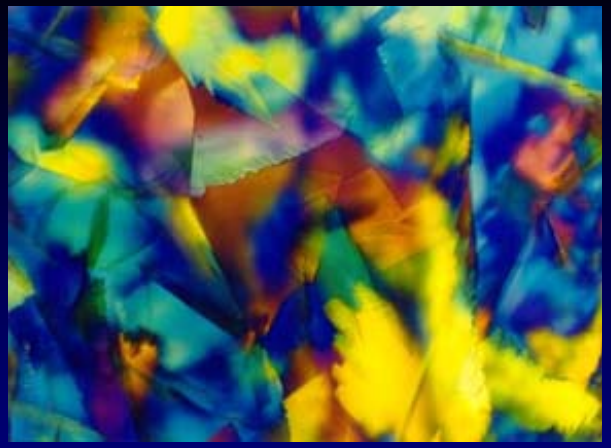
| Trial (drug) | Primary endpoint: entire cohort (*p* value) | Lipid subgroup criterion | Primary endpoint: subgroup (*p* value) |
|---|---|---|---|
| **HHS** (gemfibrozil) | -34% (0.02) | TG > 200 mg/dL<br>LDL-C/HDL-C > 5.0 | Post-hoc<br>-71% (0.005) |
| **BIP** (bezafibrate) | -7.3% (0.24) | TG ≥ 200 mg/dL | Post-hoc<br>-39.5% (0.02) |
| **FIELD** (fenofibrate) | -11% (0.16) | TG ≥ 204 mg/dL<br>HDL-C < 42 mg/dL | Post-hoc<br>-27% (0.005) |
| **ACCORD** (fenofibrate) | -8% (0.32) | TG ≥ 204 mg/dL<br>HDL-C ≤ 34 mg/dL | Prespecified<br>-31% |



# What about triglycerides?

Lifestyle!
Consider fibrate if significant risk:
- CVD, high TG, low HDL, LDL at goal
- Pancreatitis level TG

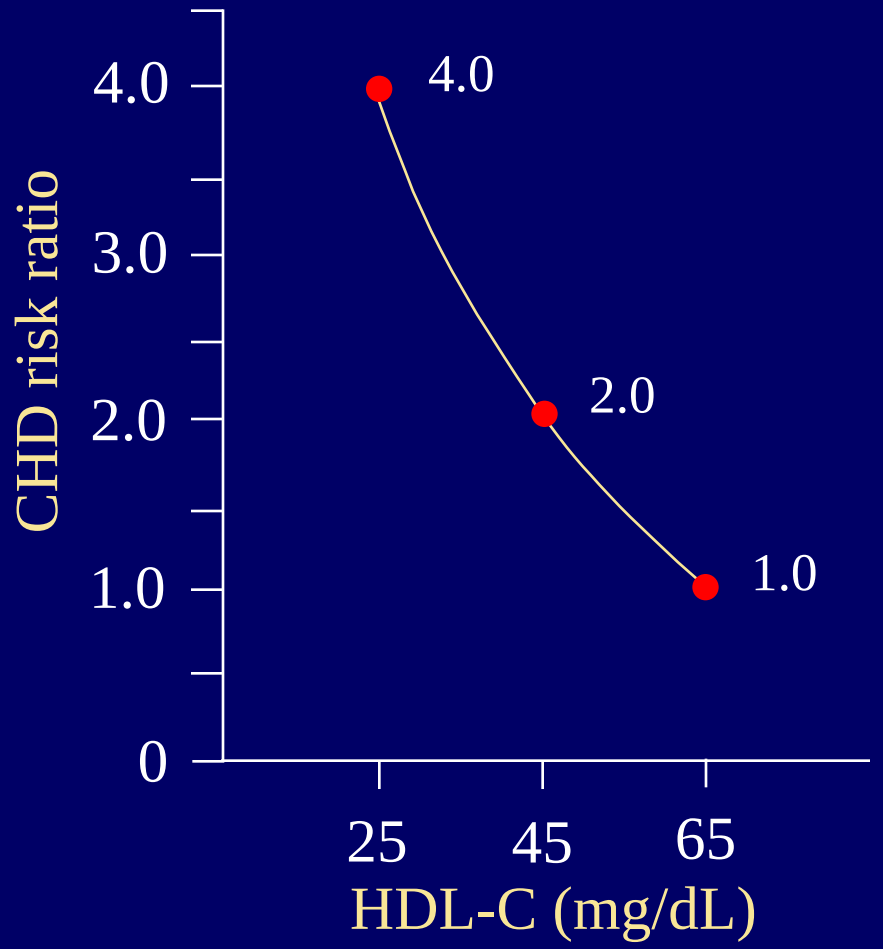
Other rx: fish oil



# What about HDL?

# HDL Cholesterol Levels and CHD Risk

**Framingham Study**




Kannel WB. *Am J Cardiol* 1983;52:9B–12B
1989;118(5 Pt 1):1012–1021

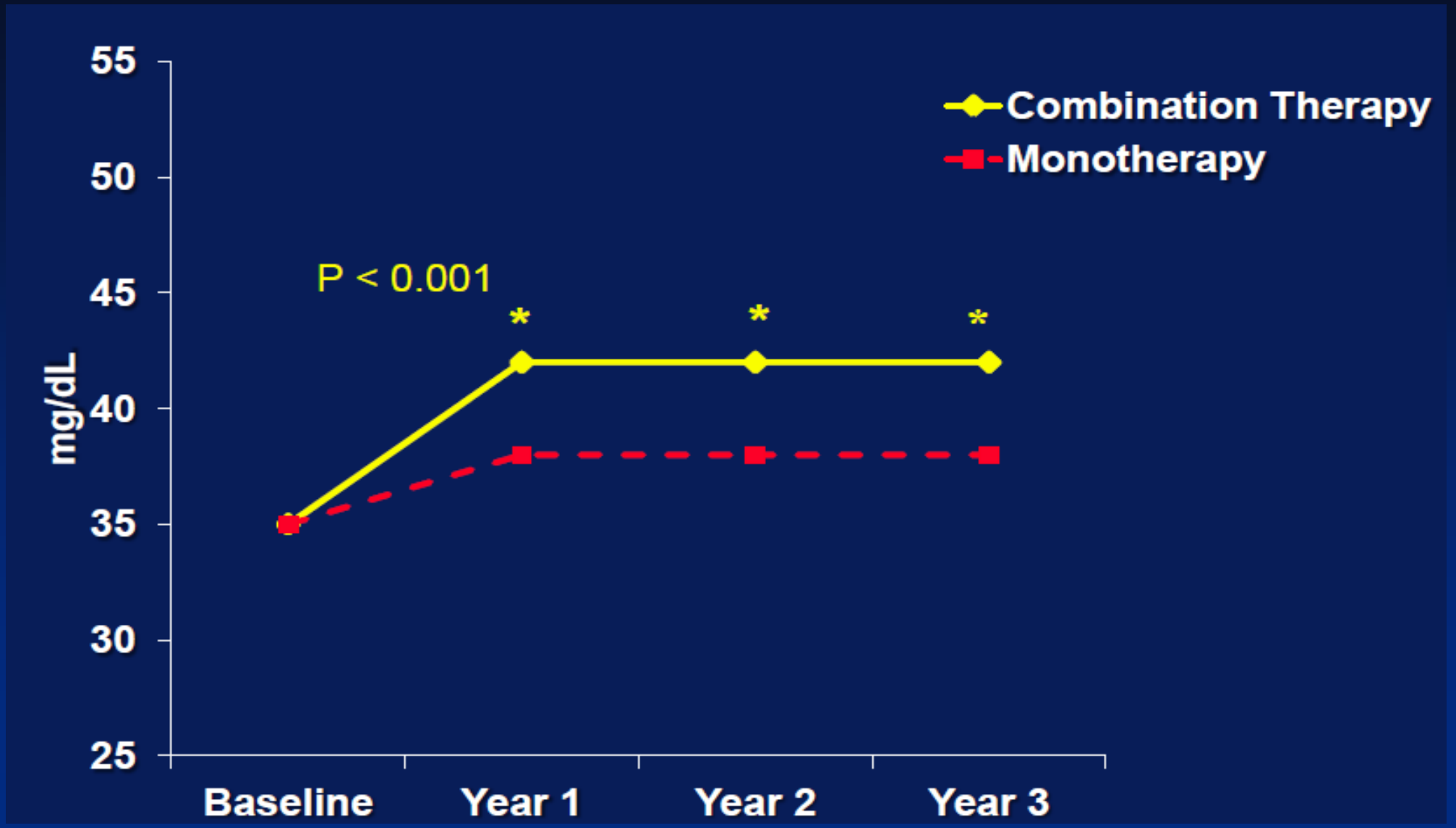
# AIM-HIGH—Design

- Purpose: “[A] rigorous test of the HDL hypothesis…”
- Subjects: N=3414 men/women (85%/15%) w/ prior CVD event and HDL-C 35 (<42/53) LDL-C 74 (algorithm), TG 163 (100-400) [median (range)]
- Randomized Therapy
  - Extended-release niacin (1500-2000 mg hs) vs
  - “Placebo” (immediate-release niacin 100-150 mg hs)
- Open-label titration/addition (keep LDL-C in 40-80 mg/dL)
  - Simvastatin 5-80 mg/d
  - Ezetimibe 10 mg/d + extended release niacin (1500-2000 mg)

