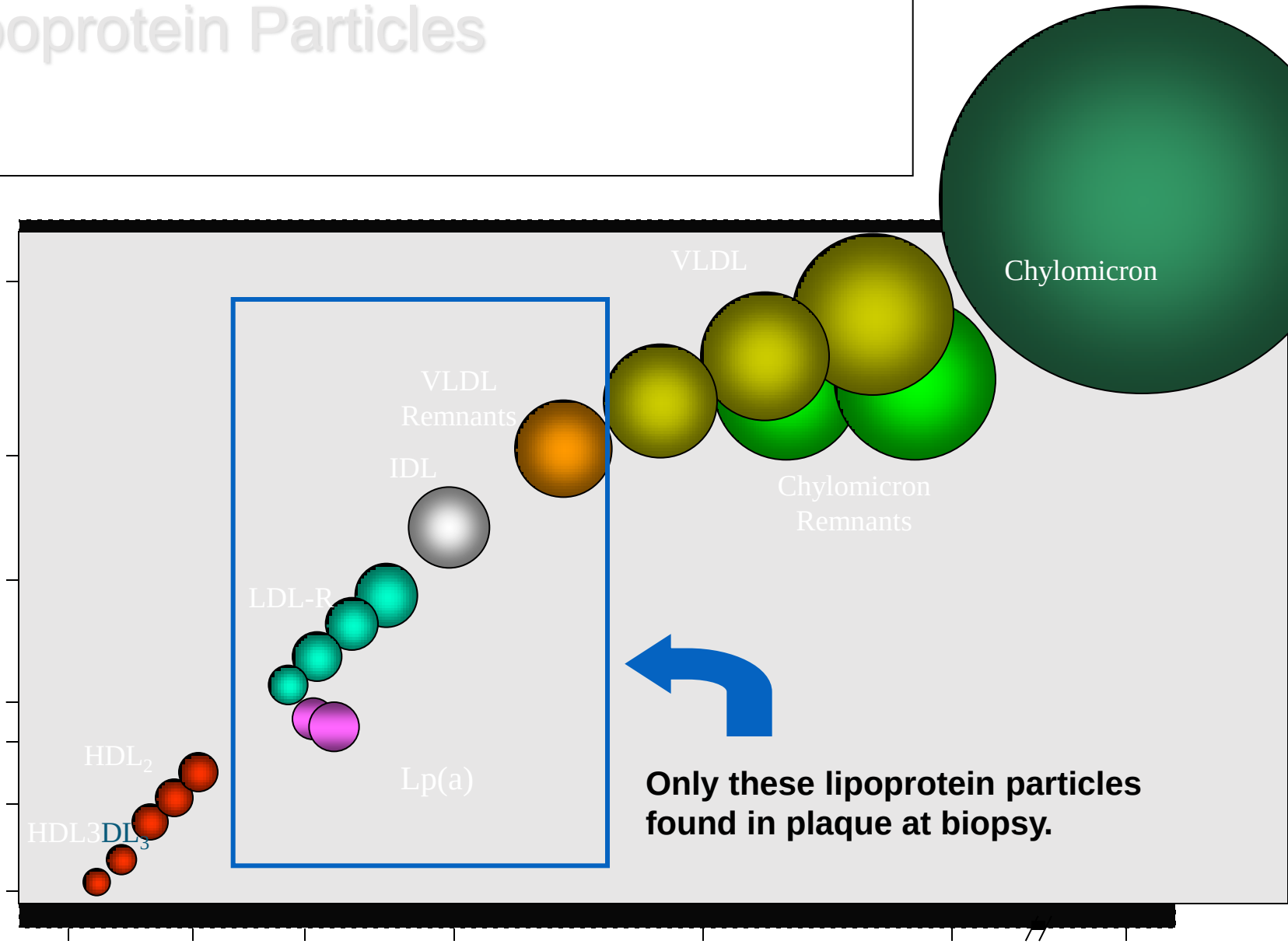
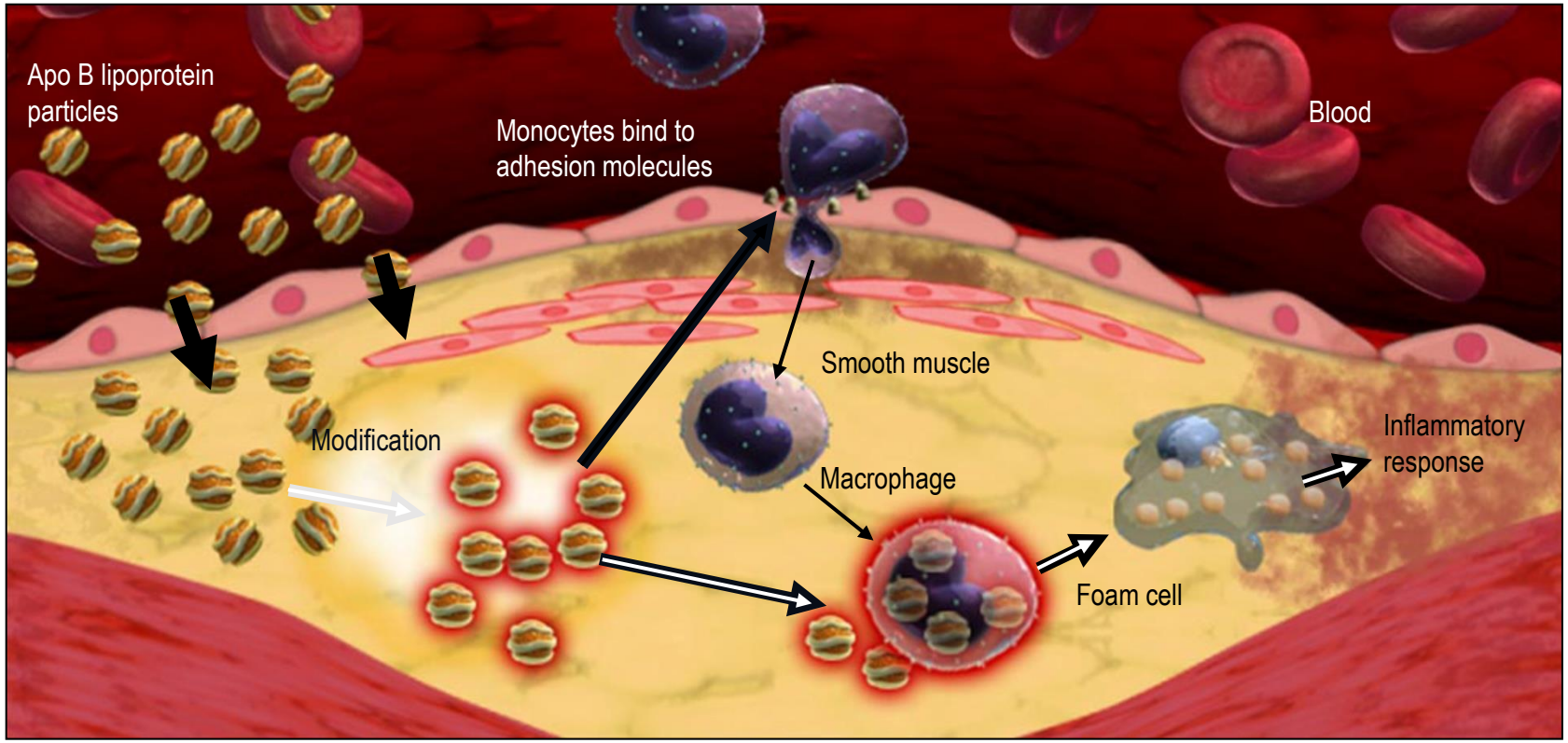
# CHOLESTEROL MANAGEMENT UPDATE - 2017

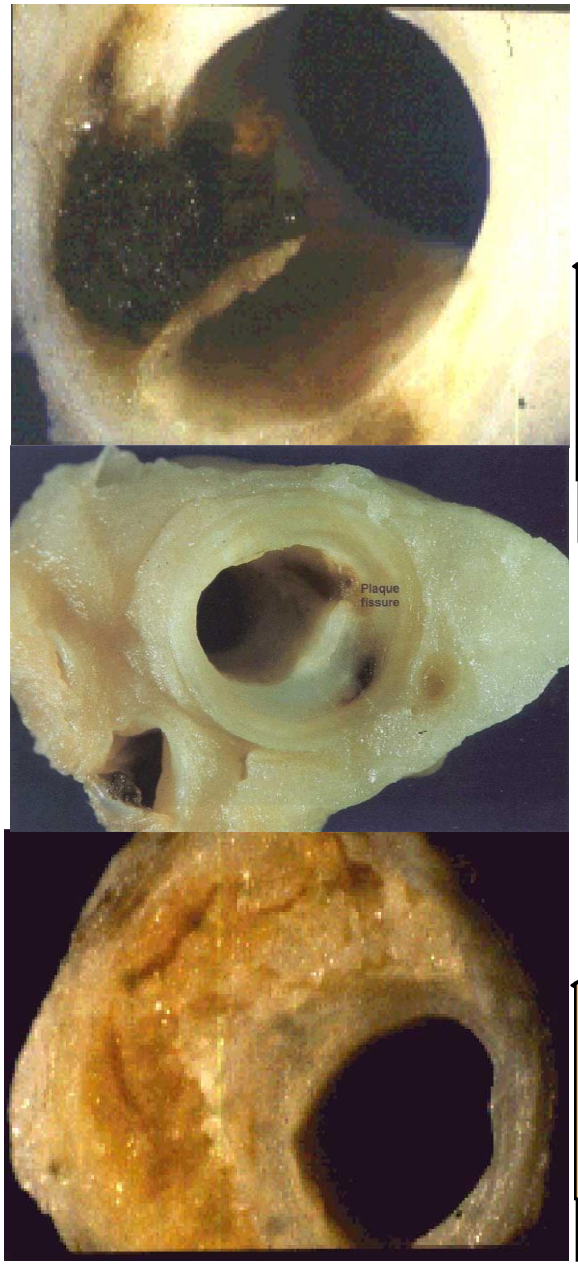
Franklin Handel, MD

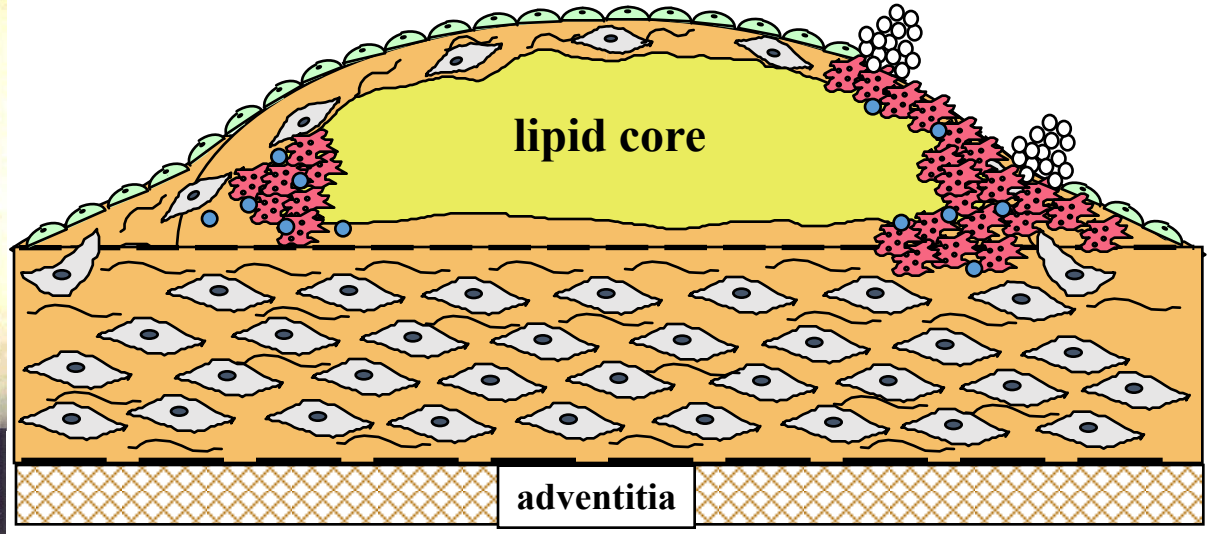
# Lipoprotein Particles

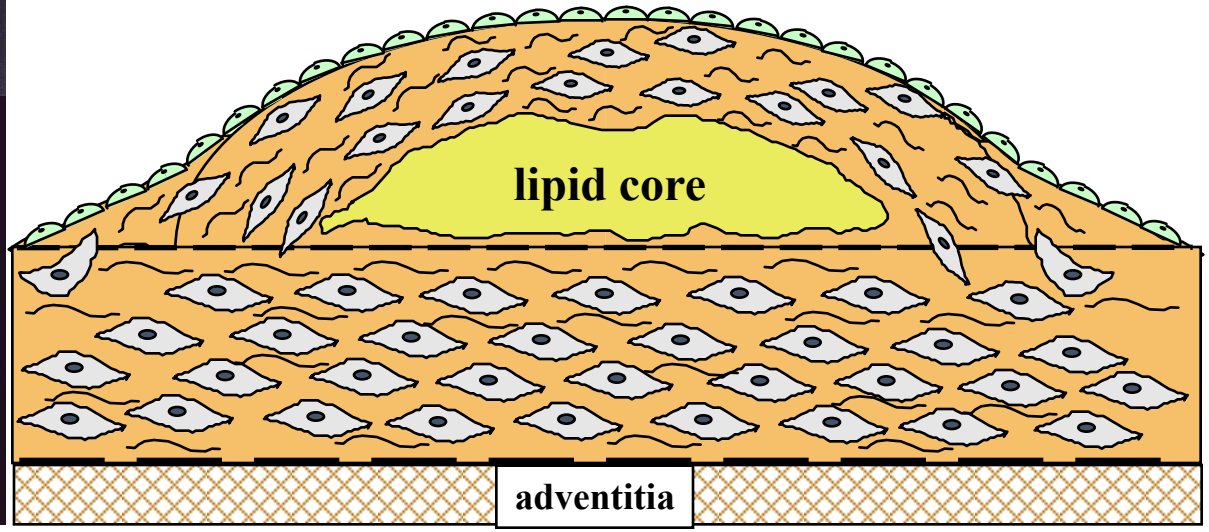


# High Plasma Apo B Lipoprotein Levels Promote Atherogenesis




Plaque
fissure


lipid core
adventitia


lipid core
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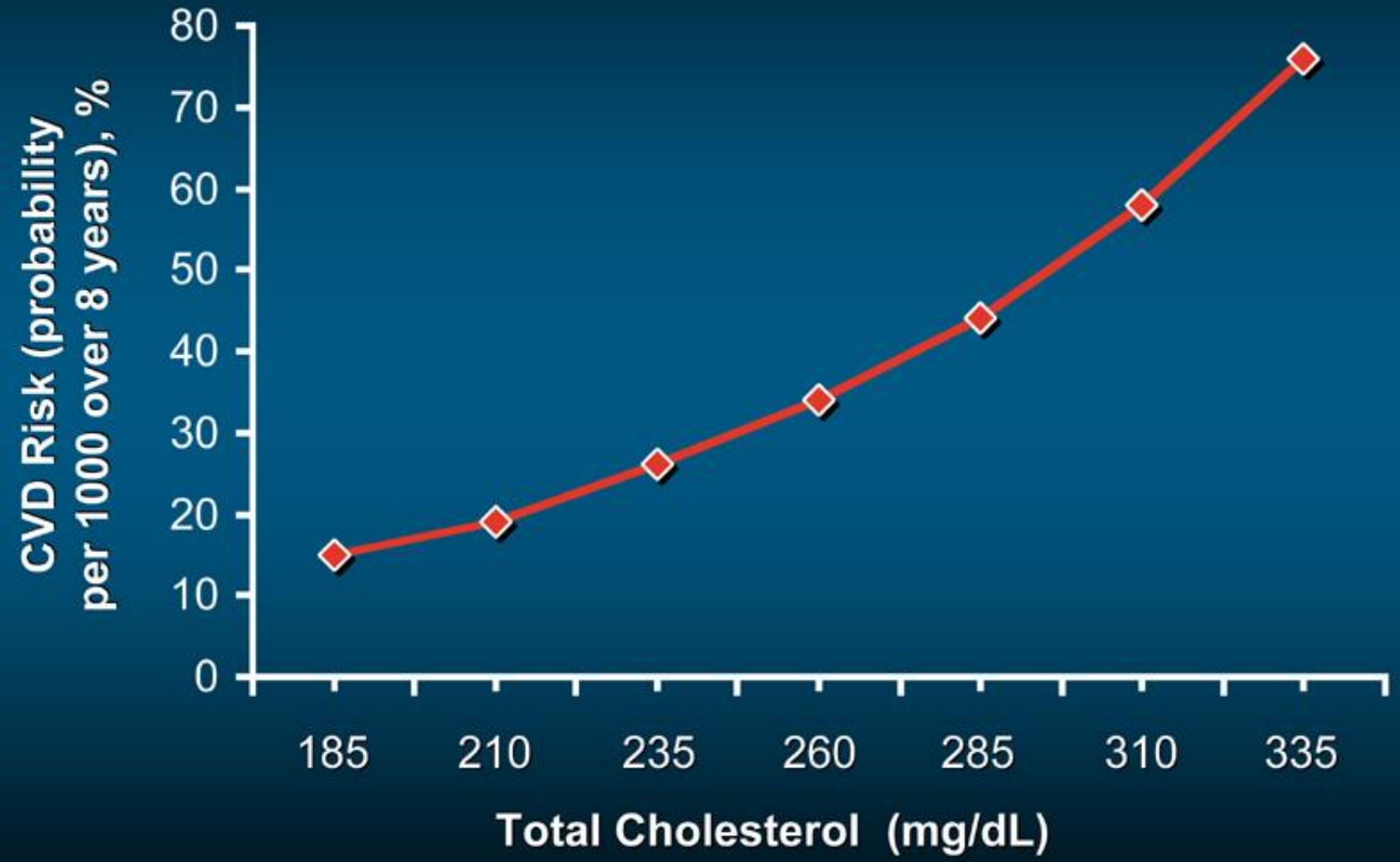
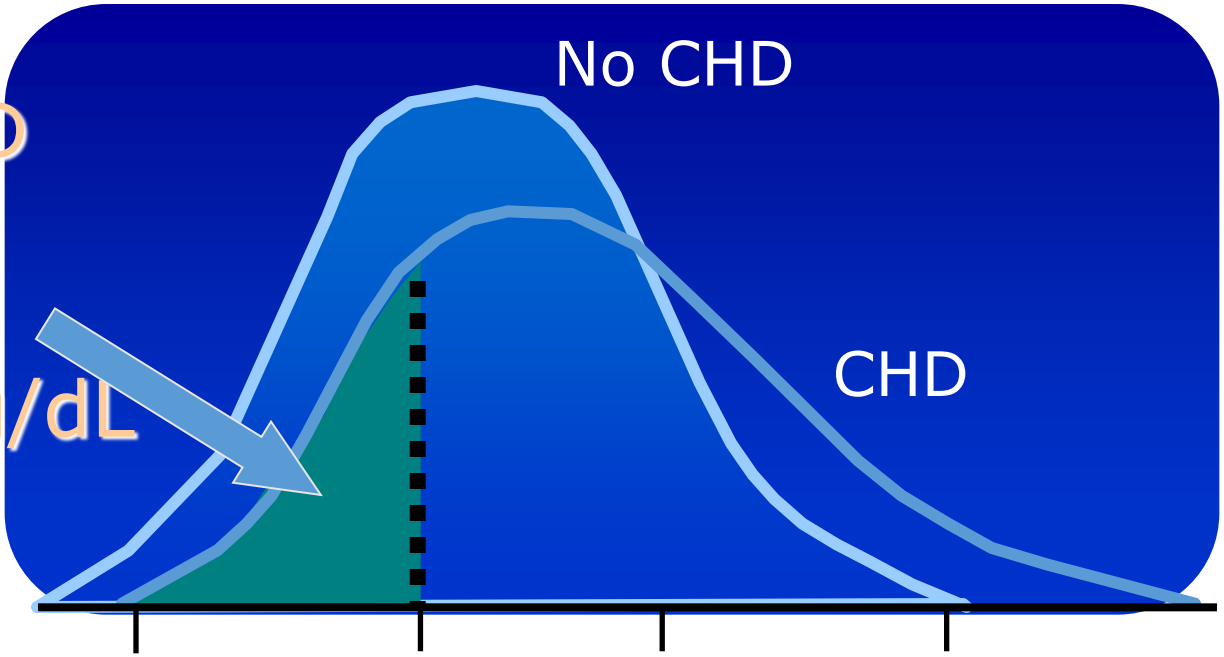
# There Is a Strong Relationship Between CVD Risk and the Presence of Dyslipidemia: Framingham