AIM-HIGH Investigators. *N Engl J Med.* 2001;365:2255-267.
AIM-HIGH Investigators. *Am Heart J.* 2011;161:471-477.e2.

# AIM-HIGH—Results

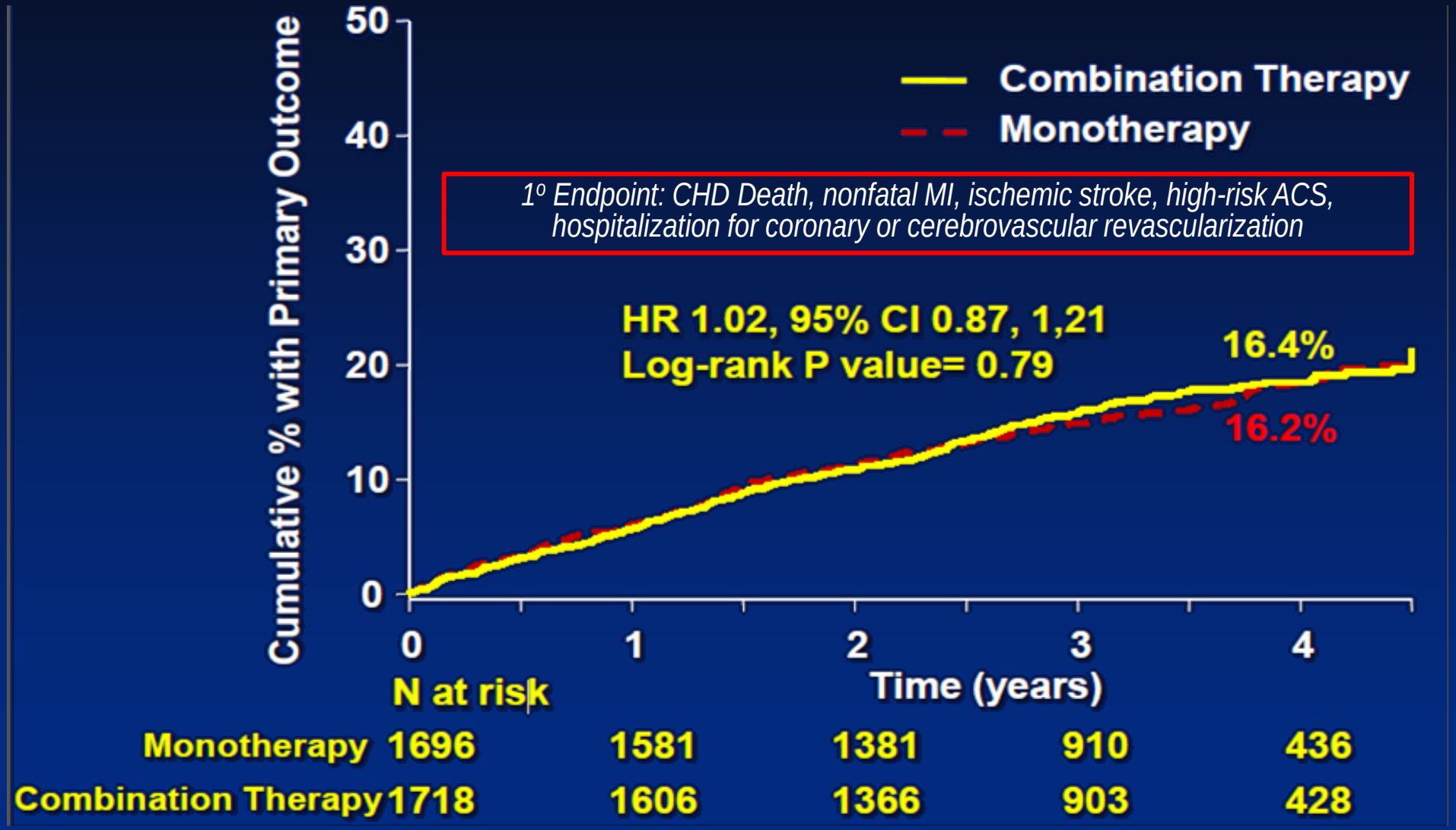
*HDL-C at Baseline and Follow-up*



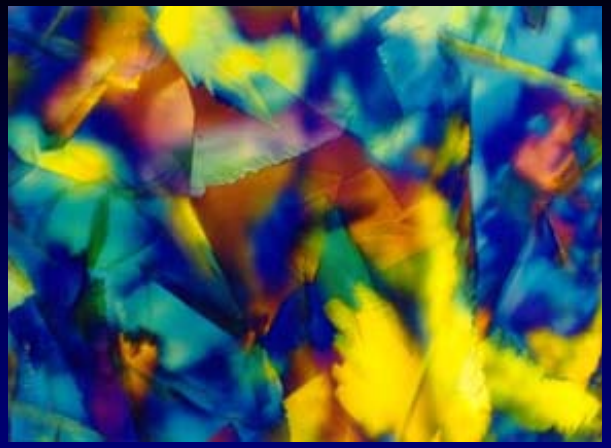

Boden WE. *N Engl J Med.* epub 15 Nov 2011; doi 10.1056/NEJMoa1107579.

# AIM-HIGH—Results

## *Primary Outcome*




Boden WE. *N Engl J Med.* epub 15 Nov 2011; doi 10.1056/NEJMoa1107579.



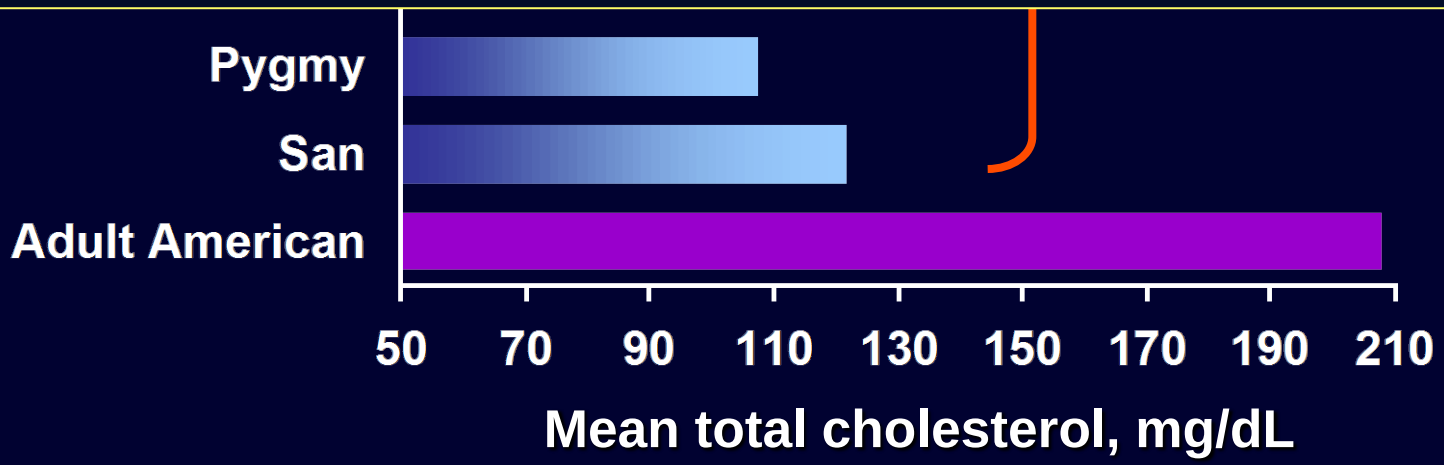
# What is an optimal LDL?

# What Is Desirable Cholesterol?

Cholesterol Levels Among Different Human Populations

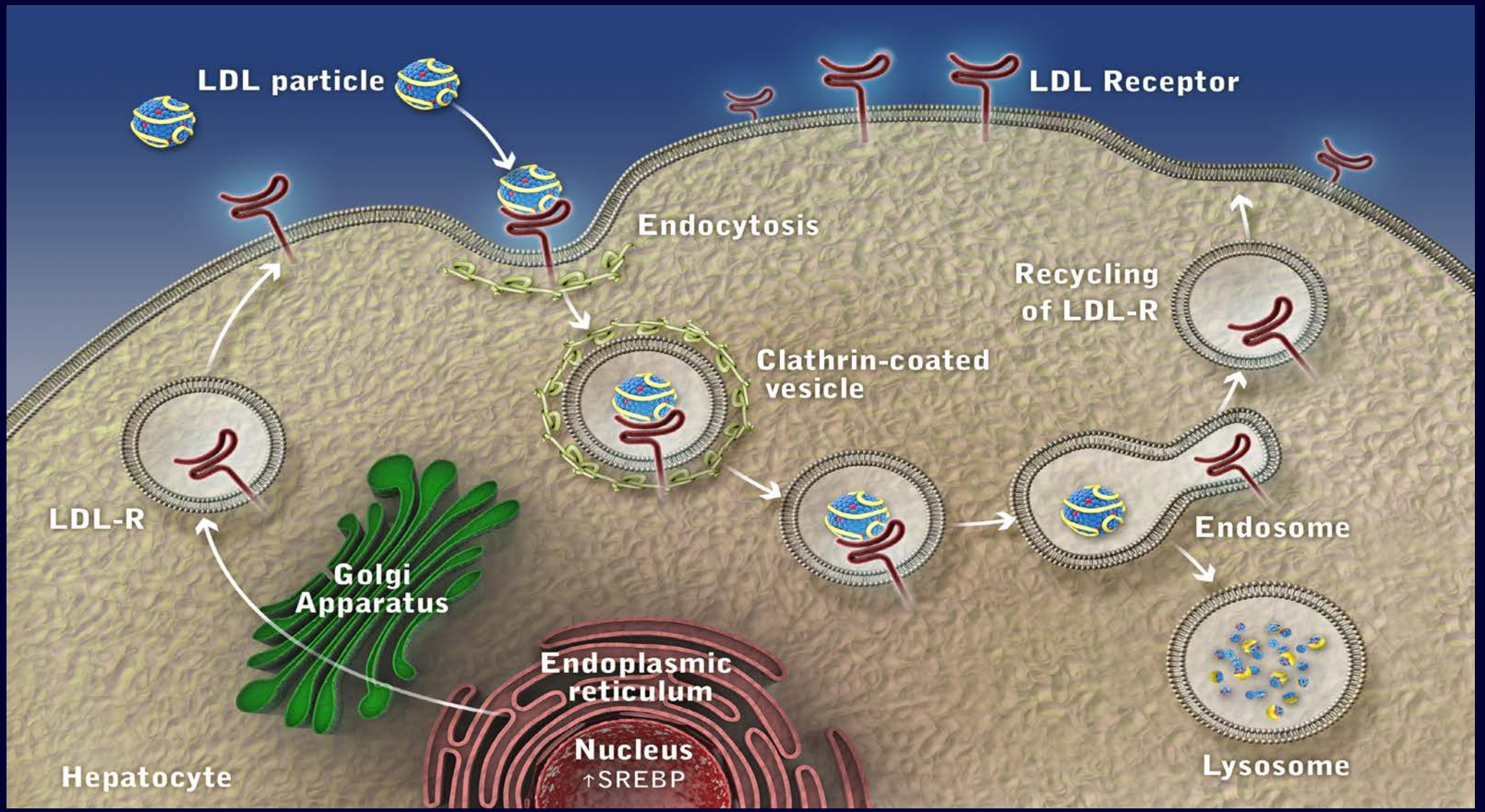
Population-based approaches?

Over the counter interventions on cholesterol?

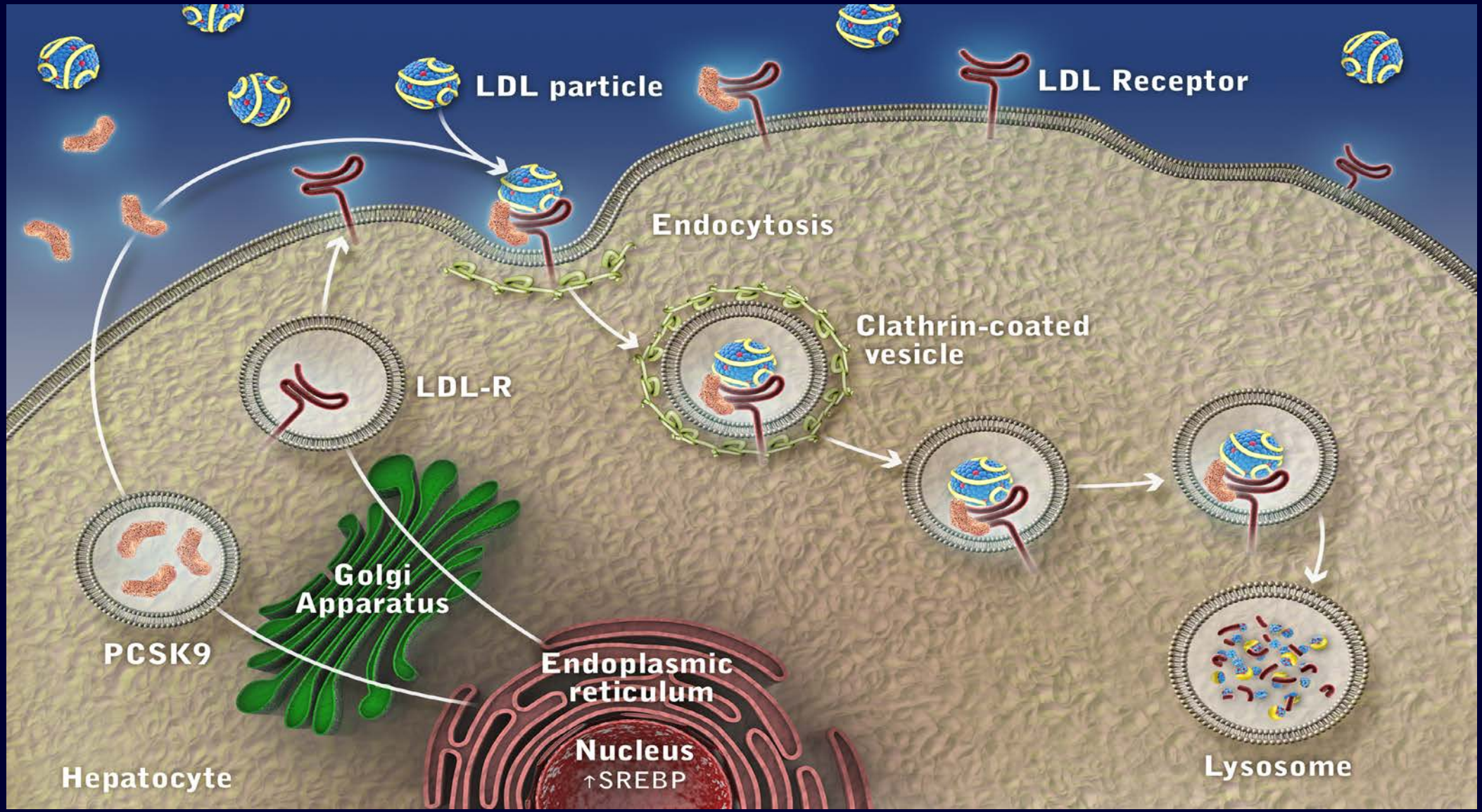



Adapted from O'Keefe JH Jr et al. *J Am Coll Cardiol*. 2004;43:2142–2146.