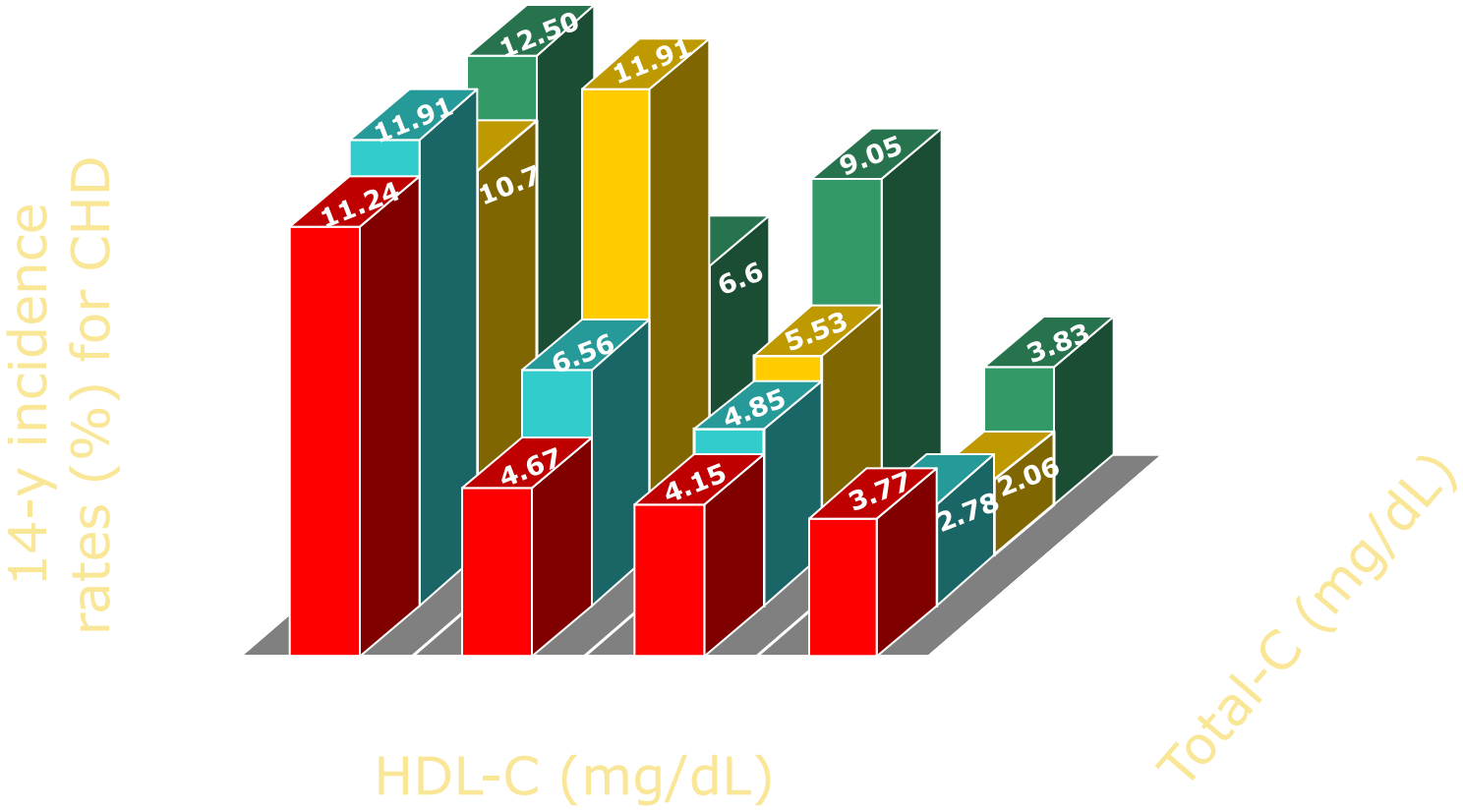

Kannel. *Hypertension*: *Physiopathology and Treatment.* 1977:888-910.

# Total Cholesterol Distribution:
*CHD vs Non-CHD Population*

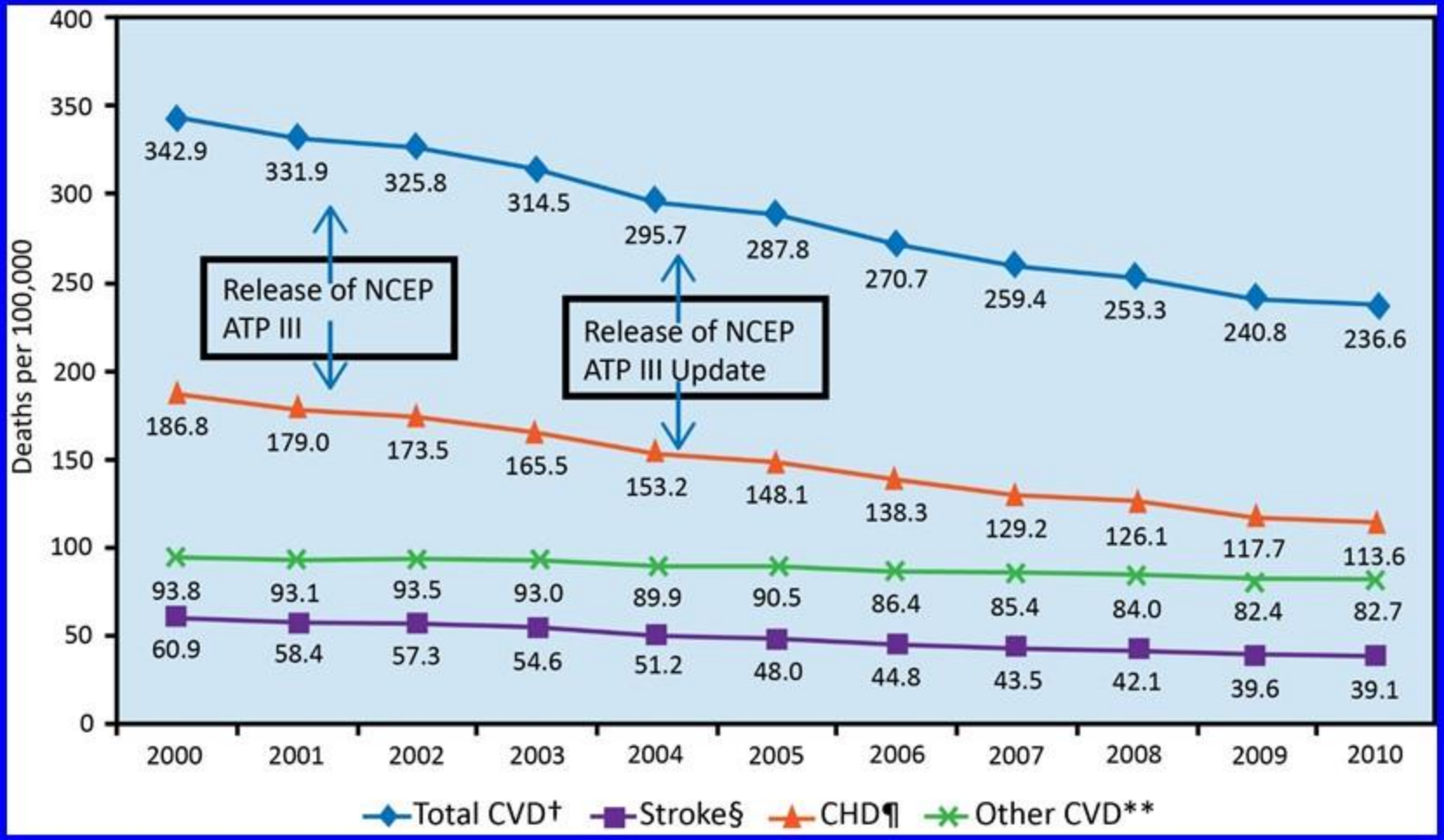
35% of CHD Occurs in People with TC<200 mg/dL



# Low HDL-C Levels Increase CHD Risk Even When Total-C Is Normal

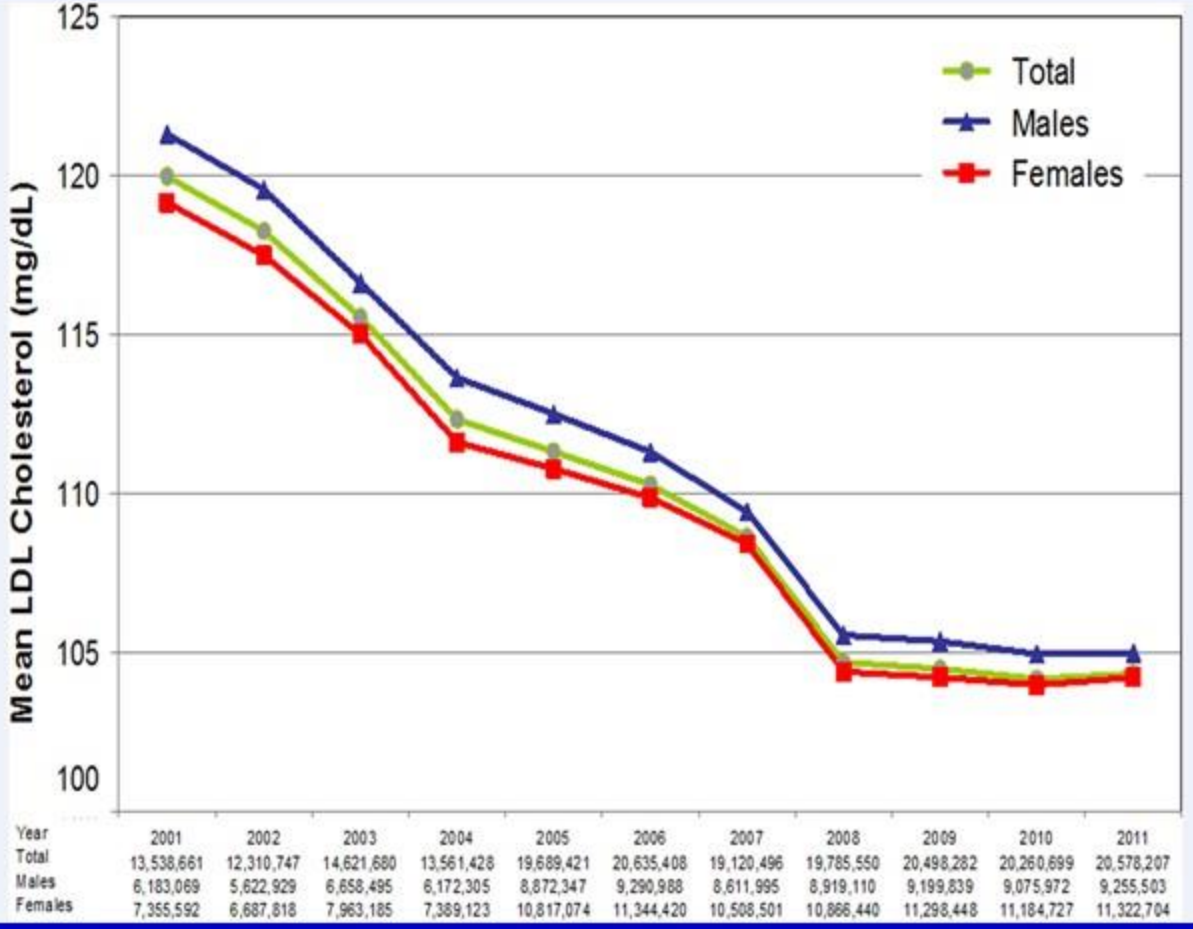


# US age-standardized death rates attributable to CVD, 2000 to 2010




Go AS, et al. Circulation. 2014;129:e28-e292.

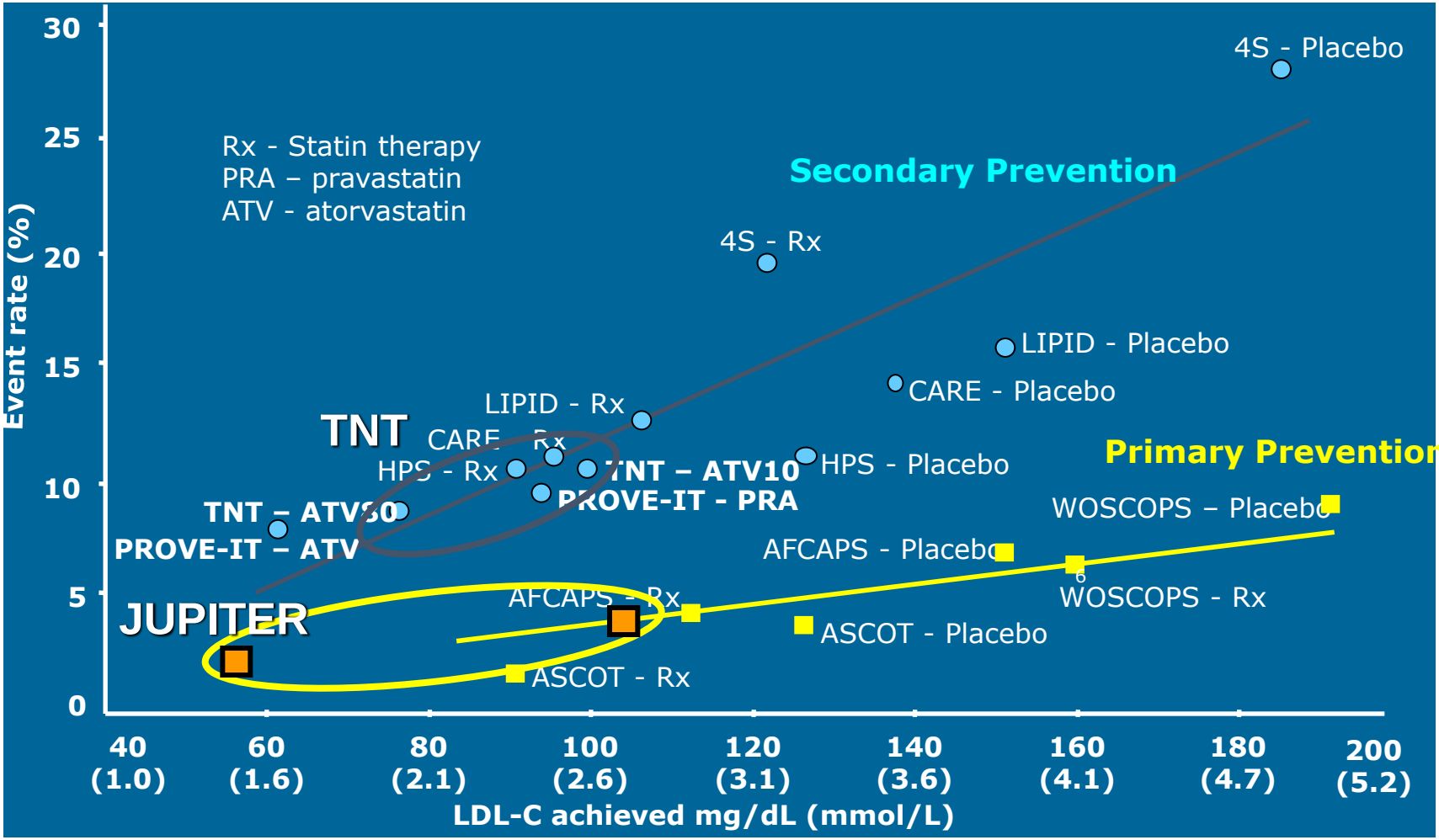
# Mean age-adjusted LDL-C trends 2001–2011 in the United States: Analysis of 105 million patient records from a single national diagnostic laboratory



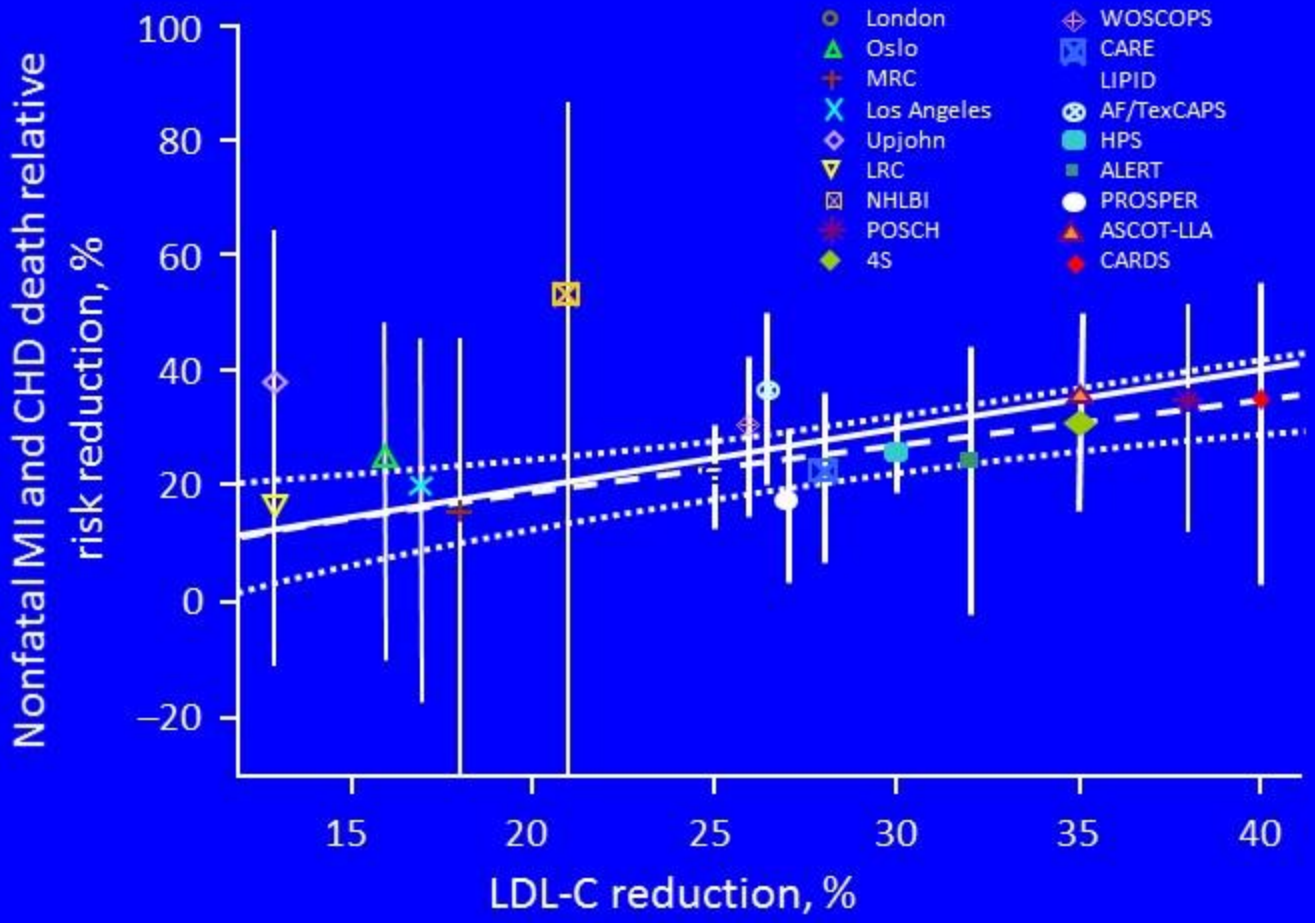

| Year | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total | 13,538,661 | 12,310,747 | 14,621,680 | 13,561,428 | 19,689,421 | 20,635,408 | 19,120,496 | 19,785,550 | 20,498,282 | 20,260,699 | 20,578,207 |
| Males | 6,183,069 | 5,622,929 | 6,658,495 | 6,172,305 | 8,872,347 | 9,290,988 | 8,611,995 | 8,919,110 | 9,199,839 | 9,075,972 | 9,255,503 |
| Females | 7,355,592 | 6,687,818 | 7,963,185 | 7,389,123 | 10,817,074 | 11,344,420 | 10,508,501 | 10,866,440 | 11,298,448 | 11,184,727 | 11,322,704 |

Kaufman HW, et al. PLoS ONE. 2013;8(5):e63416.