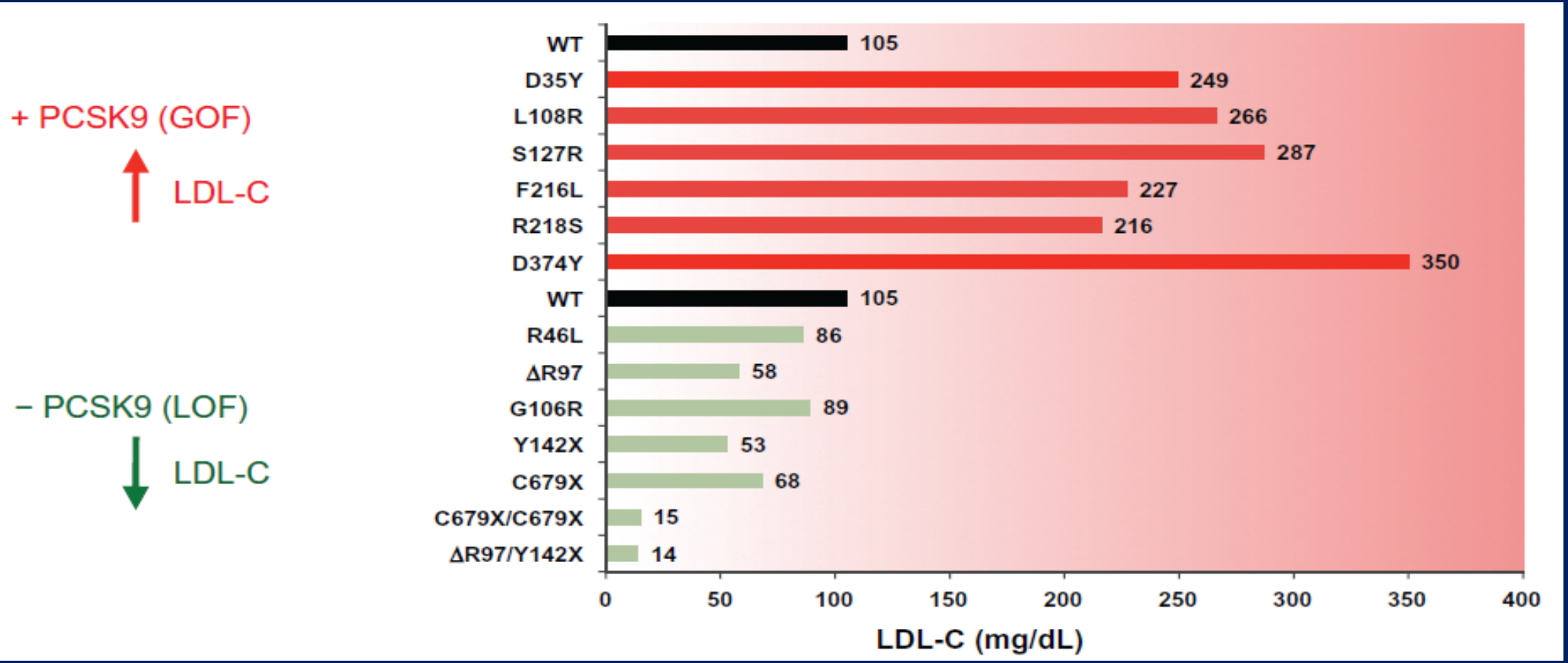
# Function and Life Cycle of the LDL Receptor