# LDL cholesterol and benefit in clinical trials
# Is lower better ?

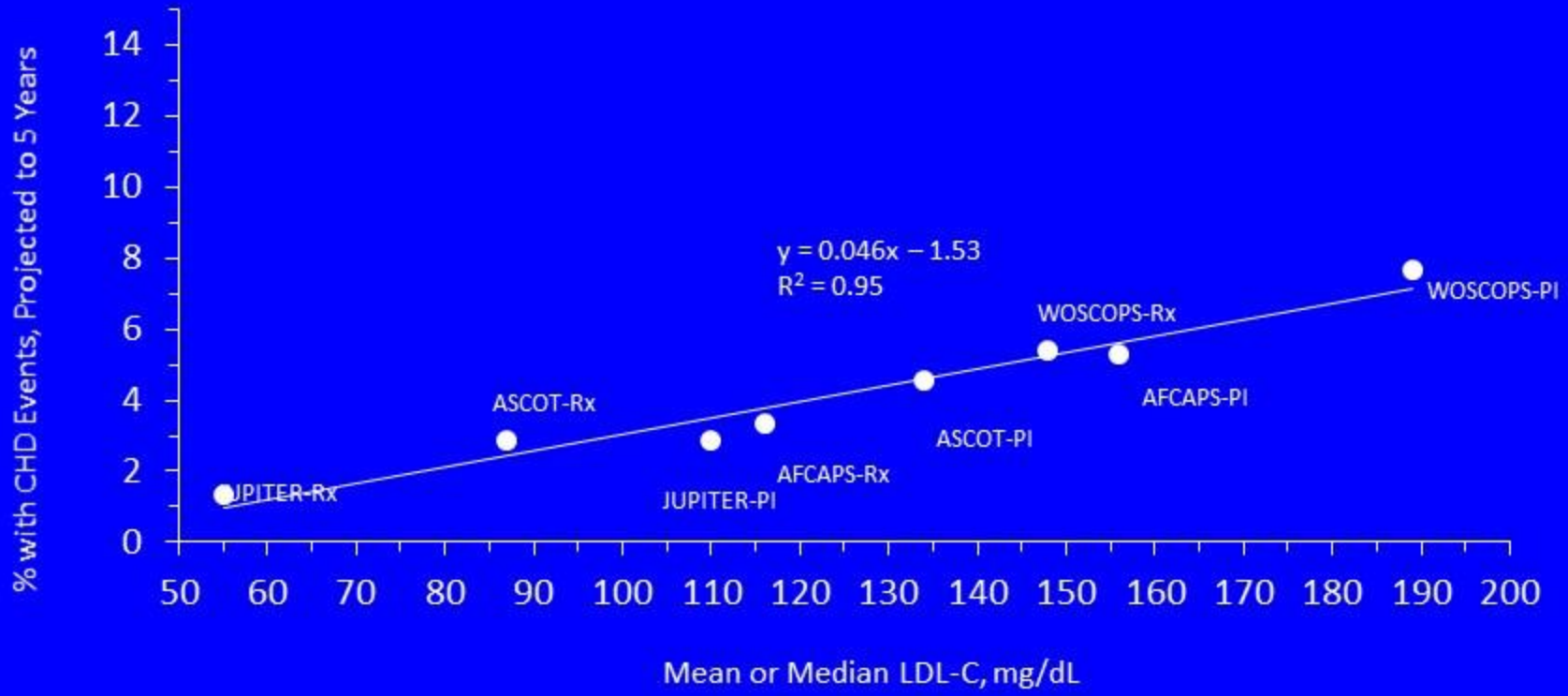


# Consistent Relationship Between LDL-C Reduction and CHD Relative Risk for all LDL-C-lowering Treatments



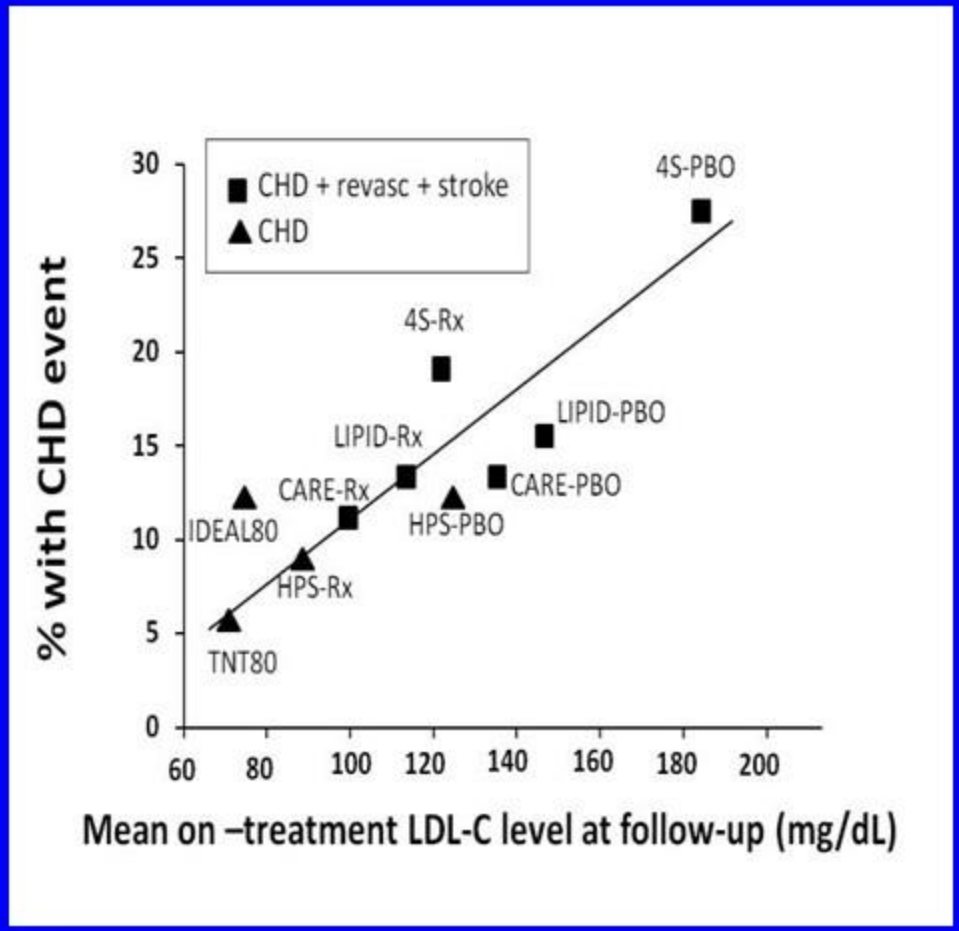

Robinson JG, et al. J Am Coll Cardiol. 2005;46:1855-1862.

# On-Treatment LDL-C and CHD Events in Primary Prevention



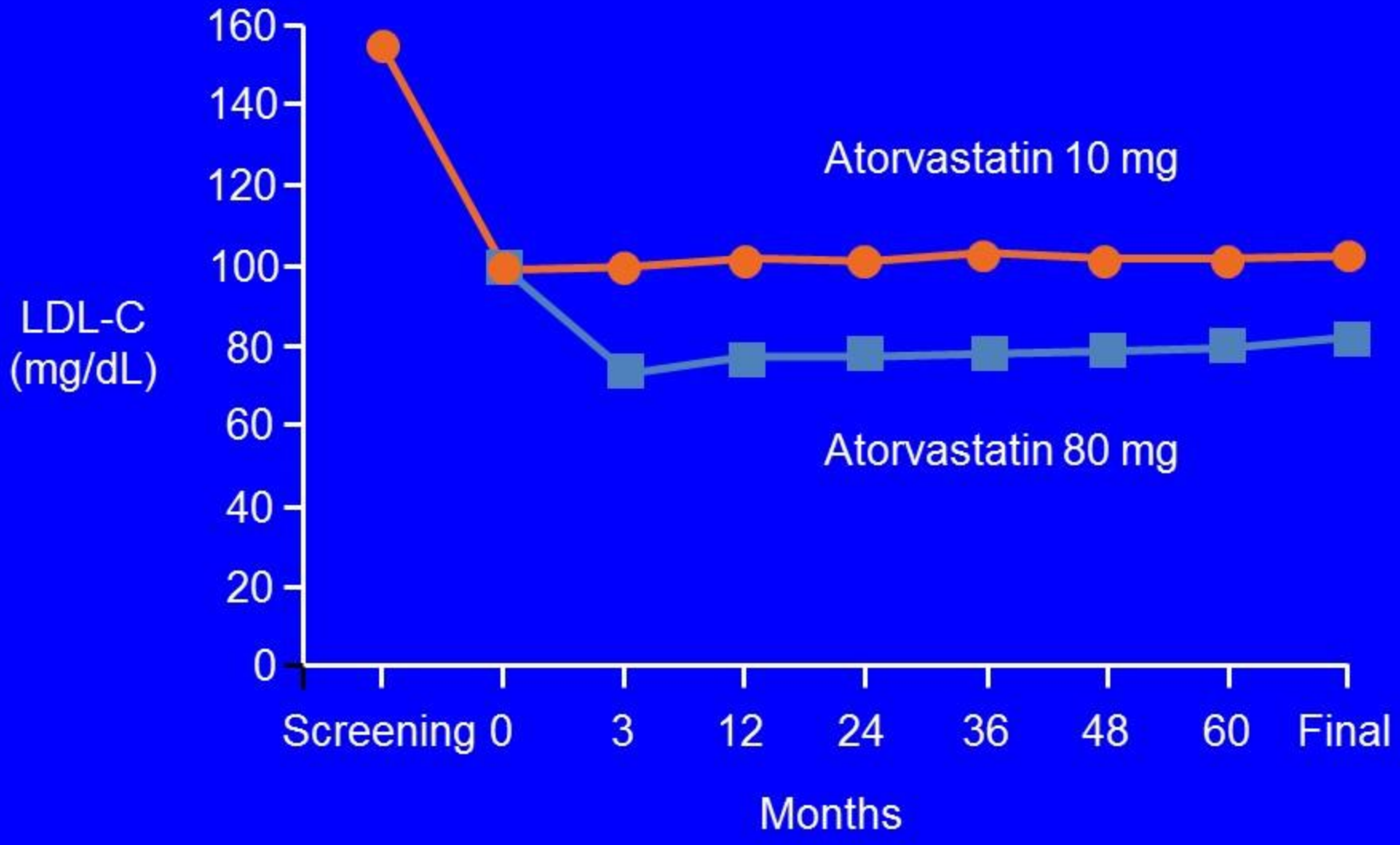

Data abstracted from original publications

# On-Treatment LDL-C and CHD Events in Secondary Prevention



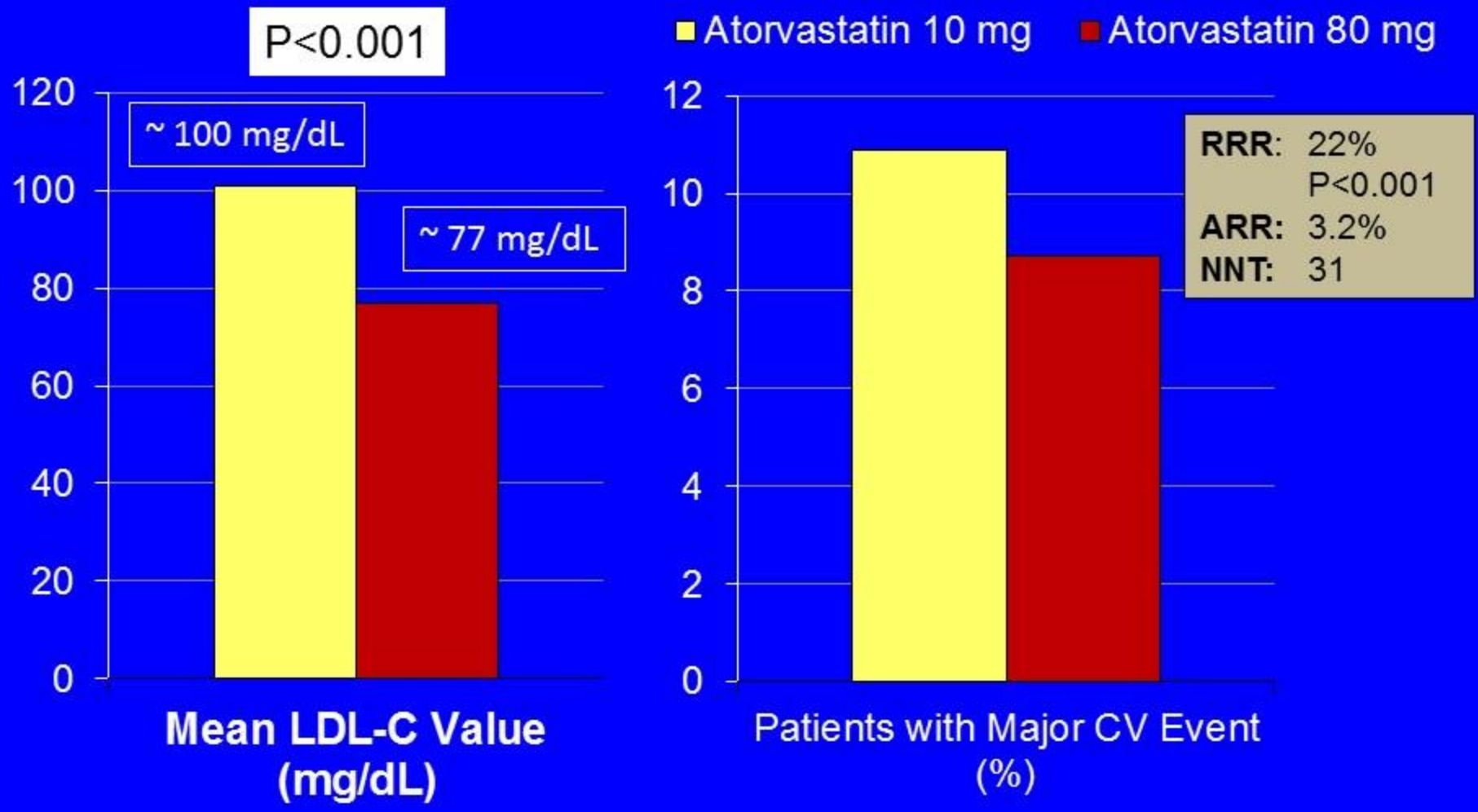

Expert Dyslipidemia Panel of IAS. J Clin Lipidol. 2014;8:29-60.

# TNT: Treatment Effects on LDL-C



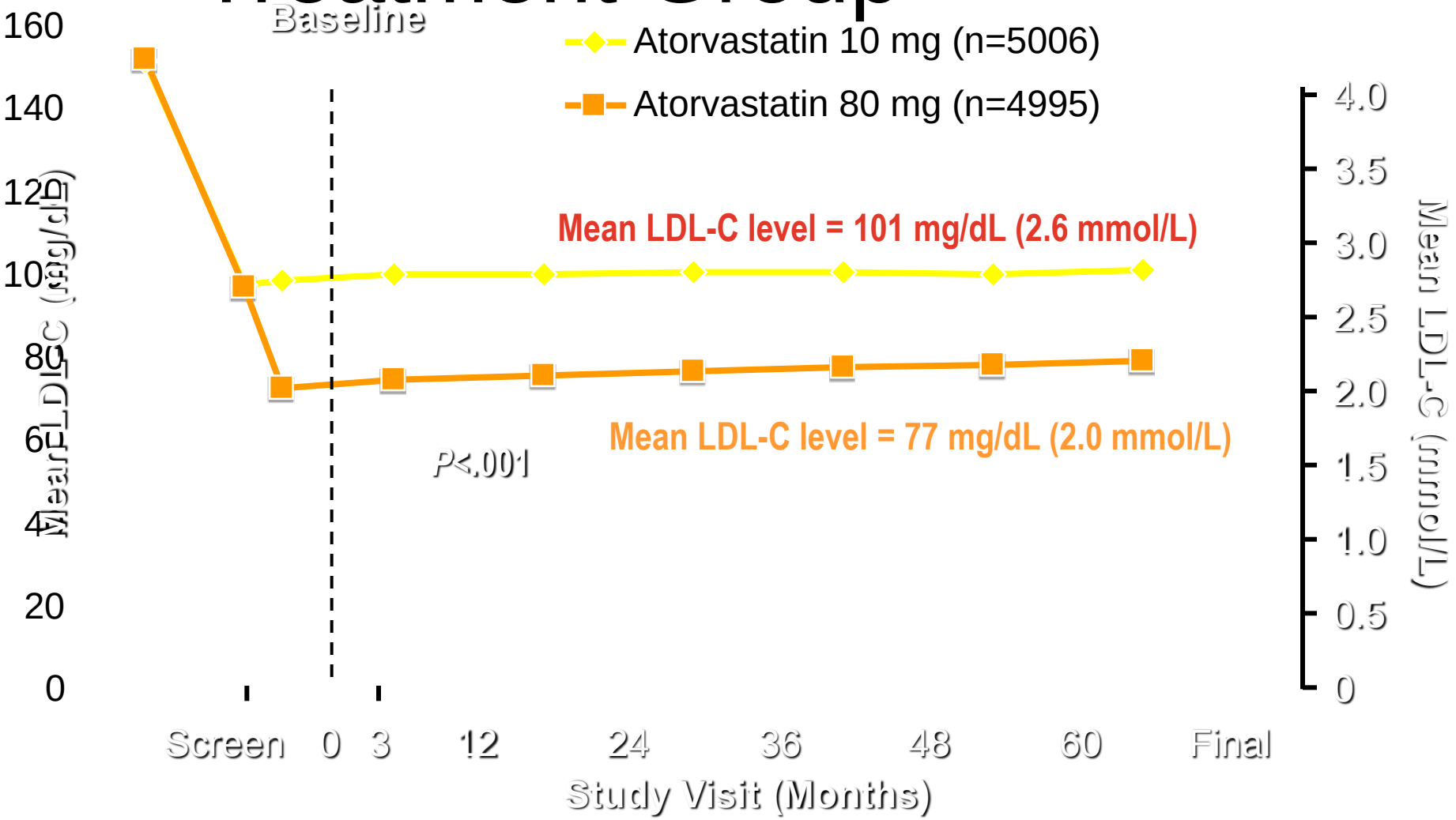

LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435.

# Treating to New Targets (TNT) in Stable CHD Patients: LDL-C Results and Primary Endpoint



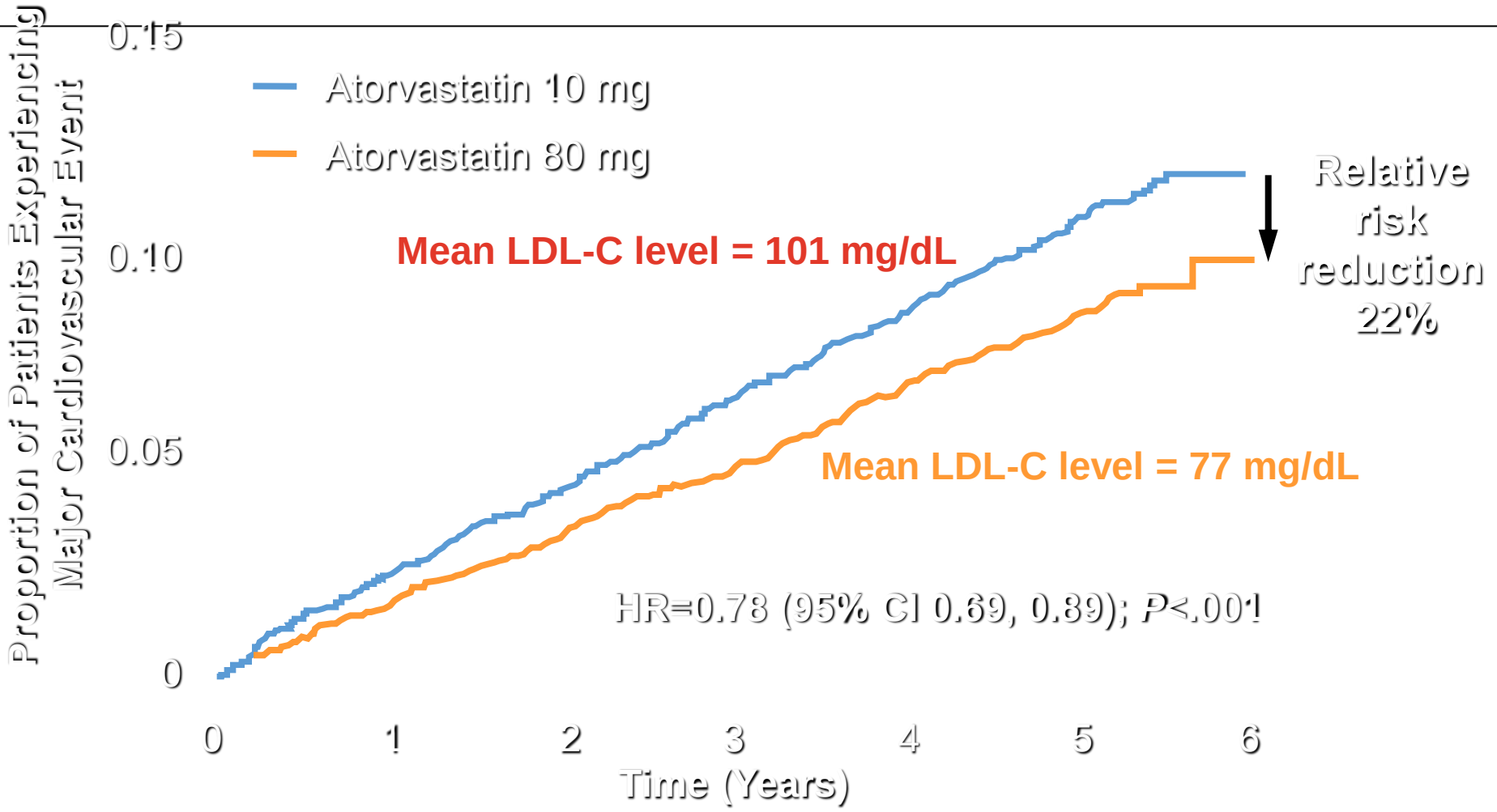

LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435.

# TNT: Changes in LDL-C by Treatment Group




LaRosa et al. *N Engl J Med.* 2005;352:1425-1435.

# TNT: Primary Efficacy Outcome Measure: Major Cardiovascular Events*




* CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

LaRosa et al. *N Engl J Med.* 2005;352:1425-1430.

# Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at which to Consider Drug Therapy

| Risk Category | Criteria | Treatment Goal | Consider Drug Therapy |
|---|---|---|---|
| | | Non-HDL-C mg/dL<br>LDL-C mg/dL | |
| **Low** | ▪ 0-1 major ASCVD risk factors<br>▪ Consider other risk indicators, if known | <130<br><100 | ≥190<br>≥160 |
| **Moderate** | ▪ 2 major ASCVD risk factors<br>▪ Consider quantitative risk scoring<br>▪ Consider other risk indicators | <130<br><100 | ≥160<br>≥130 |
| **High** | ▪ ≥3 major ASCVD risk factors<br>▪ Diabetes mellitus* (Type 1 or 2)<br>  ▪ 0-1 other major ASCVD risk factors, and<br>  ▪ No evidence of end organ damage<br>▪ Chronic kidney disease stage 3B or 4<br>▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)<br>▪ Quantitative risk score reaching the high-risk threshold | <130<br><100 | ≥130<br>≥100 |
| **Very High** | ▪ ASCVD*<br>▪ Diabetes mellitus* (Type 1 or 2)<br>  ▪ ≥2 other major ASCVD risk factors or<br>  ▪ Evidence of end organ damage | <100<br><70 | ≥100<br>≥70 |

***For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.***



Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8(5):473-88.

# Patient with HoFH

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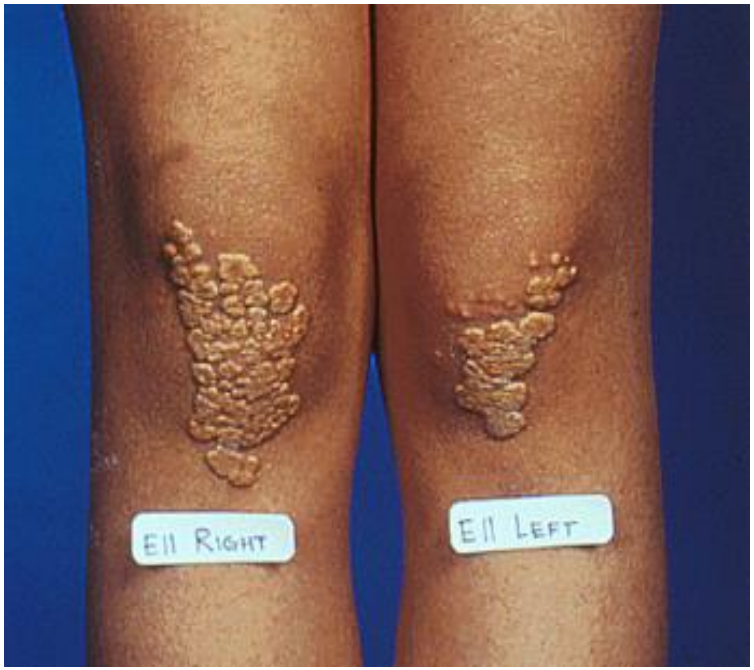
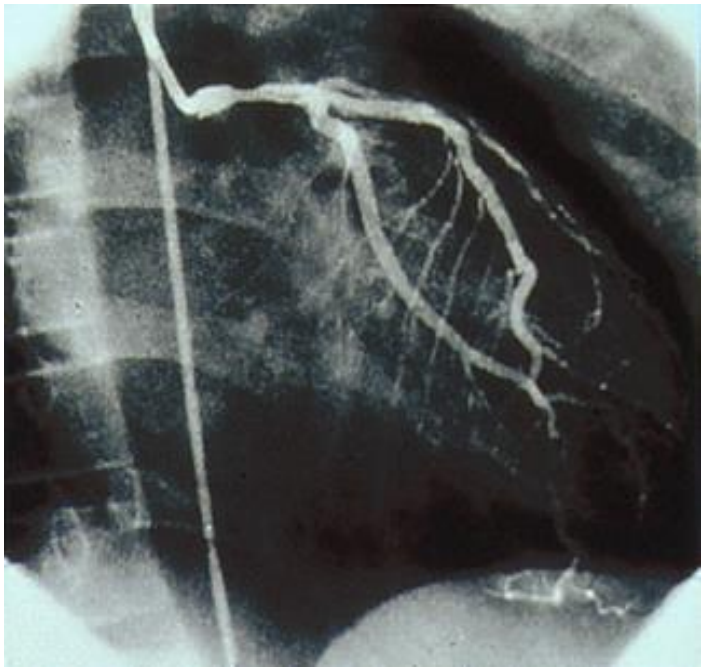
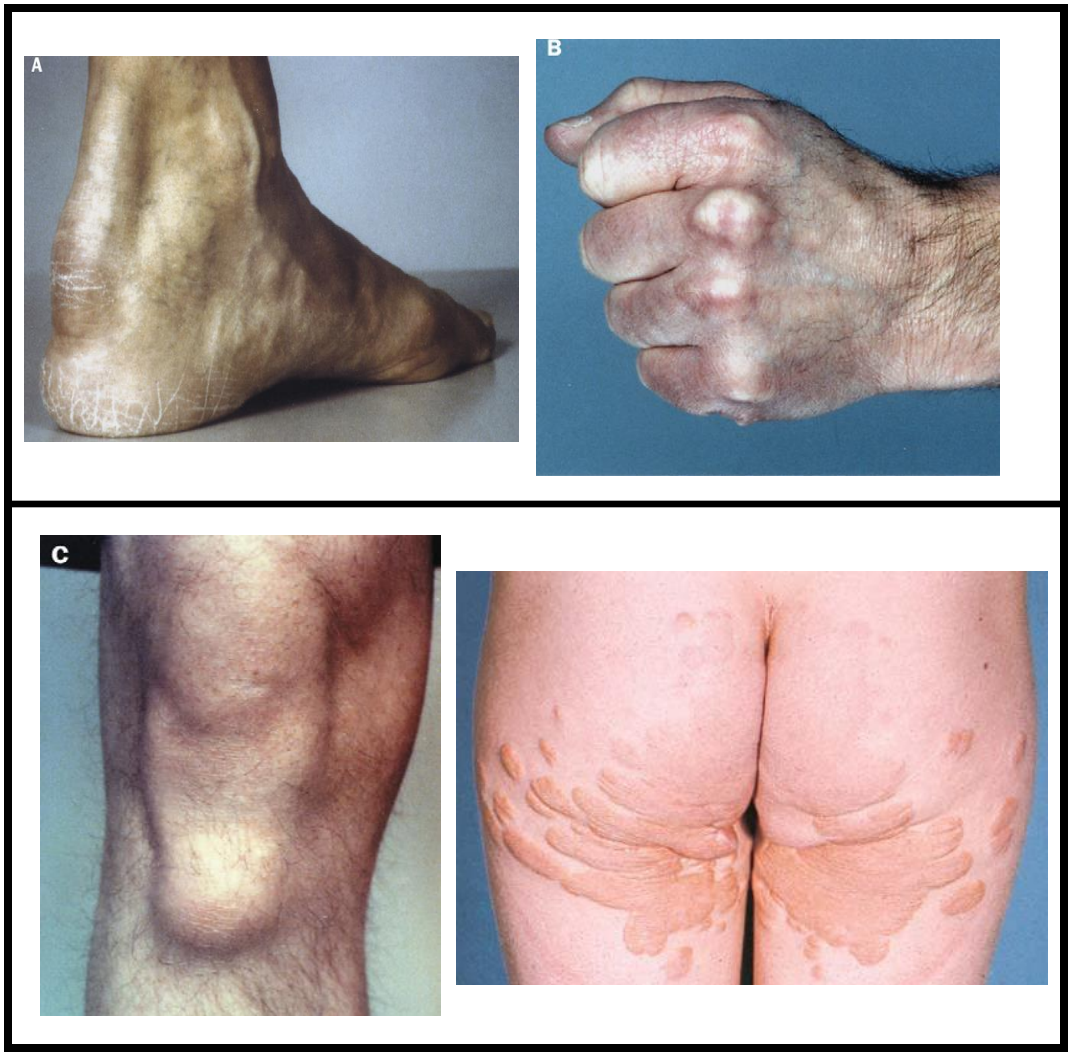
- 



# Clinical Characteristics FH




**Tendinous Xanthomas (any age)**

**Corneal Arcus (<45yo)**

**Xanthelasma (<25yo)**

# Four Major Statin Benefit Groups

1) Individuals with clinical ASCVD
2) Individuals with LDL >190
3) Individuals with dm, 40-75 yo with LDL 70-189 and without clinical ASCVD
4) Individuals without clinical ASCVD or dm with LDL 70-189 and estimated 10-year ASCVD risk >7.5%

# 4 Statin Benefit Groups

- **Clinical ASCVD***
- **LDL–C ≥190 mg/dL, Age ≥21 years**
- **Primary prevention – Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL**
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL–C 70-189 mg/dL,

# Intensity of Statin Therapy

**Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)***

| High-Intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Intensity Statin Therapy |
|---|---|---|
| Daily dose lowers LDL–C on average, by approximately ≥50% | Daily dose lowers LDL–C on average, by approximately 30% to <50% | Daily dose lowers LDL–C on average, by <30% |
| **Atorvastatin (40†)–80 mg**<br>**Rosuvastatin 20** *(40)* **mg** | **Atorvastatin 10** *(20)* **mg**<br>**Rosuvastatin** *(5)* **10 mg**<br>**Simvastatin 20–40 mg‡**<br>**Pravastatin 40** *(80)* **mg**<br>**Lovastatin 40 mg**<br>*Fluvastatin XL 80 mg*<br>**Fluvastatin 40 mg bid**<br>*Pitavastatin 2–4 mg* | *Simvastatin 10 mg*<br>**Pravastatin 10–20 mg**<br>**Lovastatin 20 mg**<br>*Fluvastatin 20–40 mg*<br>*Pitavastatin 1 mg* |

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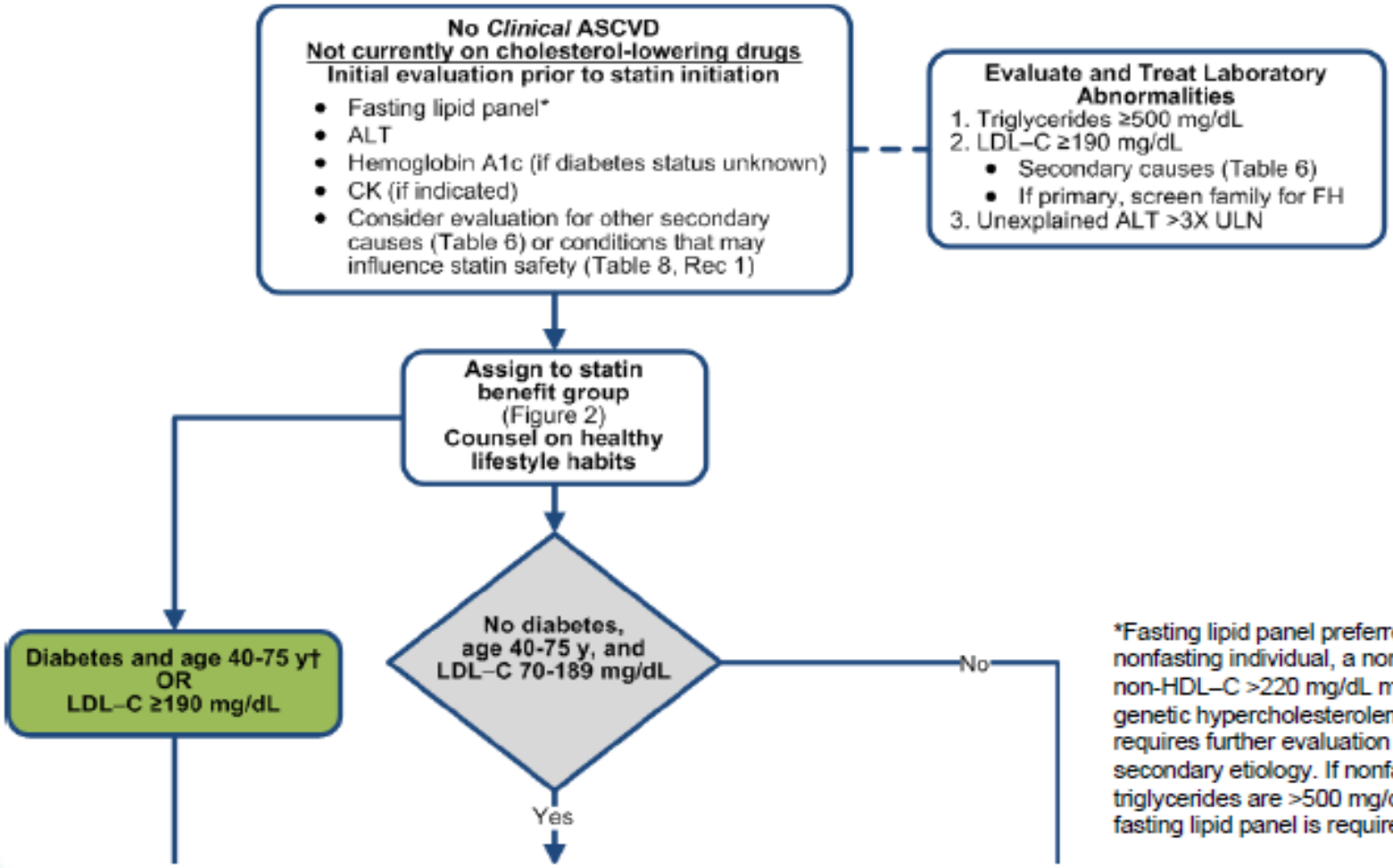
***For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.***



Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8(5):473-88.

# Primary Prevention

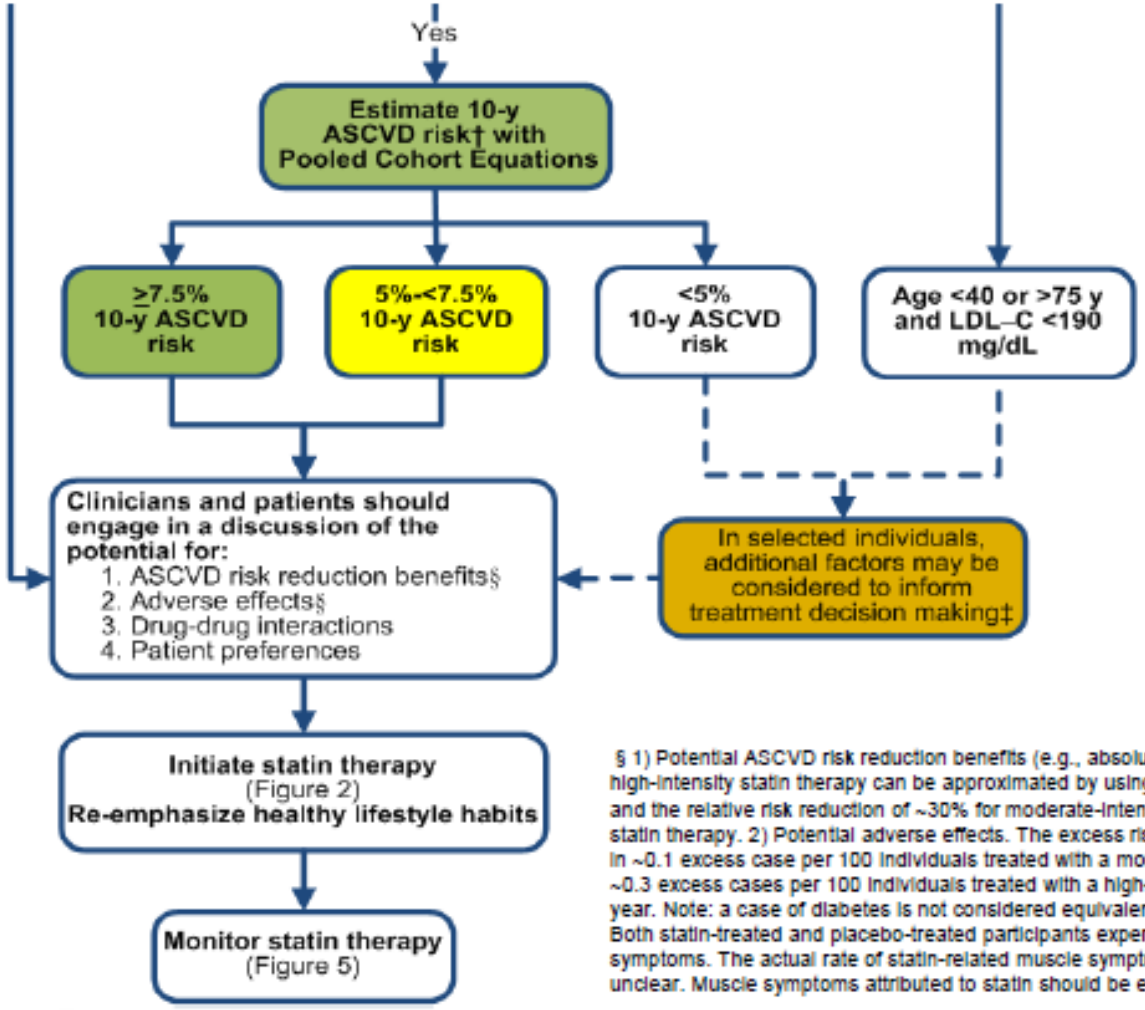
## *Initiating Statin Therapy*




*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL–C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.