# The Role of PCSK9 in the Regulation of LDL Receptor Expression



# Effect of Human Mutations in PCSK9 on Plasma LDL-C



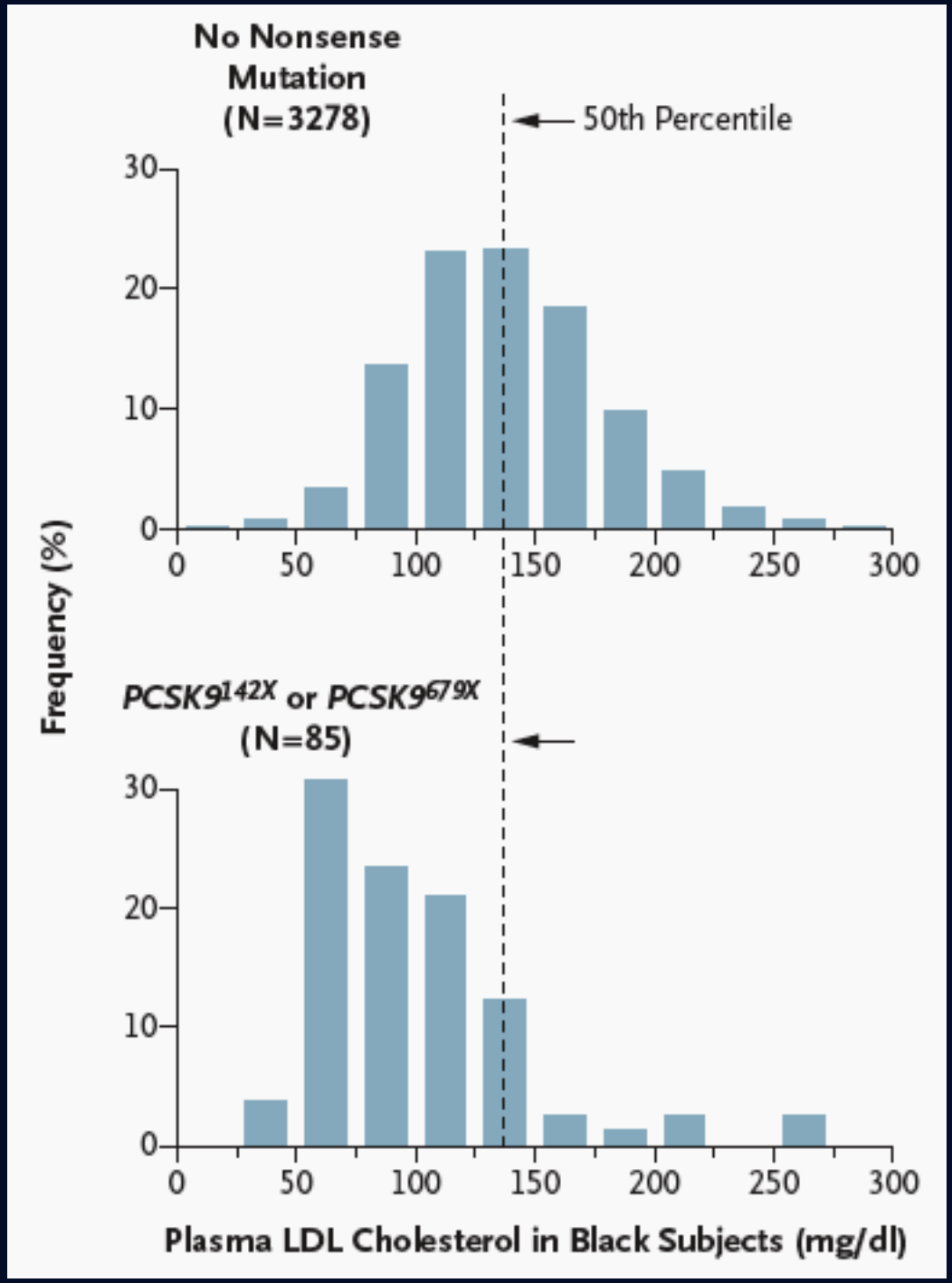

Poirier S & Mayer G, *Drug Des Dev Ther* 7:1135, 2013

The NEW ENGLAND JOURNAL of MEDICINE

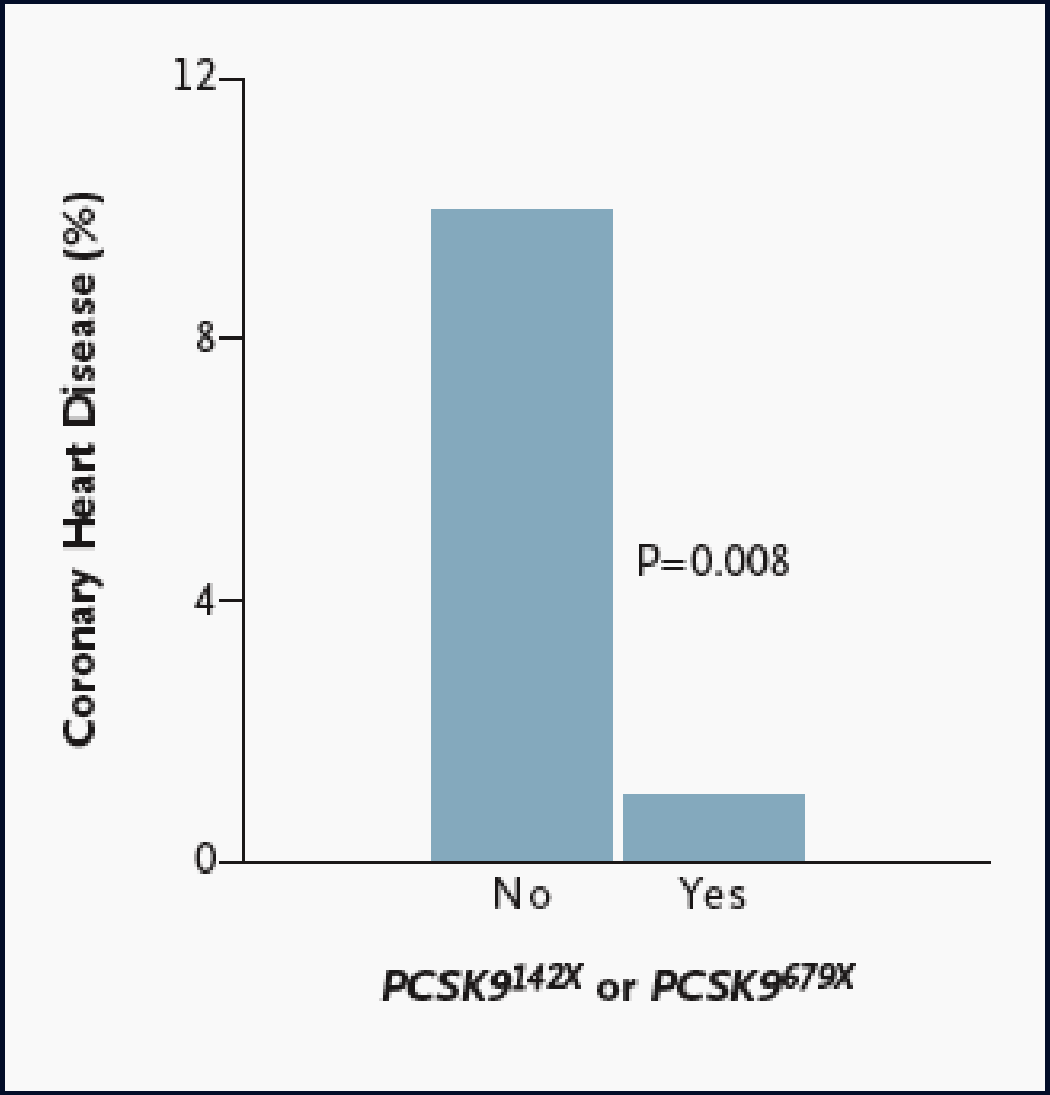
ORIGINAL ARTICLE

# Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

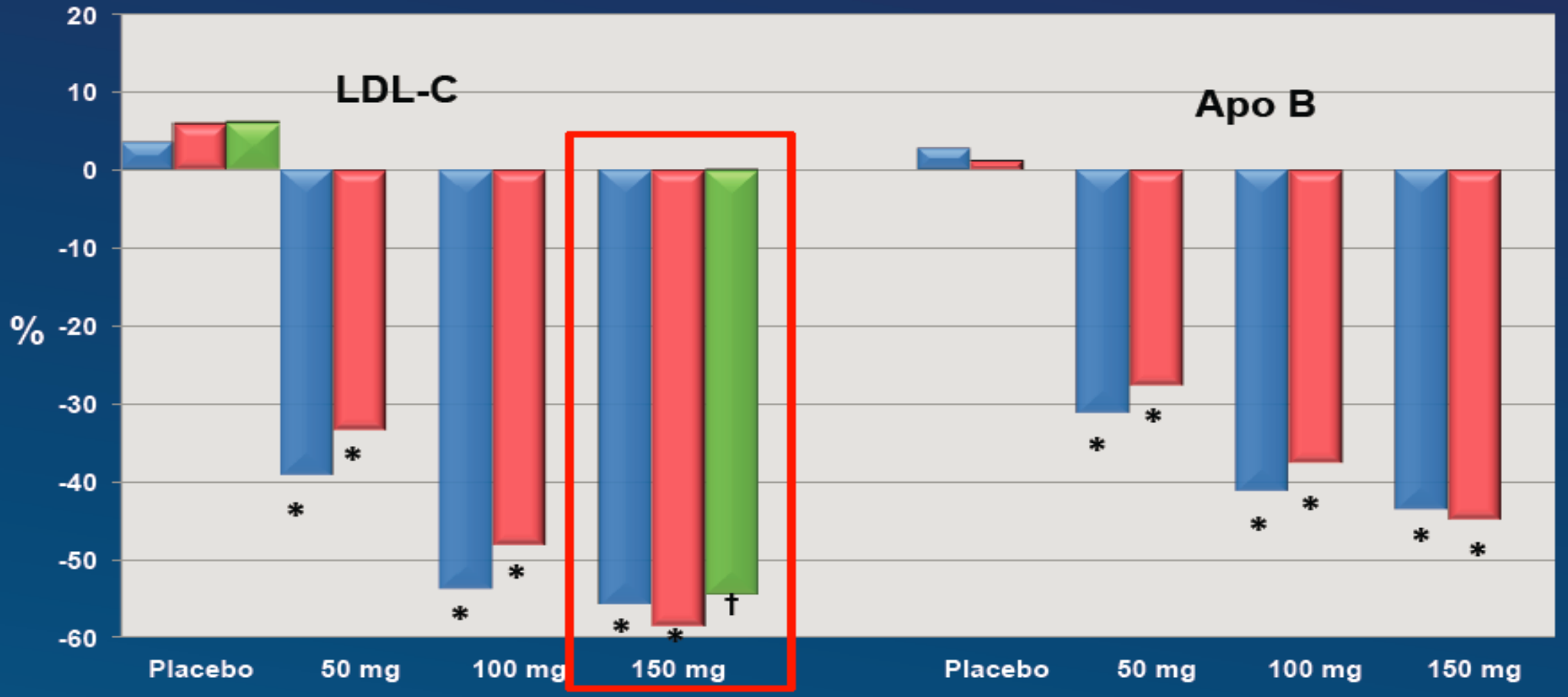
Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.