# Primary Prevention

## *Initiating Statin Therapy* (con't)



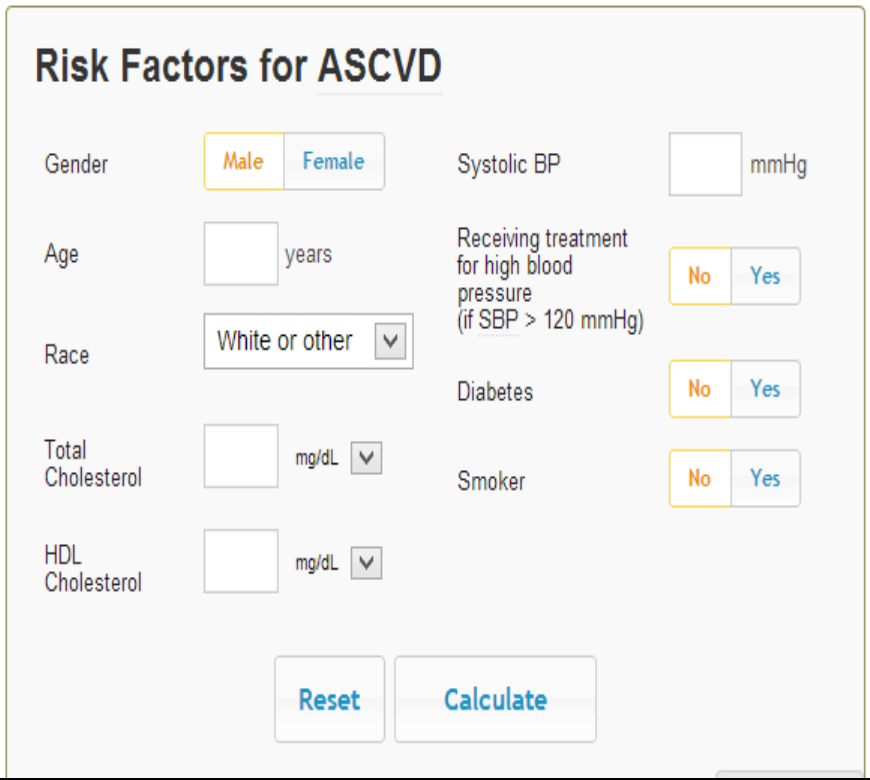

†The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.

‡These factors may include primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, sensitivity-C-reactive protein ≥2 mg/L ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity (For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.

§ 1) Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: a case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.

# Pooled Cohort Risk Assessment Equations

## Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event




http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

# INTENSITY OF STATIN THERAPY IN PRIMARY AND SECONDARY PREVENTION

**Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)***

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# STATIN SAFETY RECOMMENDATIONS

- SELECT THE APPROPRIATE DOSE
- KEEP POTENTIAL SIDE EFFECTS AND DRUG-DRUG INTERACTION IN MIND (GRADE A)
- IF HIGH OR MODERATE INTENSITY STATIN NOT TOLERATED, USE THE MAXIMUM TOLERATED DOSE INSTEAD

# Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - CAC score ≥300 Agaston units
  - ABI <0.9
- Statin use still requires discussion between clinician and patient

# Management of Muscle Symptoms on Statin Therapy

- It is reasonable to evaluate and treat muscle symptoms including pain, cramping, weakness, or fatigue in statin-treated patients according to the management algorithm
- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy

# Management of Muscle Symptoms on Statin Therapy (cont.)

If unexplained severe muscle symptoms or fatigue develop during statin therapy:

- Promptly discontinue the statin
- Address possibility of rhabdomyolysis with:
  - CK
  - Creatinine
  - Urinalysis for myoglobinuria

# Management of Muscle Symptoms on Statin Therapy (cont.)

If mild-to-moderate muscle symptoms develop during statin therapy:

- Discontinue the statin until the symptoms are evaluated
- Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
- If after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms

*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency or primary muscle diseases

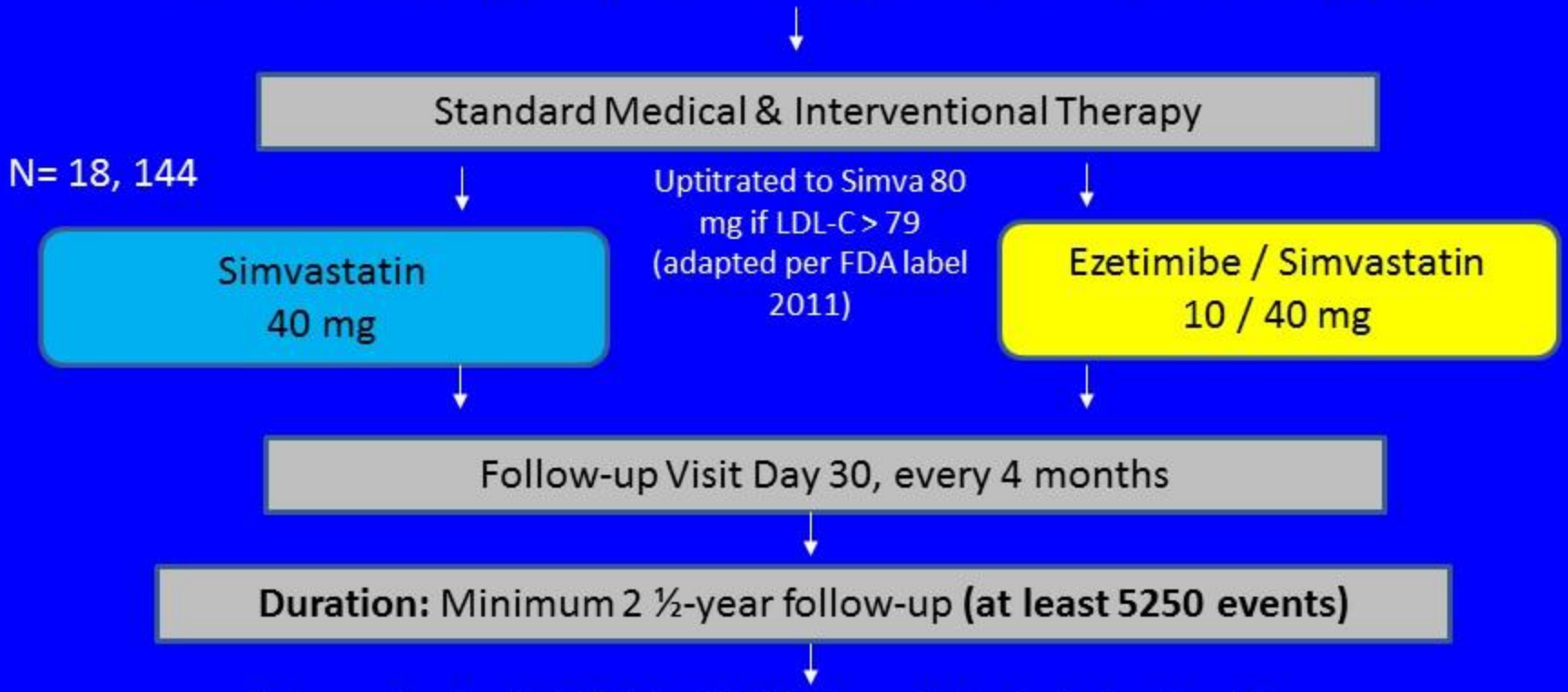
# Statin-Treated Individuals
# Nonstatin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a nonstatin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - *Clinical* ASCVD <75 years of age
    - Baseline LDL-C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred

# IMPROVE-IT Study Design

## Patients stabilized post ACS ≤ 10 days:

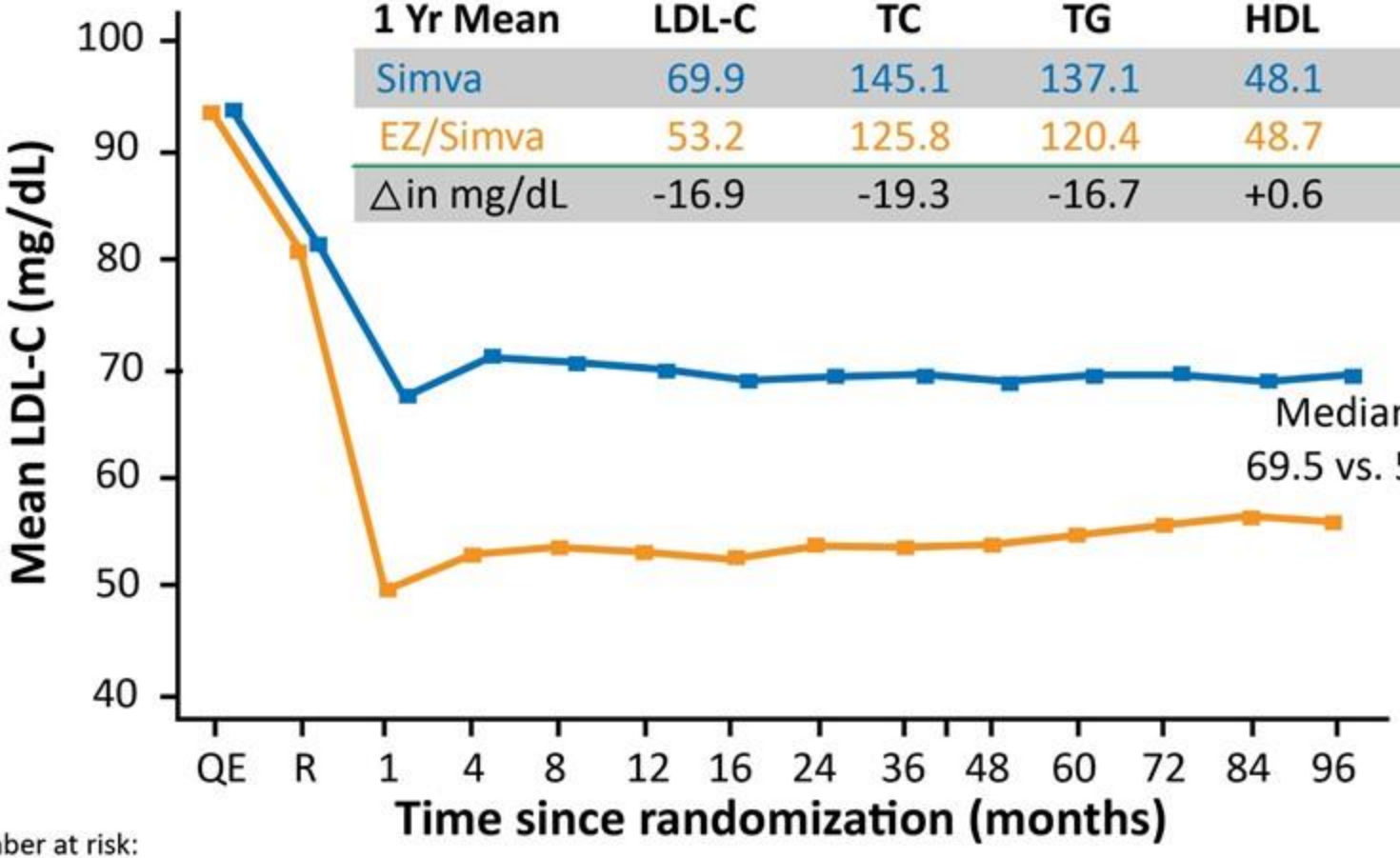
LDL-C 50 – 125 mg/dL (or 50-100 mg/dL if prior lipid-lowering Rx)




Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

# LDL-C and Lipid Changes

| 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 |
| △in mg/dL | -16.9 | -19.3 | -16.7 | +0.6 | -0.5 |

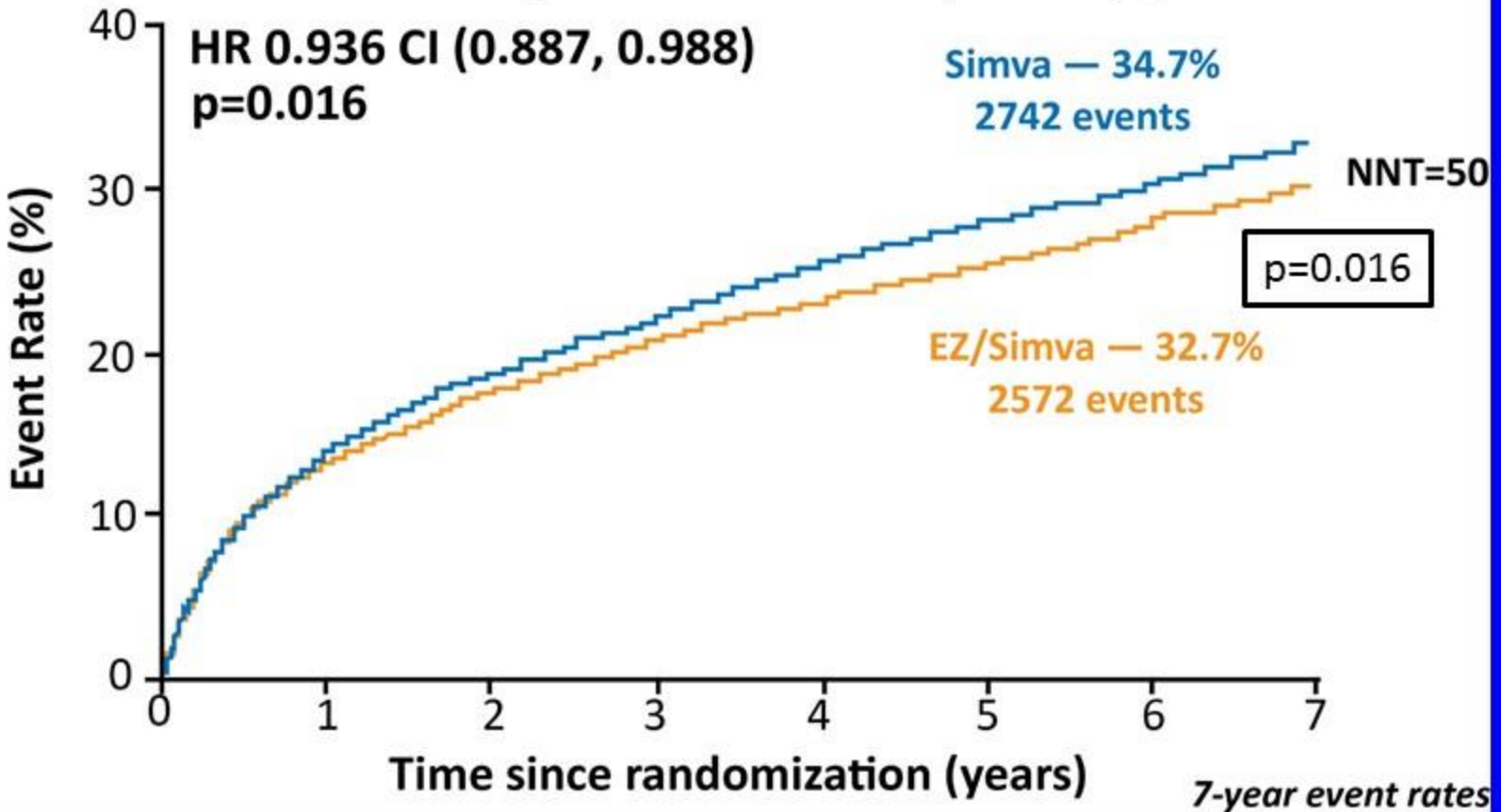



Number at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EZ/Simva | 8990 | 8889 | 8230 | 7701 | 7264 | 6864 | 6583 | 6256 | 5734 | 5354 | 4508 | 3484 | 2608 | 1078 |

# Primary Endpoint—ITT

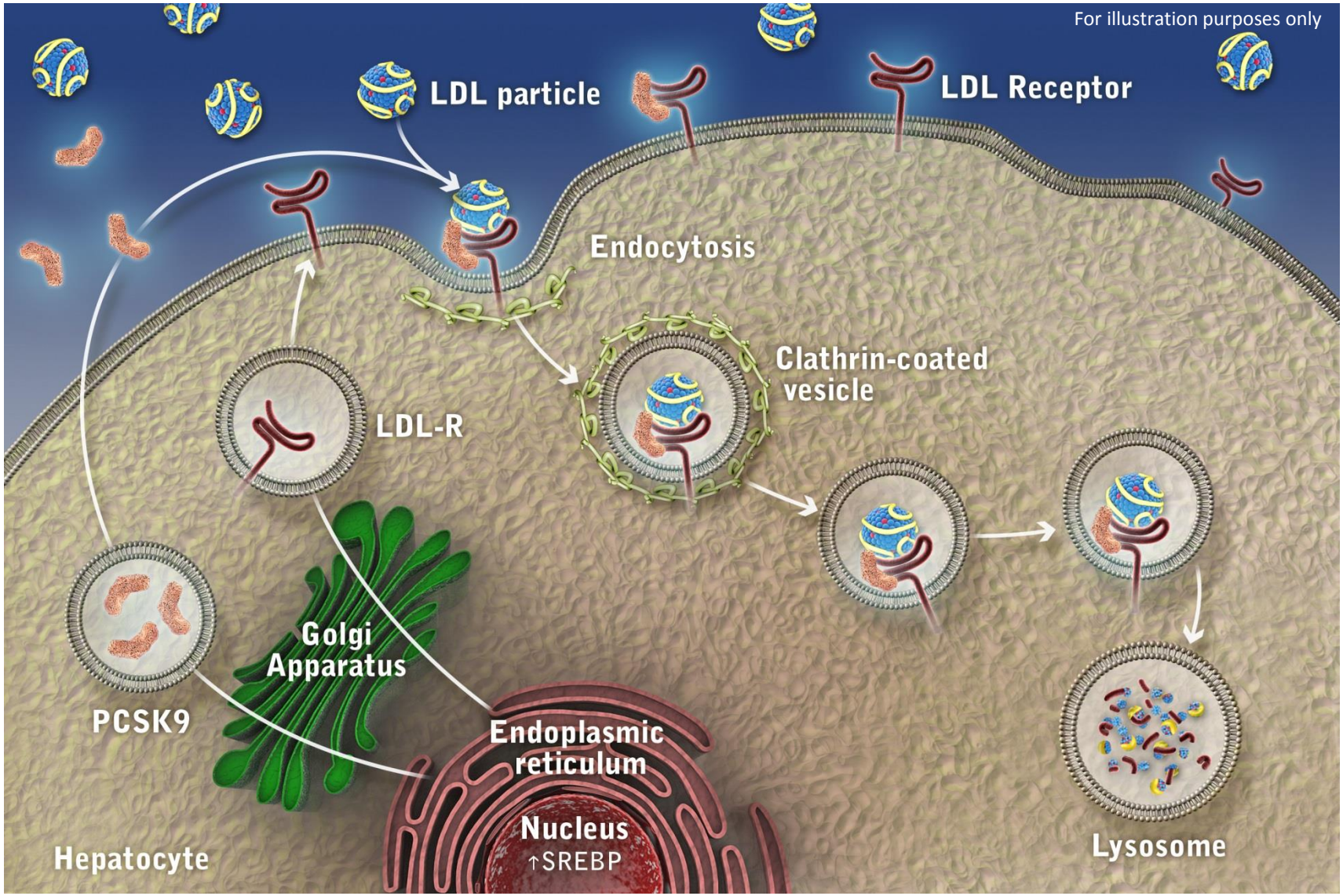
*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*



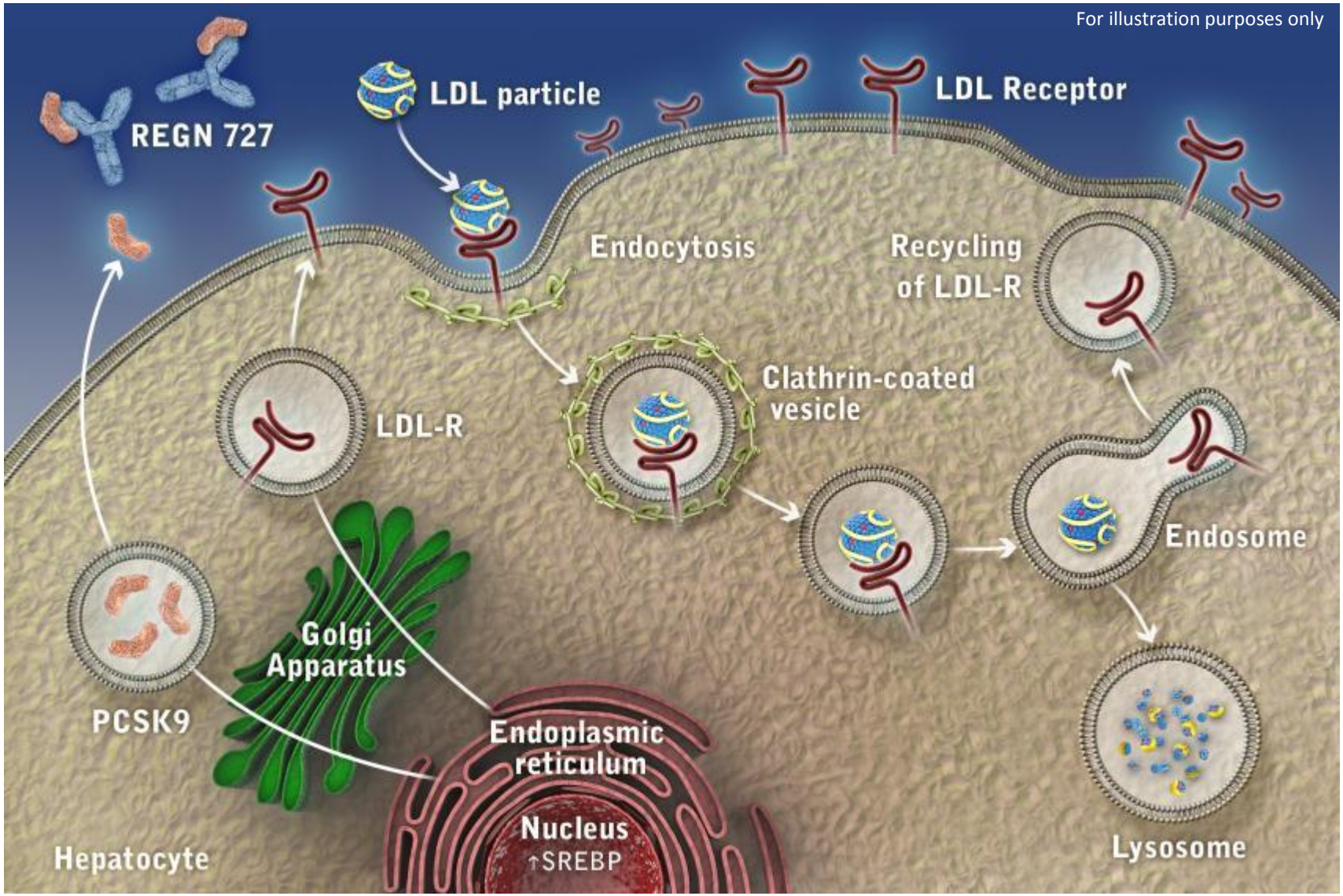
# Summary of Key Differences

| | ATP-III | AHA/ACC |
|---|---|---|
| Basis for recommendations | Expert opinion based on pathophysiology, observational, & RCT data | Evidence-based recommendations based on RCTs and systematic reviews |
| Risk stratification | CHD equivalents, risk factors, 10-year risk of MI | 4 specific risk groups based on benefits in clinical trials |
| Risk calculation | Framingham risk score | Pooled cohort equation |
| Goals of therapy | LDL & non-HDL levels (stratified by risk) | Statin intensity (% LDL reduction) |
| Role for monitoring | Fasting lipid panel to assess achievement of goal | Fasting lipid panel to assess adherence/therapeutic response |
| Role of non-statin agents | Encouraged use if needed to achieve LDL or non-HDL goal | Discourages use in most patients because of lack of evidence on improving outcomes |

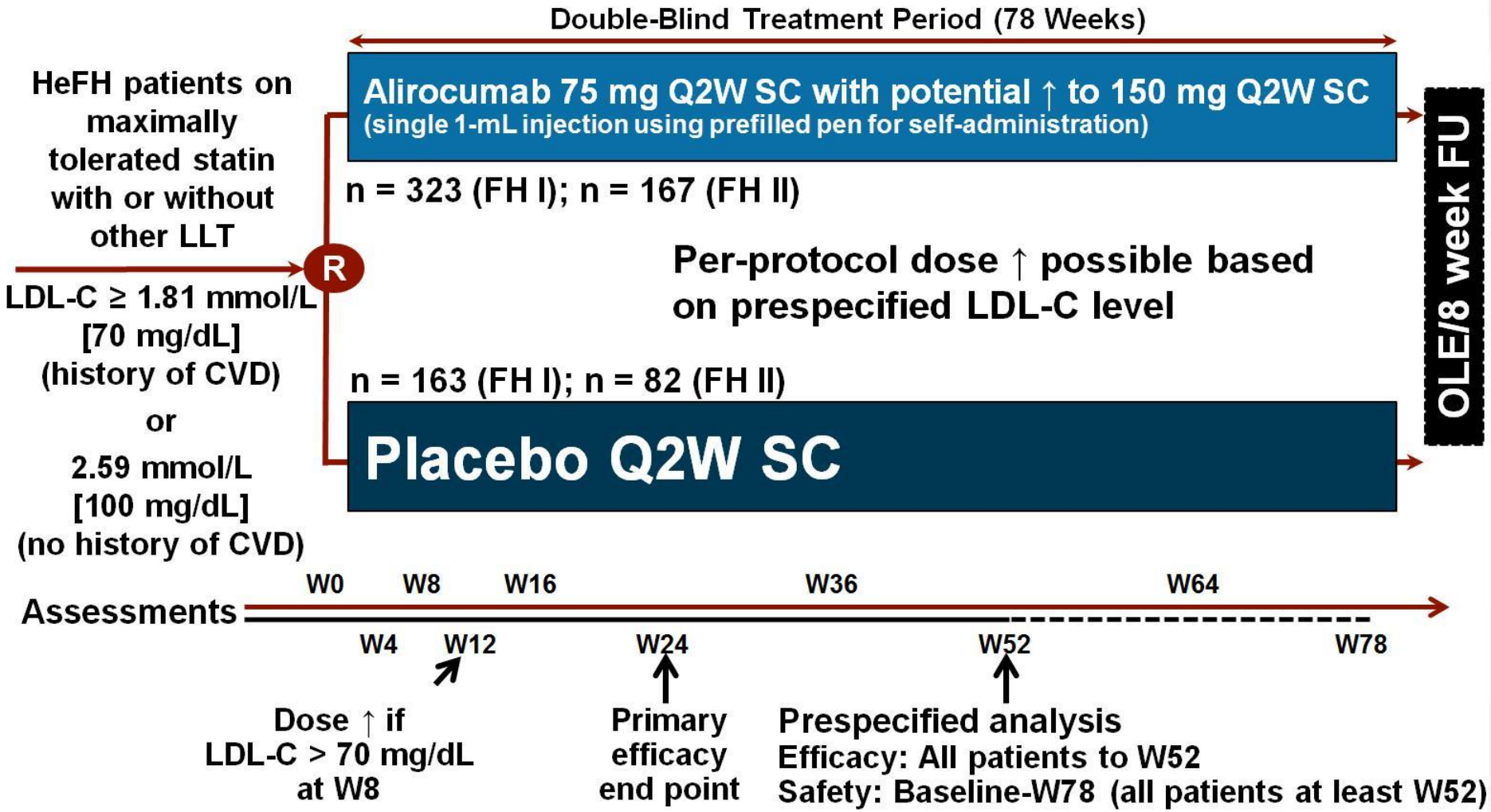
# The Role of PCSK9 in the Regulation of LDL Receptor Expression



# Impact of an PCSK9 mAb on LDL Receptor Expression



# Alirocumab Trials
## *ODYSSEY FH I and FH II Studies*



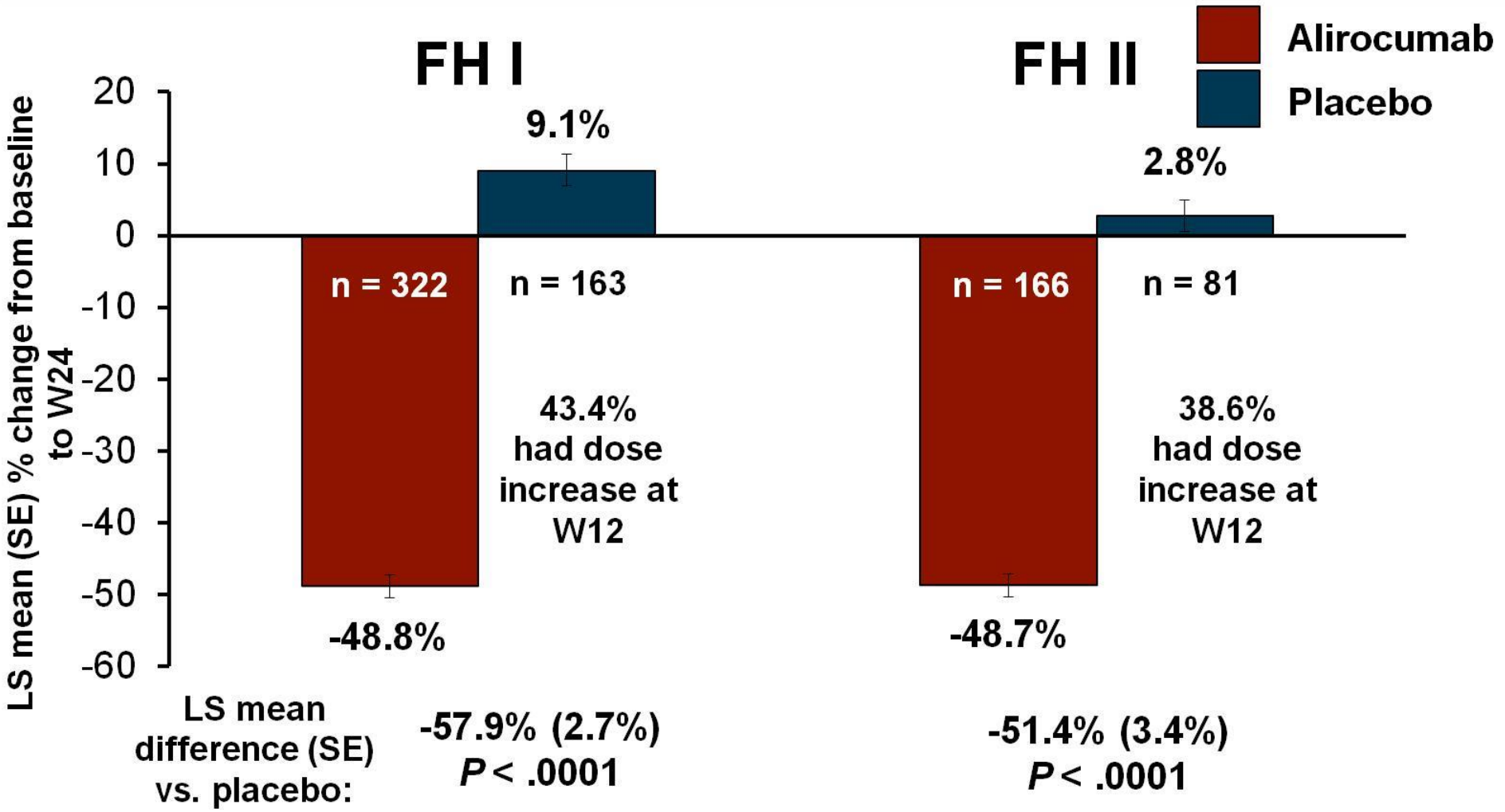

ClinicalTrials.gov. NCT01623115; ClinicalTrials.gov. NCT01709500; Kastelein JJ, et al. ESC. 2014.

# FH I and FH II
## *Baseline Characteristics*

- Patients recruited from lipid centers (well treated)
- Mean age: 51.7 to 53.2 years
- Sex distribution: 51.5% to 57.7% male
- CHD history: 34.1% to 47.9%
- All patients with background of maximally tolerated statin with or without other LLT
  - High-intensity statin (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily): 80.8% to 87.8%
  - Ezetimibe: 55.7% to 67.1%
- **Mean LDL-C: 3.5 to 3.7 mmol/L**

Kastelein JJ, et al. ESC. 2014.

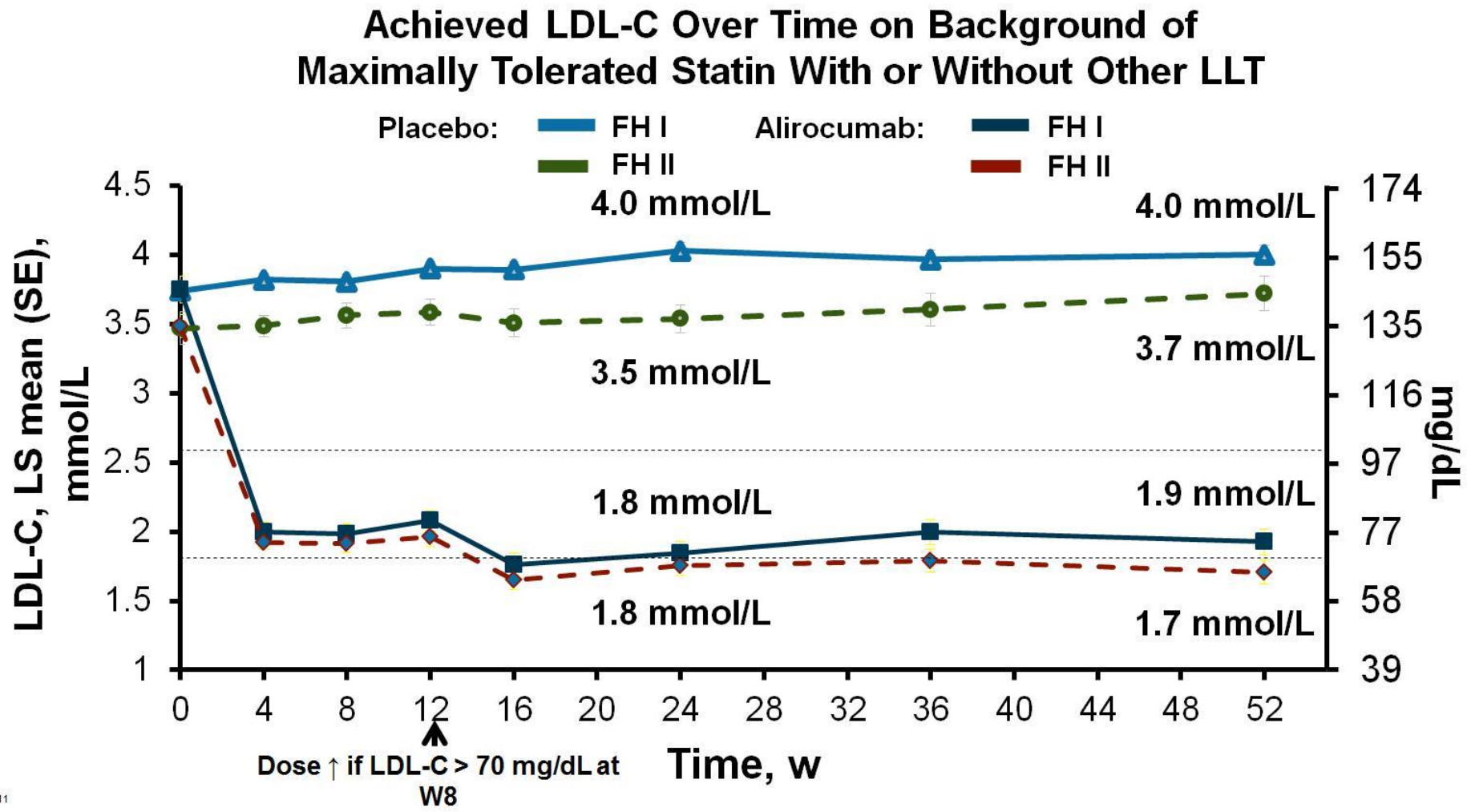
# FH I and FH II
## *Results at W24*




ITT analysis.

Kastelein JJ, et al. ESC. 2014..

# FH I and FH II
## *Results Over 52 Weeks*



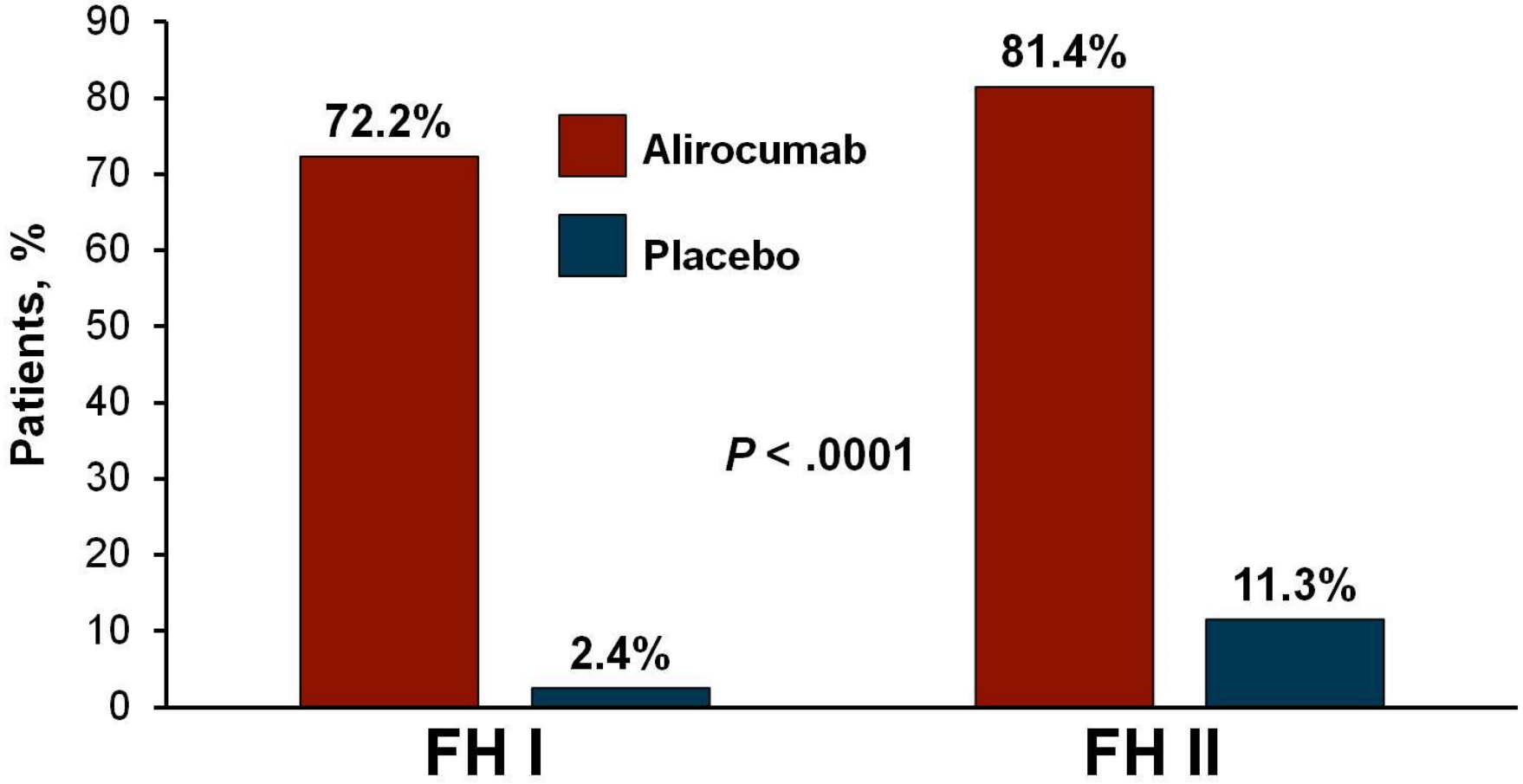

11

ITT analysis.

Kastelein JJ, et al. ESC. 2014.