No Nonsense Mutation (N=3278)
50th Percentile
30
20
10
0
0
50
100
150
200
250
300
Frequency (%)
PCSK9142X or PCSK9679X (N=85)
30
20
10
0
0
50
100
150
200
250
300
Plasma LDL Cholesterol in Black Subjects (mg/dl)

# Lifelong Low Cholesterol Via PCSK9 Mutations Are Associated With Protection Against CAD But No Other Abnormalities



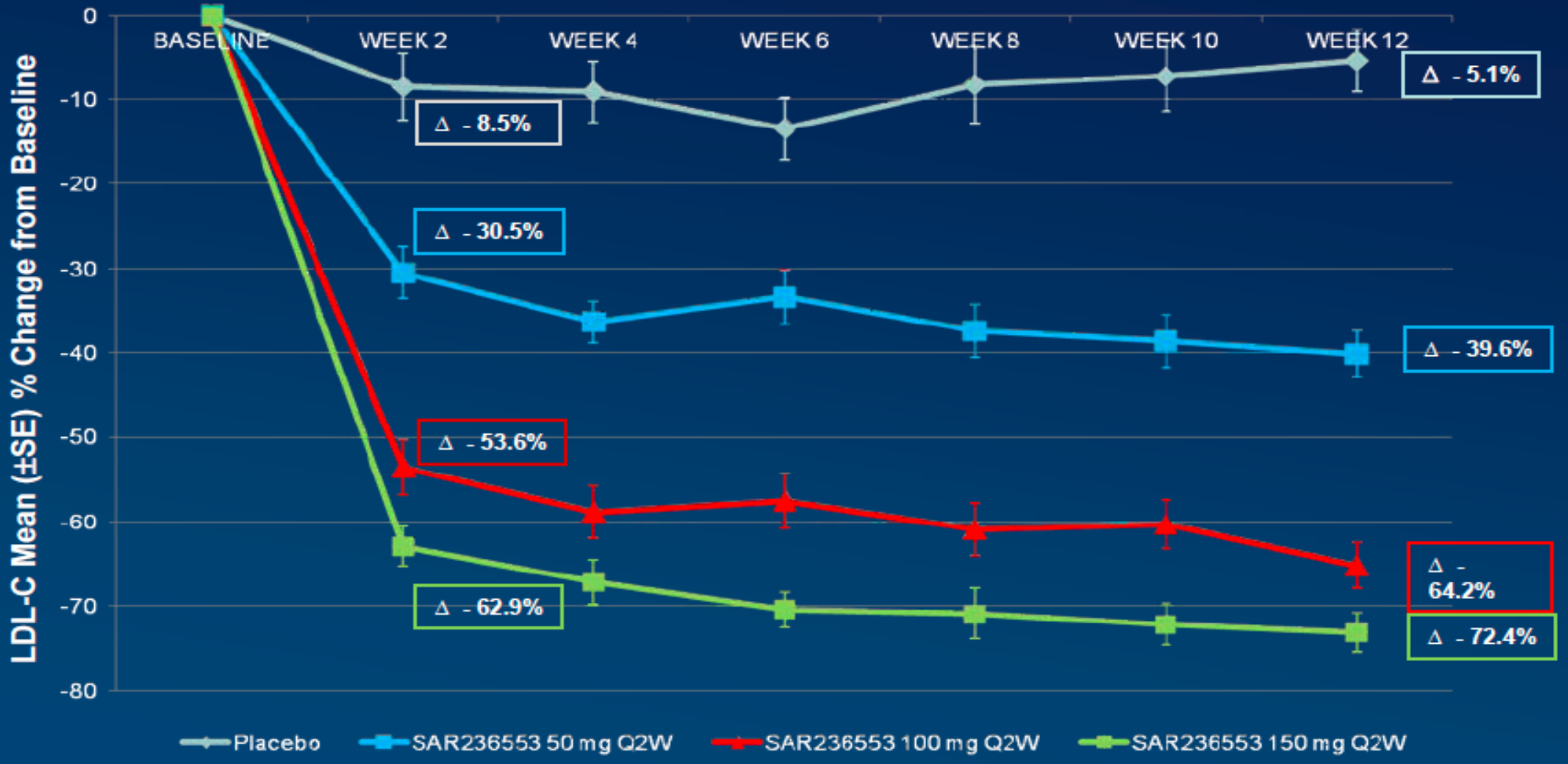
# ApoB & LDL-C Response
## Mean % Change from Baseline, Day 57




Alirocumab

Stein et al NEJM 2012; 366:1108-18

# Alirocumab Administered 2 weekly (Q2W) SC: Change in Calculated LDL-C from Baseline to Week 12




Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

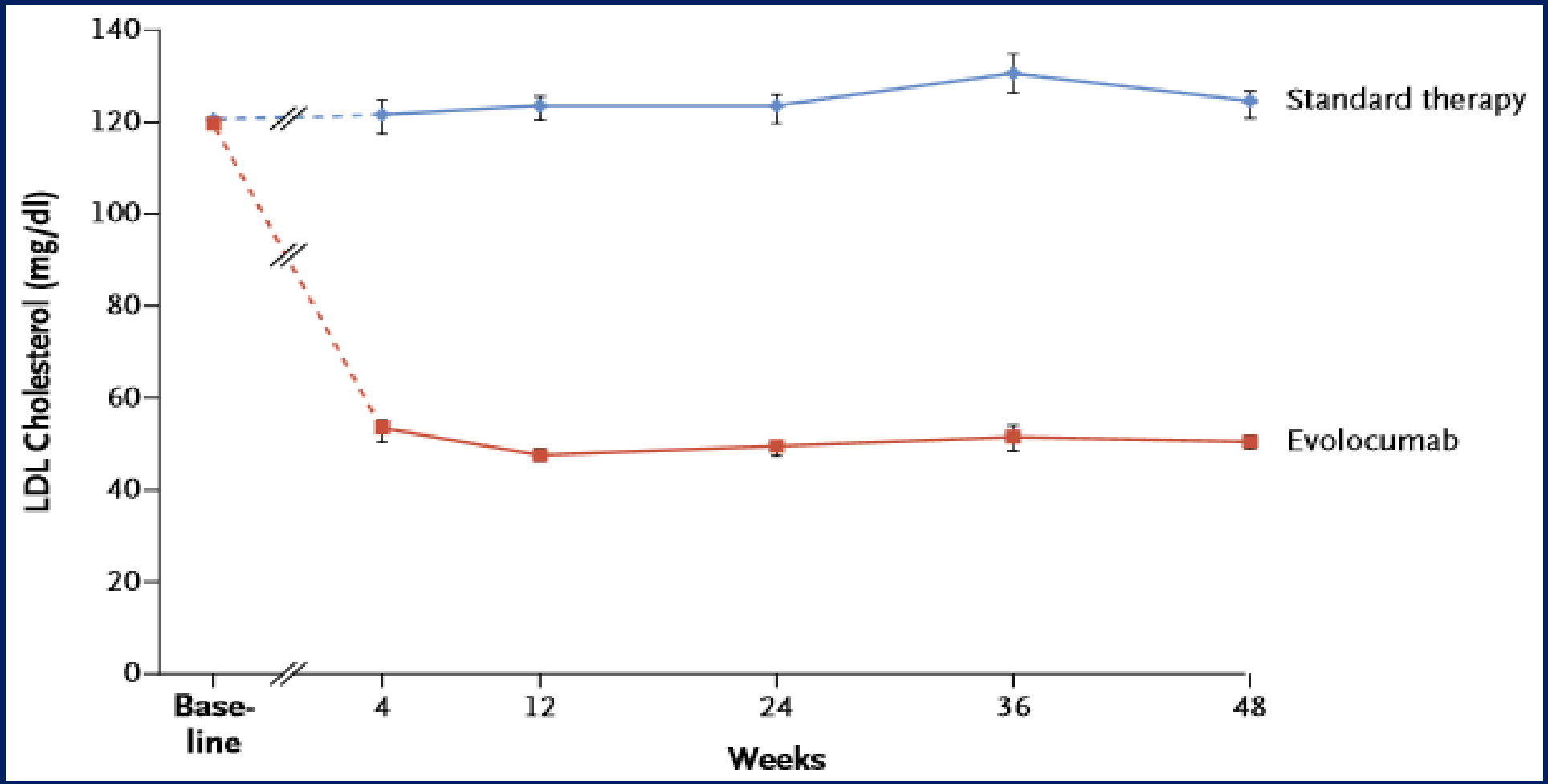
McKenney et al JACC 2012;59:2344-53

# Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events: OSLER-1 & OSLER-2

- Evolucumab in patients with high CVD risk
- 4465 participants from 1 of 12 Phase 2 or 3 studies ("parent trials")
- Randomly assigned, 2:1 ratio to either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard rx or standard rx.
- Primary outcome: incidence of adverse events.
- Secondary end point: % change in the LDL-C.