# FH I and FH II

## *Percentage Reaching LDL-C Goals at W24*

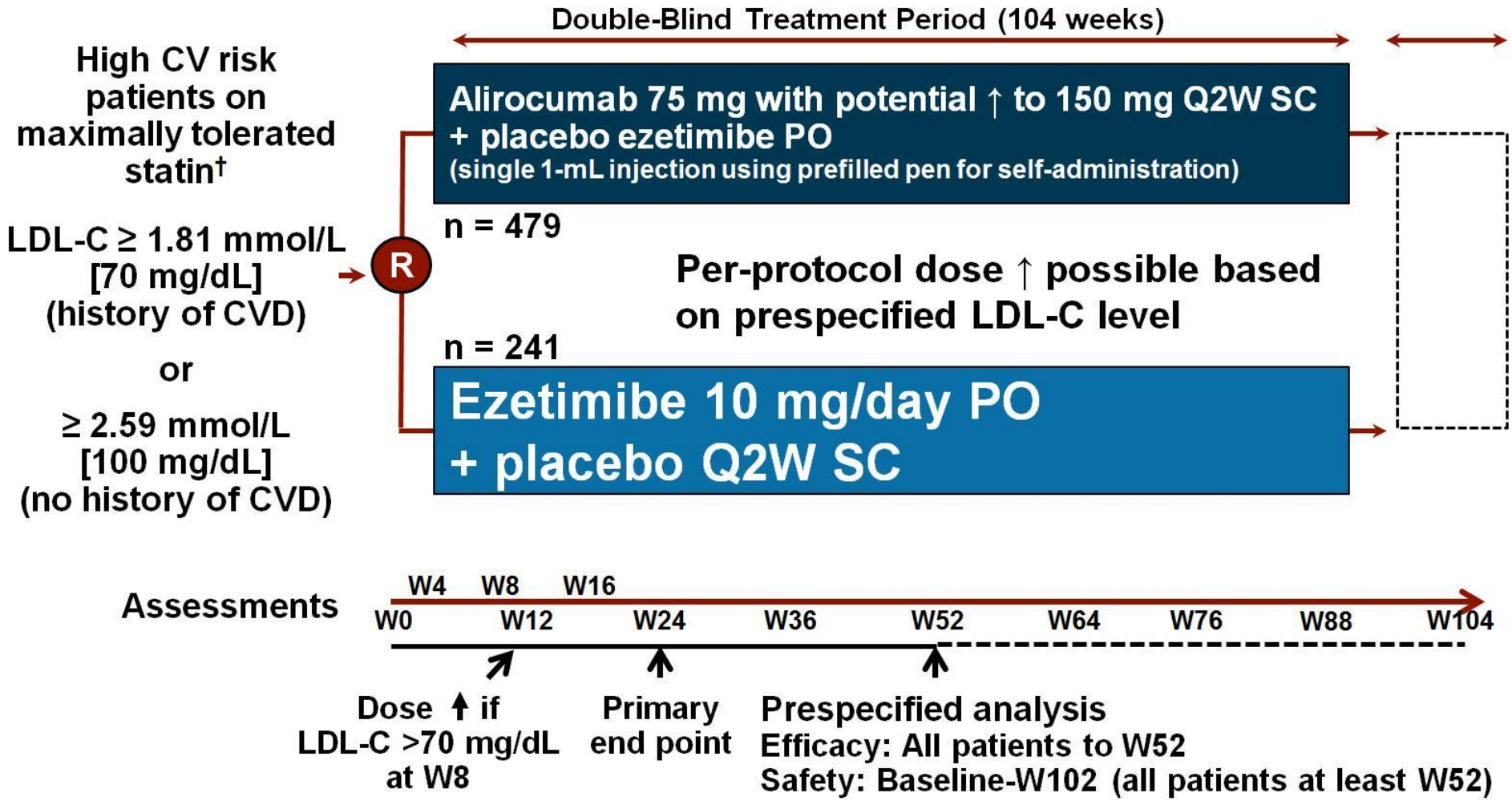



†Very high risk: < 1.81 mmol/L (70 mg/dL); high risk: < 2.59 mmol/L (100 mg/dL).

ITT analysis.

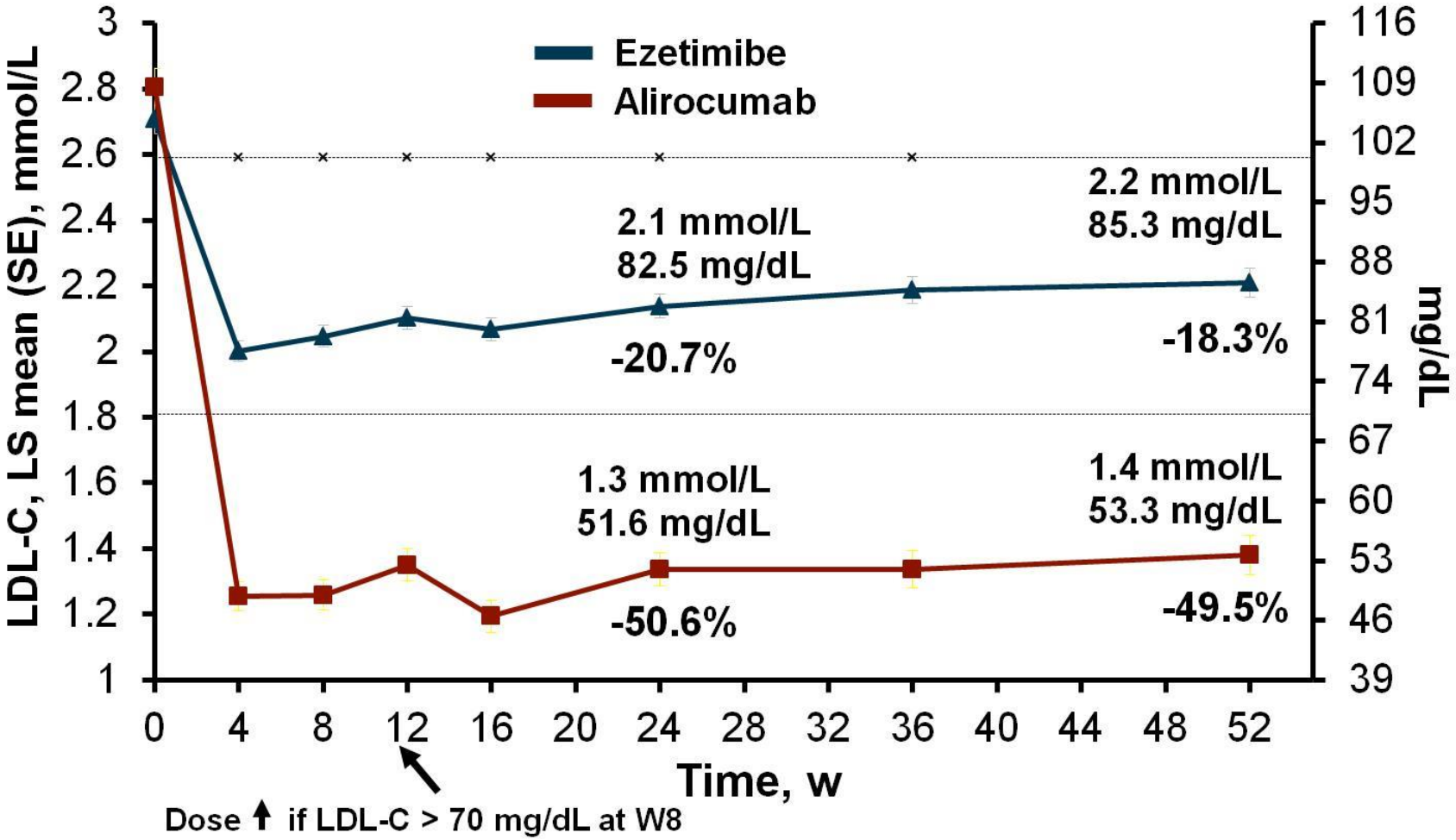
Kastelein JJ, et al. ESC. 2014.

# ODYSSEY Combo II Study




Cannon CP, et al. ESC. 2014.

# Combo II
## *Results Over 52 Weeks*

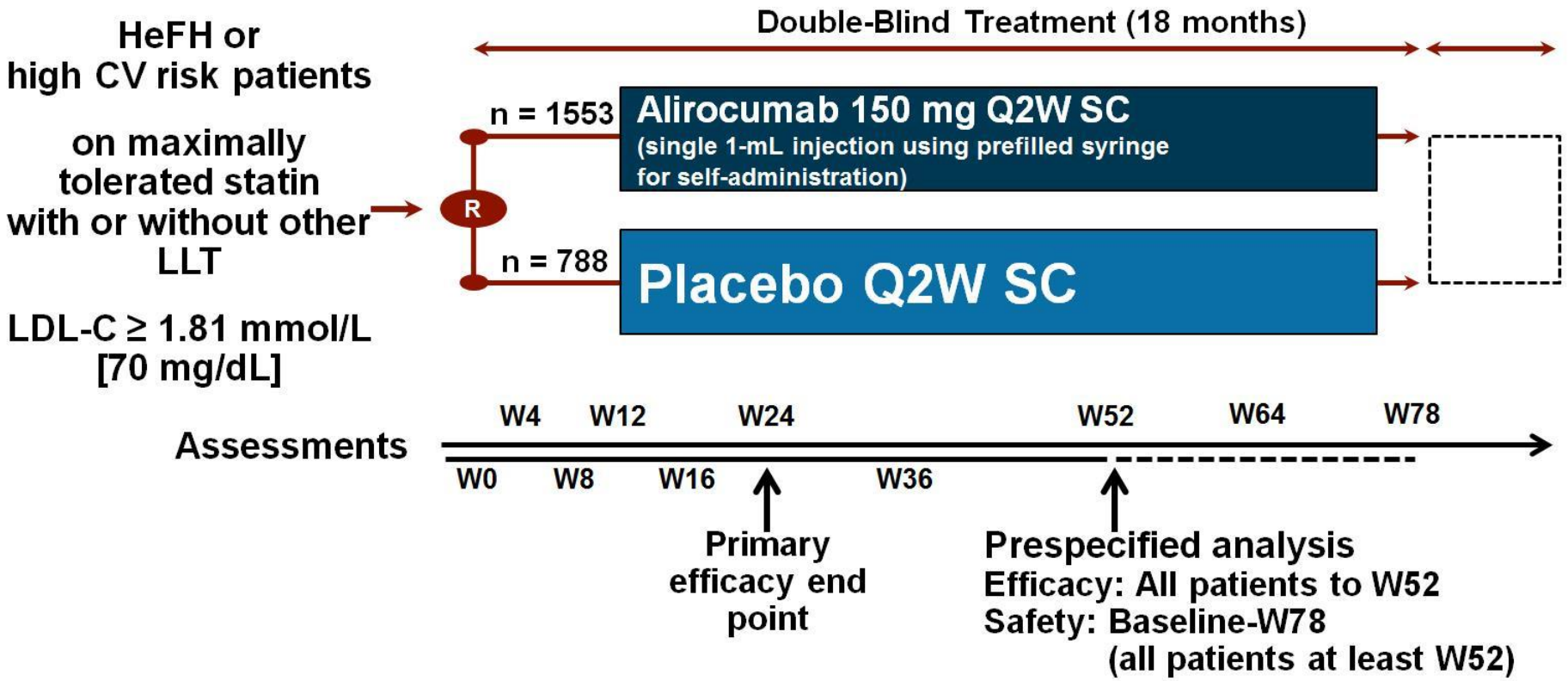



ITT analysis.

Cannon CP, et al. ESC. 2014.

# ODYSSEY Long-term Study

## *Design*




**86% (2011/2341) completed 52 weeks (both treatment arms)**

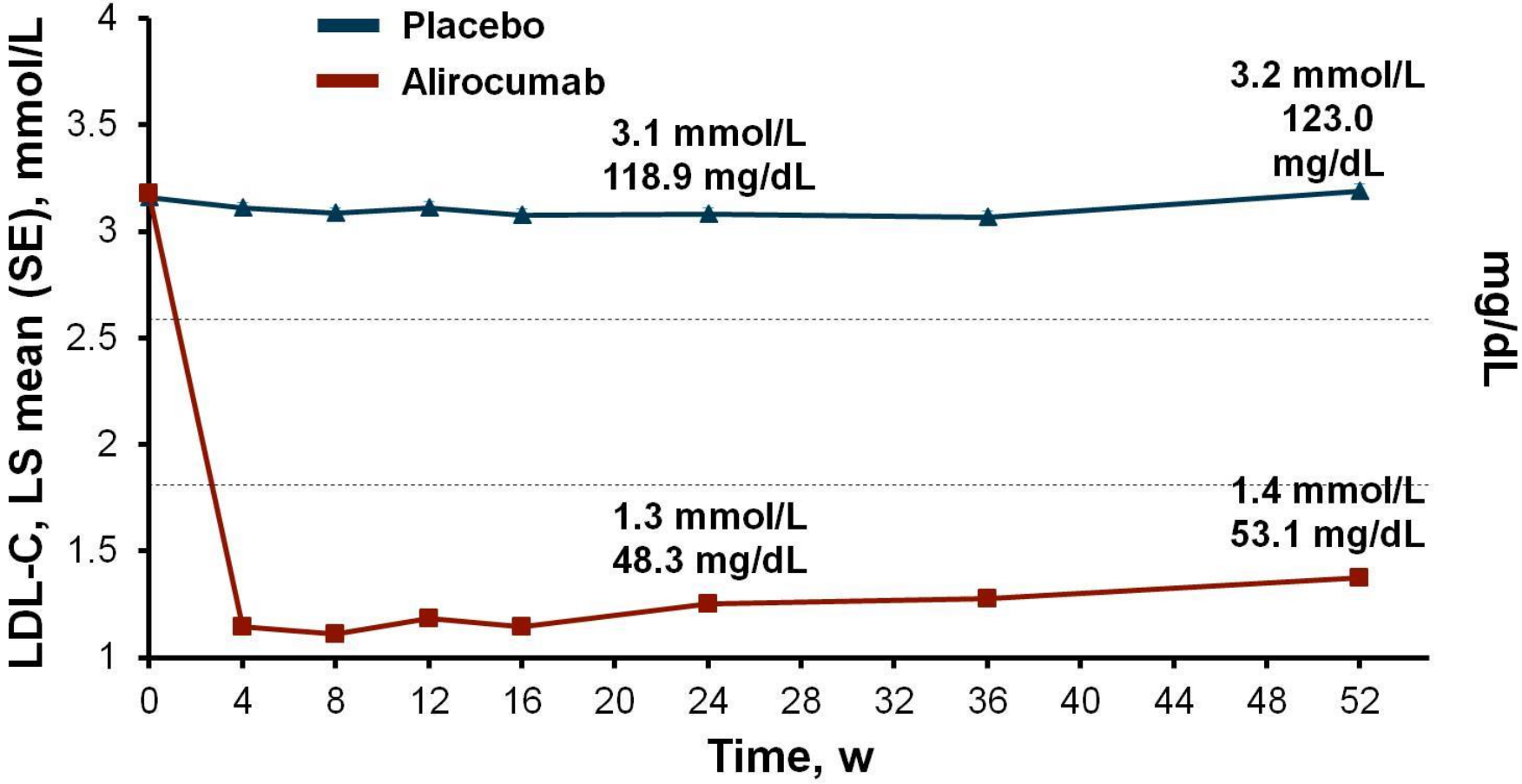
**26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis**

**Mean treatment duration: 65 weeks (both treatment arms)**

ClinicalTrials.gov. NCT01507831.
Robinson J, et al. ESC. 2014.

# ODYSSEY Long-term Study

## *LDL-C Reduction*

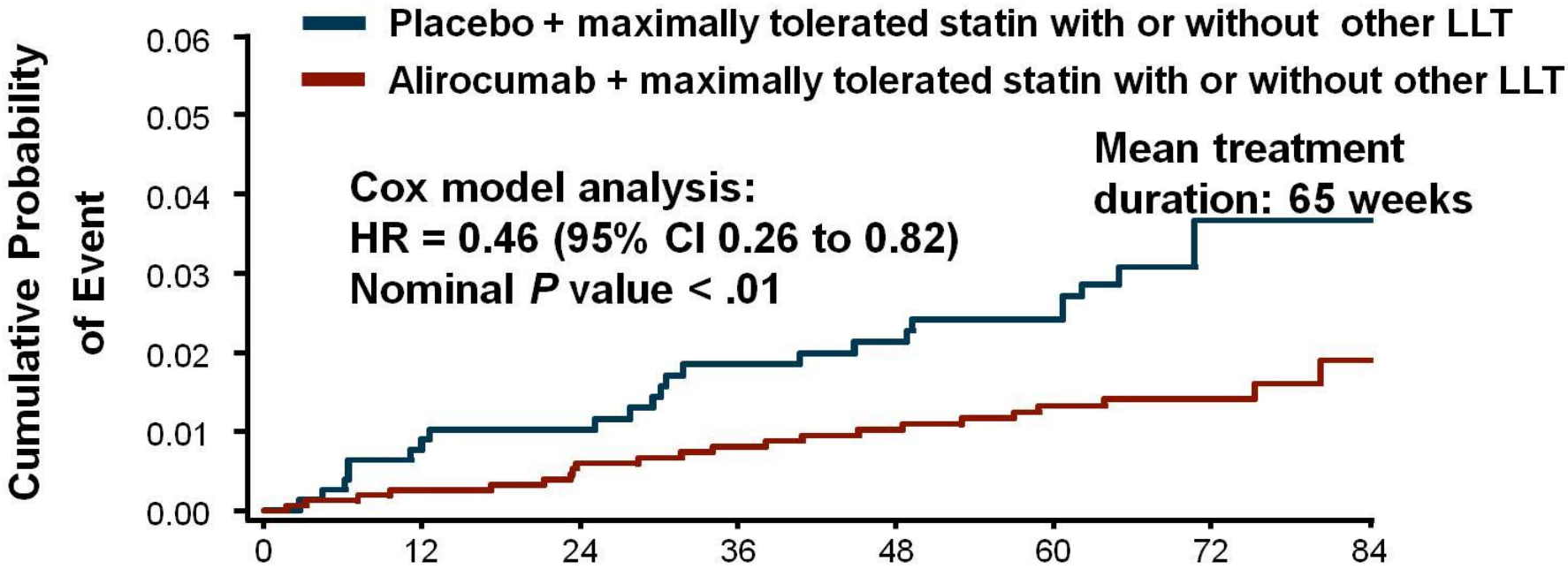



Robinson J, et al. ESC. 2014.

# ODYSSEY Long-term Study

## *CV Death*

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event
Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 788 | 776 | 731 | 703 | 682 | 667 | 321 | 127 |
| Alirocumab | 1550 | 1534 | 1446 | 1393 | 1352 | 1335 | 642 | 252 |

*Primary end point for the ODYSSEY Outcomes trial: CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, UA requiring hospitalization.

Robinson J, et al. ESC. 2014.

# Results of the GLAGOV Trial

## Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound

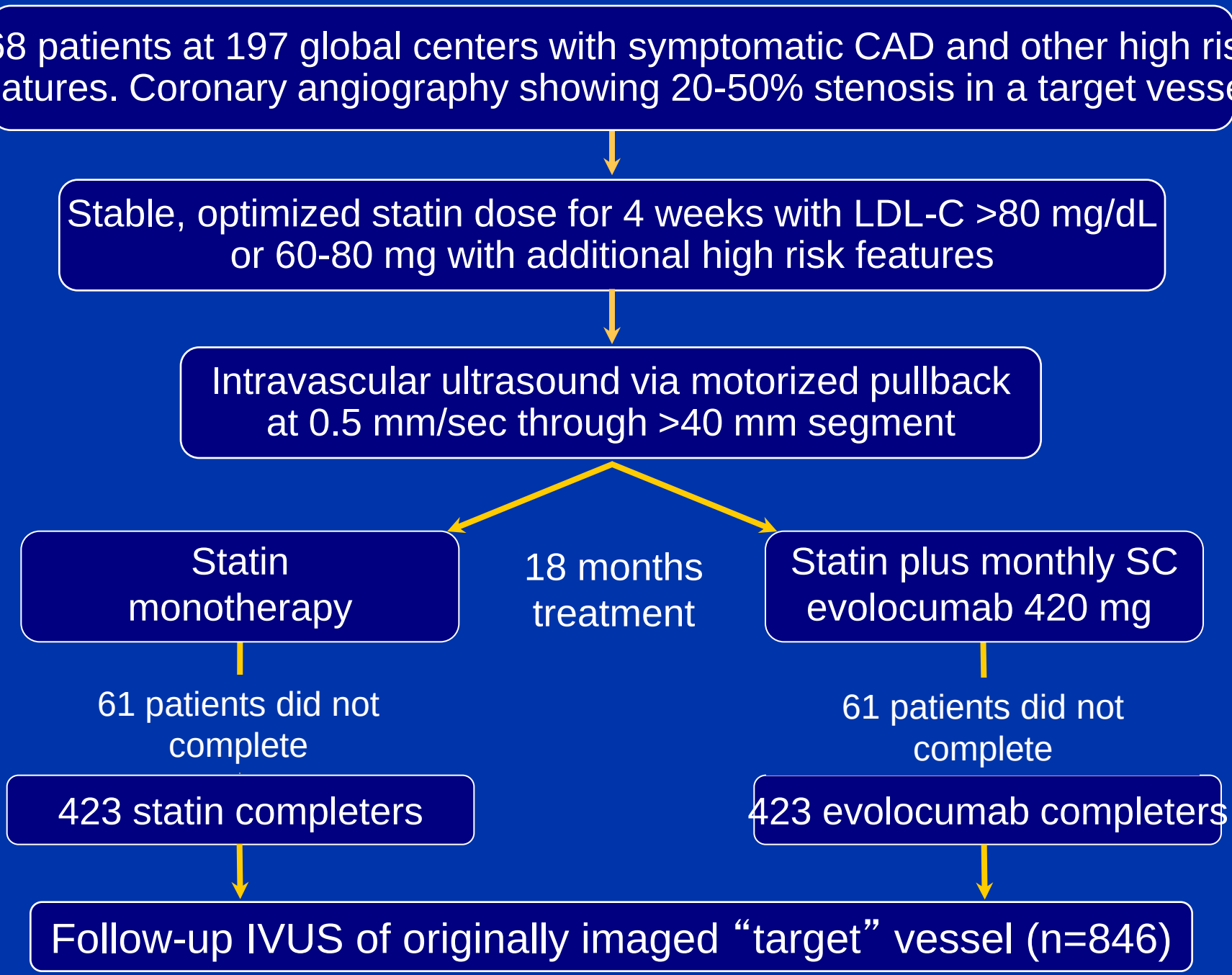
Steven E. Nissen MD
Stephen J. Nicholls MBBS PhD