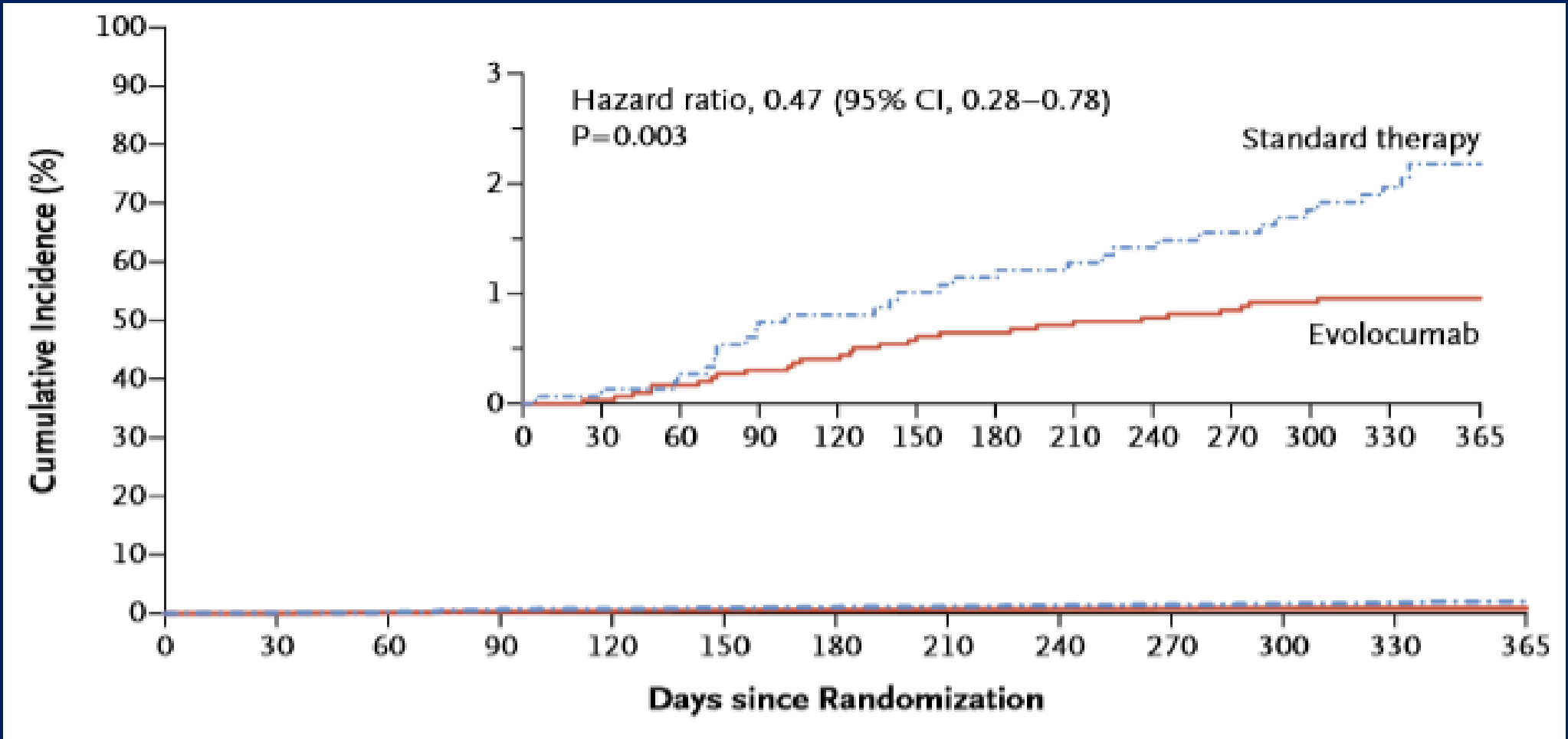
Sabatine MS et al, *NEJM* 372:1500, 2015

# OSLER-1 & OSLER-2: LDL-C Levels over Time

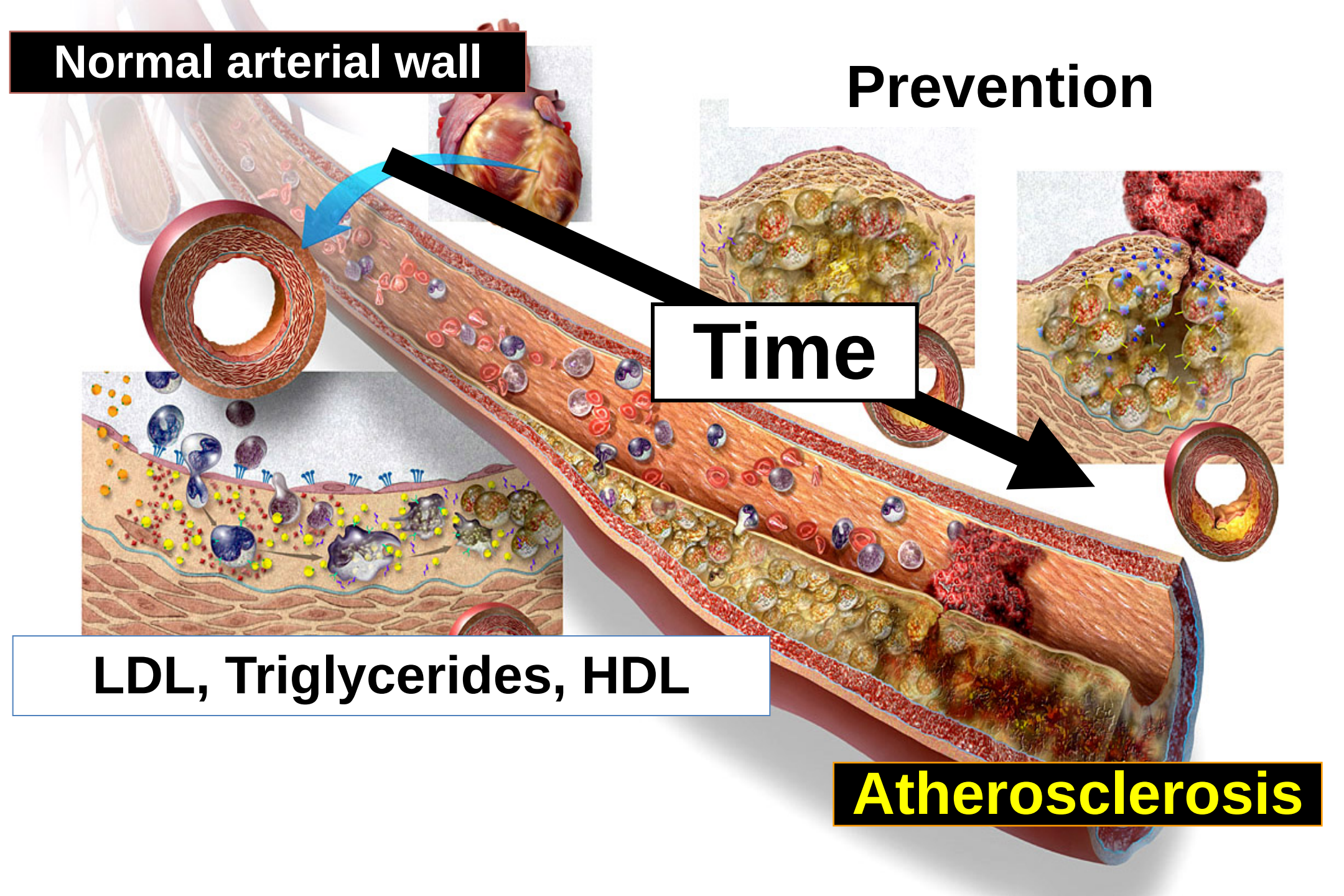



Sabatine MS et al, *NEJM* 372:1500, 2015

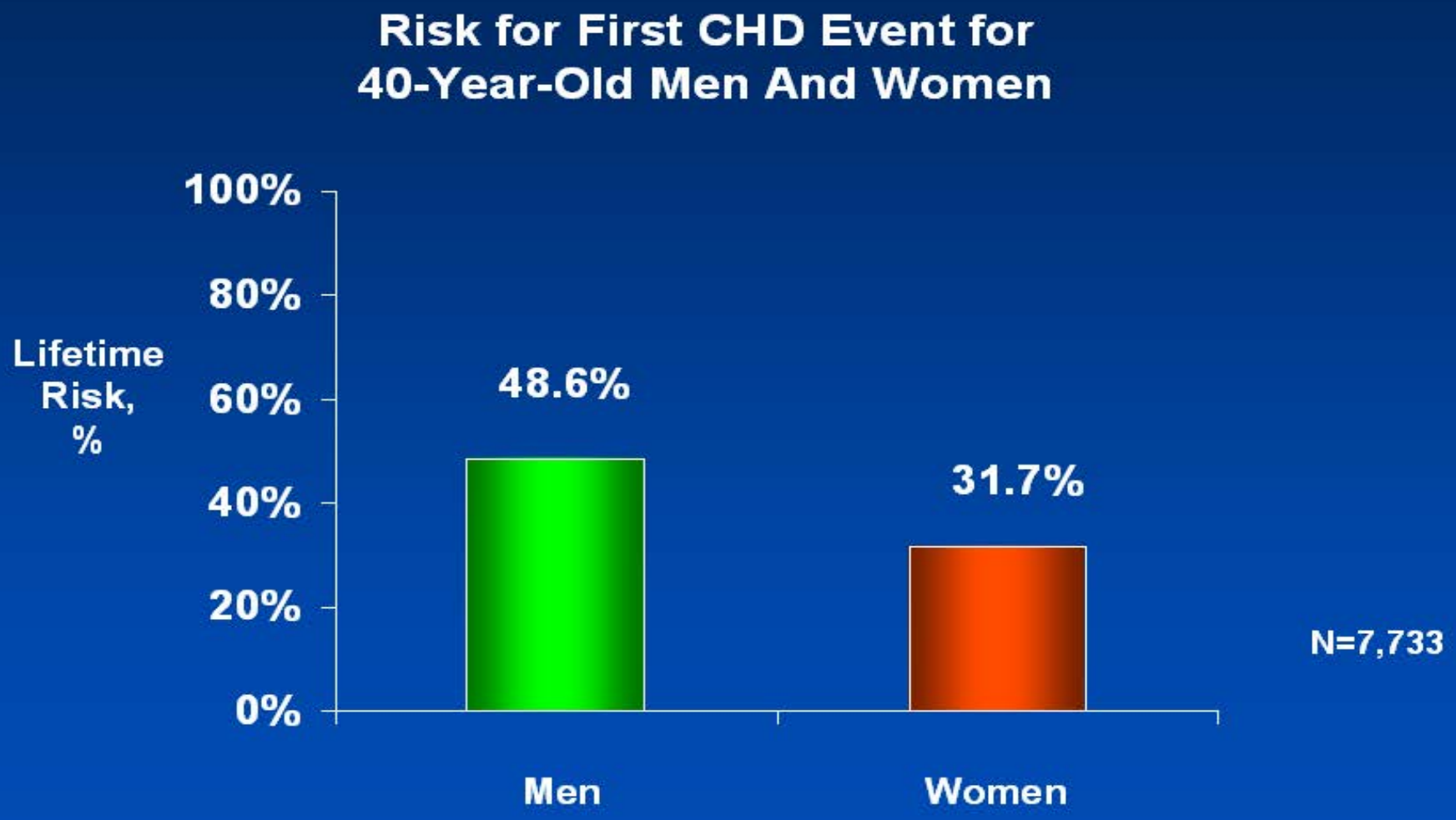
# OSLER-1 & OSLER-2: Cumulative Incidence of CVD Events




Sabatine MS et al, *NEJM* 372:1500, 2015


Normal arterial wall
Prevention
Time
LDL, Triglycerides, HDL
Atherosclerosis

# Lifetime Risk of Developing CHD Is High




Lloyd-Jones DM et al. *Lancet.* 1999;353:89–92.

# Atherosclerosis Begins Early in Life: Incidence in Male Trauma Victims

| Study Group | N | Mean Age (yr) | Athero-sclerosis Incidence (%) | Cross-Sectional Area Narrowing (%) | |
|---|---|---|---|---|---|
| | | | | >50% | 75%-90% |
| Enos et al[1] (Korean War) | 300 | 22.1 | 77.3 | — | — |
| Virmani et al[2] (Korean War) | 94 | 20.5 | 56.0 | 19.0 | 6.4 |
| McNamara et al[3] (Vietnam War) | 105 | 22.1 | 45.0 | — | 5.0 |
| Joseph et al[4] (University of Louisville) | 95 | 25.6 | 75.8 | 21.0 | 9.0 |

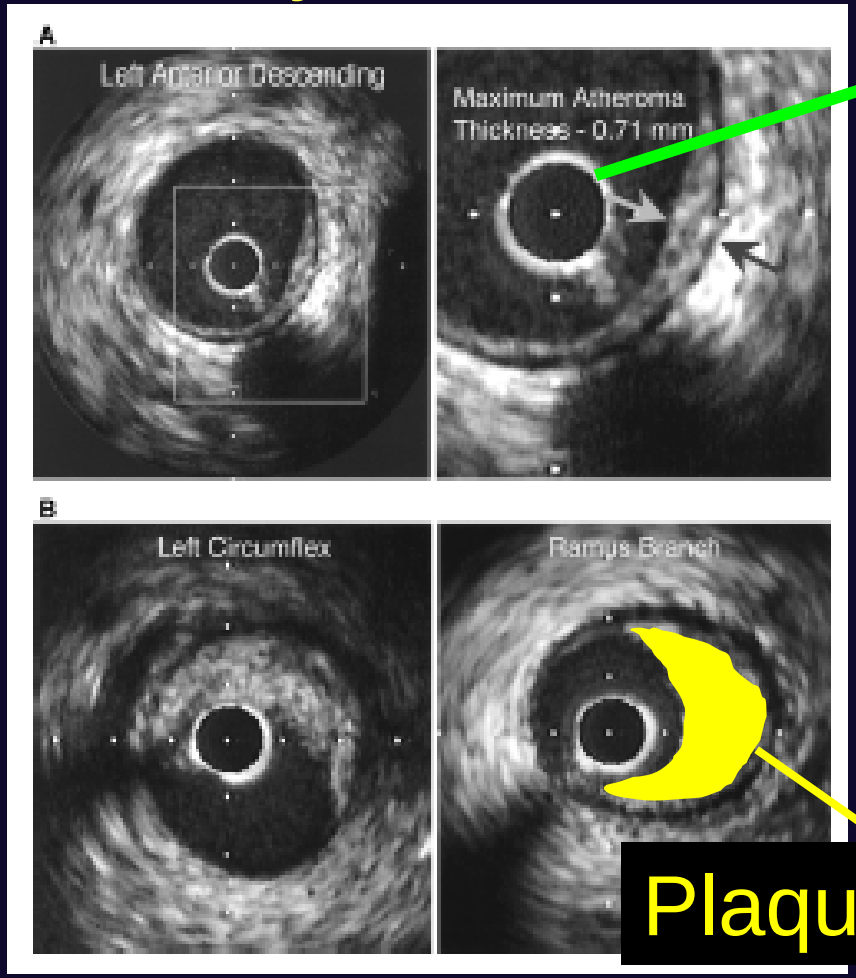

1. Enos W, et al. *J Am Med Assoc*. 1955; 158:912-914
2. Virmani R, et al. *Arch Pathol Lab Med*. 1987; 111:972-976
3. McNamara J, et al. *J Am Med Assoc.* 1971; 216:1185-1187
4. Adapted with permission from Joseph A, et al. *J Am Coll Cardiol*. 1993;22:459-467.

# High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults

## Evidence From Intravascular Ultrasound

E. Murat Tuzcu, MD; Samir R. Kapadia, MD; Eralp Tutar, MD; Khaled M. Ziada, MD; Robert E. Hobbs, MD; Patrick M. McCarthy, MD; James B. Young, MD; Steven E. Nissen, MD

30 yo female




Lesions present:
1 of 6 teenagers

Circulation 2001 2705-9

**“Atherosclerosis is a pediatric disease.”**

Strong et al
JAMA, 281, 727-35,’ 99

# Principles of Prevention

## Dyslipidemia Rx

Guidelines only “guide”:
- Value in patient groups for treatment
- Lower likely better; can use LDL cutpoints

Statin Intolerance: Caution....
- vit D? lowest dose

Triglycerides matter – more evidence needed
- secondary causes
- Fibrates if elevated TG/low HDL, significant risk

Eating/Lifestyle matters – more implementation

After 100+ years of study, progress continues.

And “truth” continues to evolve….