### Disclosure

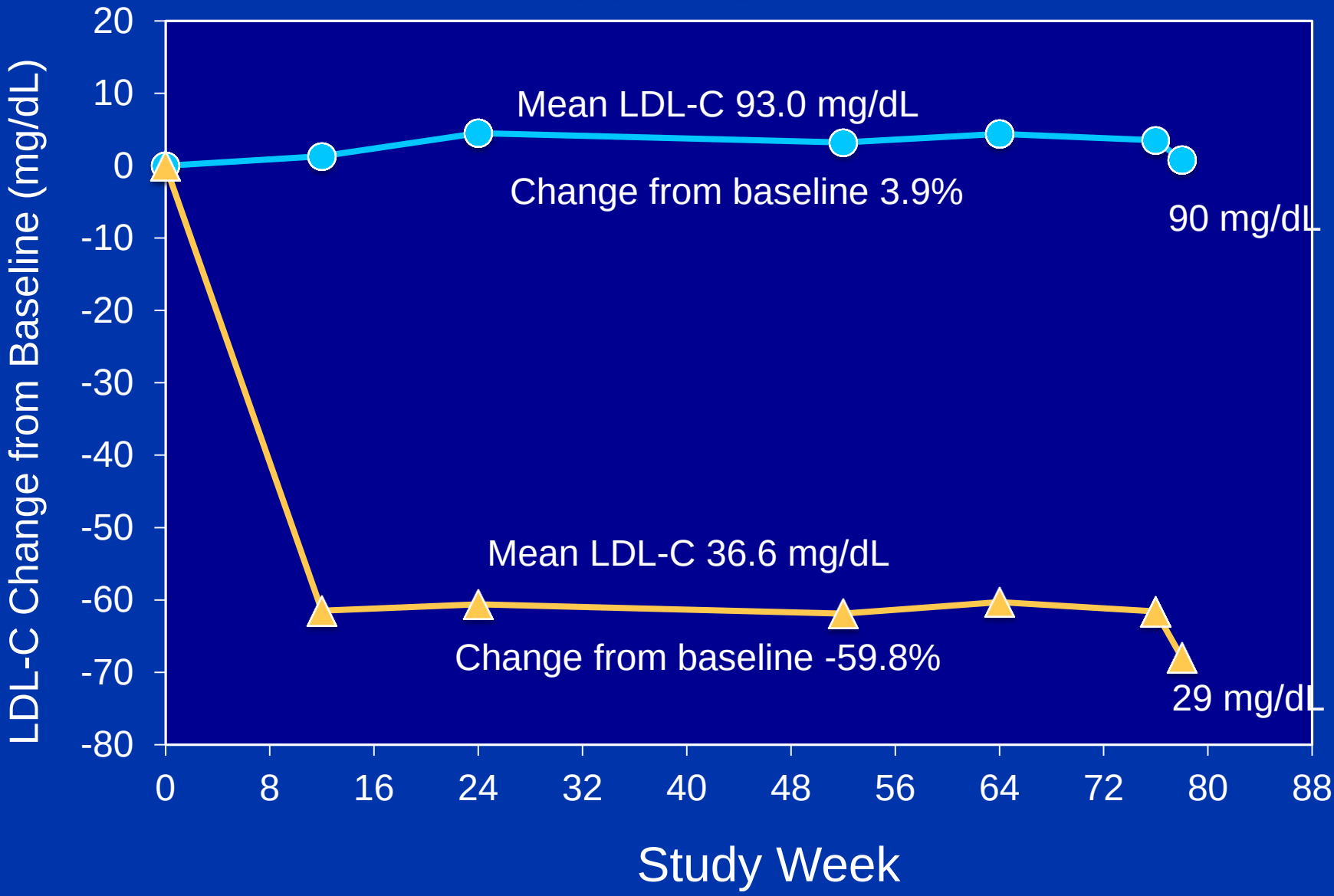
***Sponsor:*** Amgen

***Clinical Trials:*** Abbvie**,** Amgen, AstraZeneca, Cerenis, Eli Lilly, Esperion, Takeda, Novo Nordisk, The Medicines Company, and Pfizer.

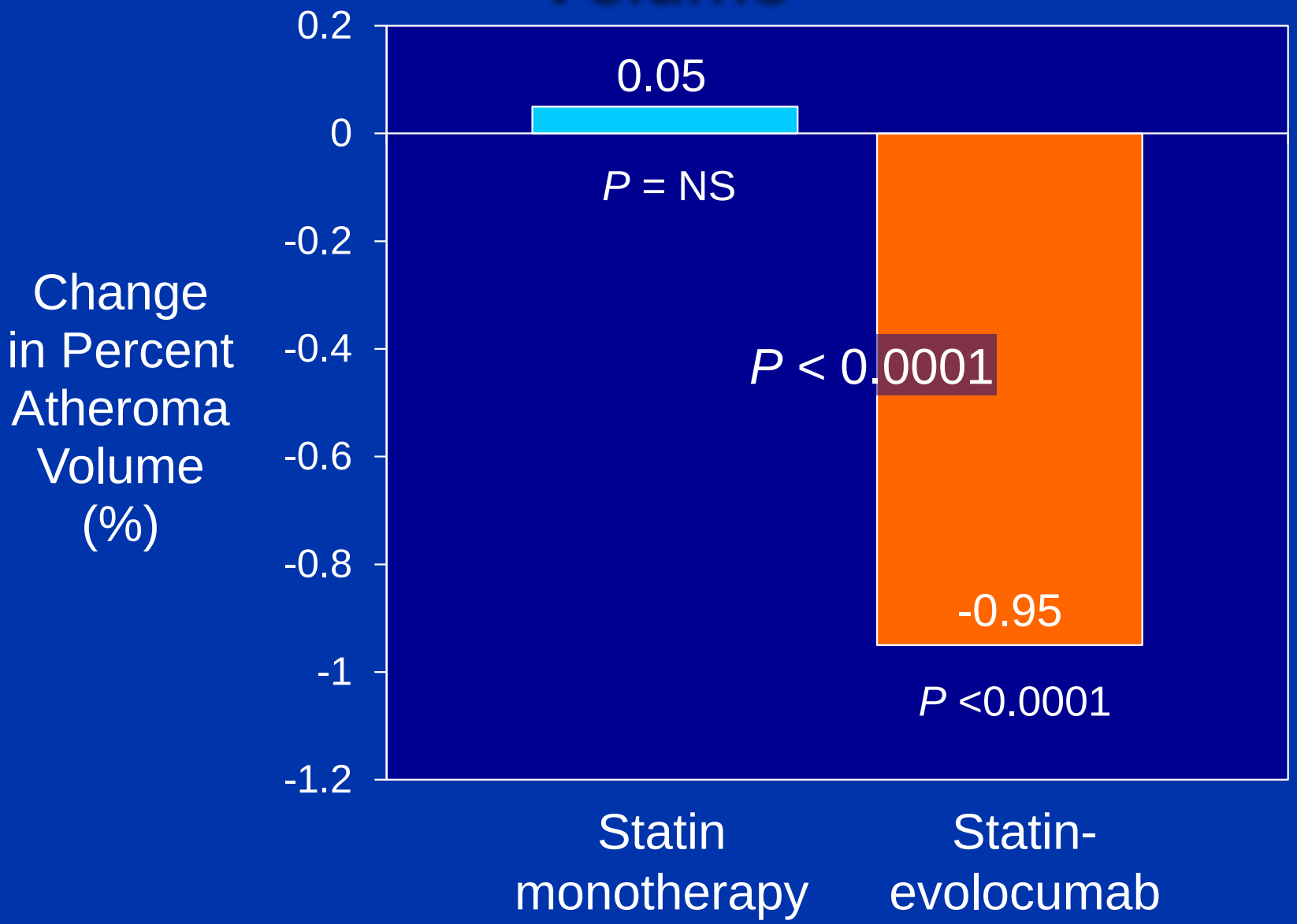
Companies are directed to pay any honoraria directly to charity. No personal reimbursement is accepted for directing or participating in clinical trials.


968 patients at 197 global centers with symptomatic CAD and other high risk features. Coronary angiography showing 20-50% stenosis in a target vessel
Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features
Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment
Statin monotherapy
18 months treatment
Statin plus monthly SC evolocumab 420 mg
61 patients did not complete
61 patients did not complete
423 statin completers
423 evolocumab completers
Follow-up IVUS of originally imaged “target” vessel (n=846)

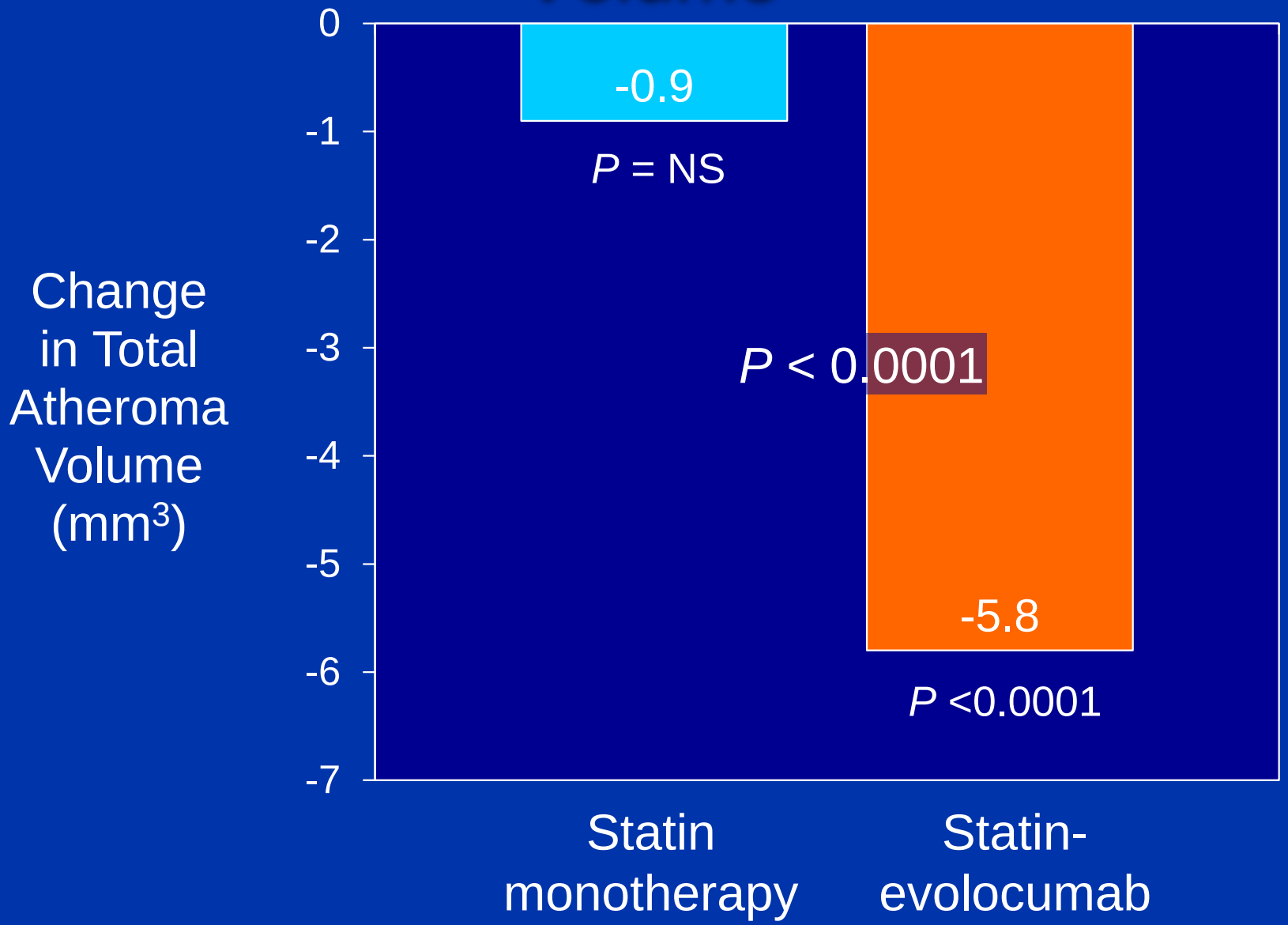
# Change in LDL-Cholesterol During Treatment



# Primary Endpoint: Percent Atheroma Volume



# Secondary Endpoint: Total Atheroma Volume



# FOURIER

## Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

*American College of Cardiology – 66th Annual Scientific Session*

*Late-Breaking Clinical Trial*

*March 17, 2017*

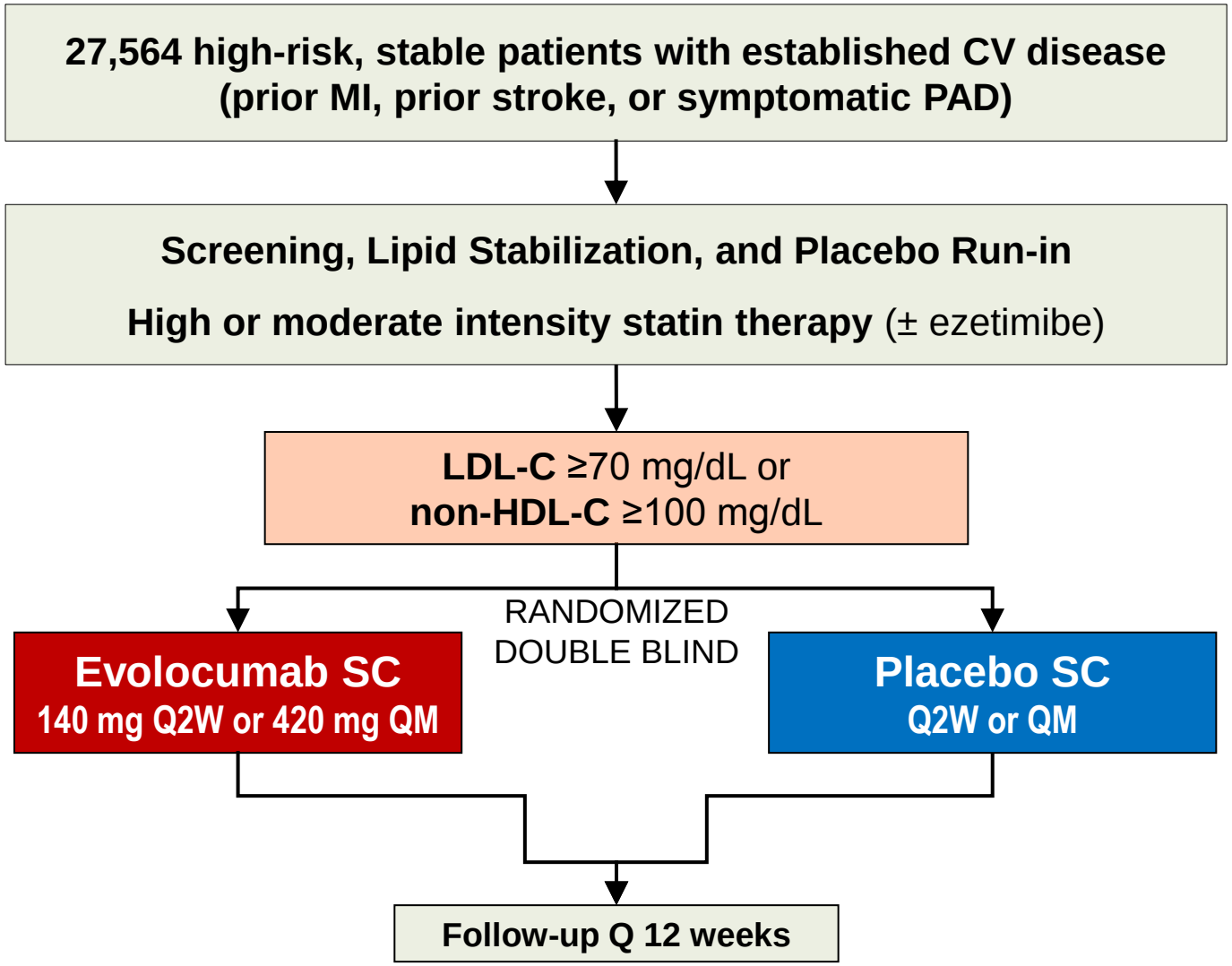
**An Academic Research Organization of**
**Brigham and Women's Hospital and Harvard Medical School**

# Objectives

***In patients with established cardiovascular disease on statin therapy:***

- **Test whether the addition of evolocumab reduces the incidence of major cardiovascular events**
- **Examine the long-term safety & tolerability of evolocumab**
- **Investigate the efficacy and safety of achieving unprecedented low levels of LDL-C**

# Trial Design






Sabatine MS et al. *Am Heart J* 2016;173:94-101

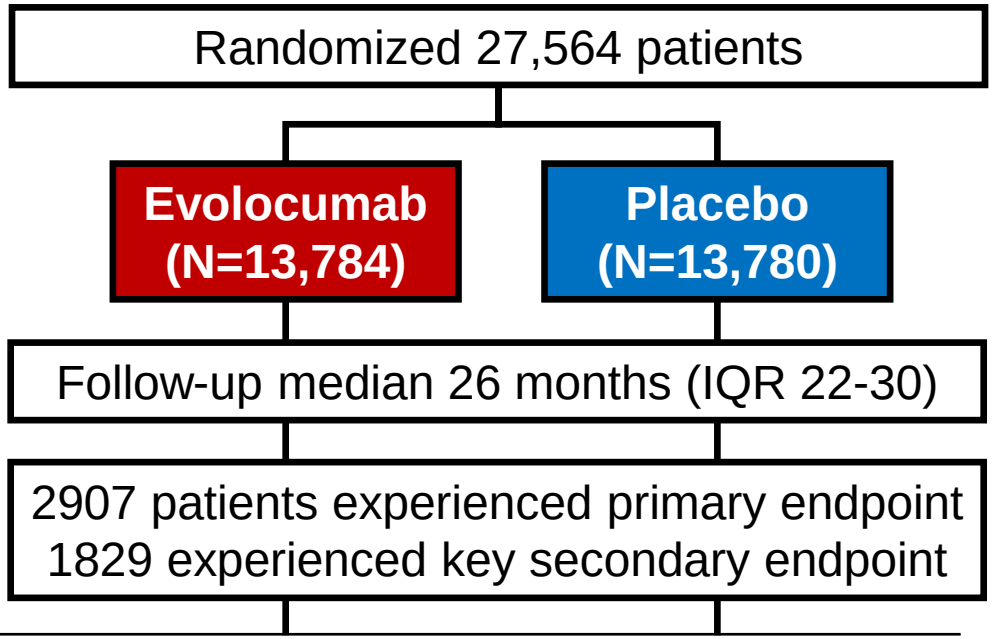
# Endpoints

- **Efficacy**
  - **Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc**
  - **Key secondary: CV death, MI or stroke**
- **Safety**
  - **AEs/SAEs**
  - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
  - **Development of anti-evolocumab Ab (binding and neutralizing)**
- **TIMI Clinical Events Committee (CEC)**
  - **Adjudicated all efficacy endpoints & new-onset diabetes**
  - **Members unaware of treatment assignment & lipid levels**



Sabatine MS et al. *Am Heart J* 2016;173:94-101

# Follow-up




| | | |
|---|---|---|
| **Premature perm. drug discontinuation** | **5.6%/yr** | **5.8%/yr** |
| **Withdrew consent** | **0.29%/yr** | **0.35%/yr** |
| **Lost to follow-up** | **5 patients** | **13 patients** |

*Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up*

# Baseline Characteristics

| Characteristic | Value |
|---|---|
| **Age**, years, mean (SD) | **63 (9)** |
| **Male sex** (%) | **75** |
| **Type of cardiovascular disease** (%) | |
| Myocardial infarction | **81** |
| Stroke (non-hemorrhagic) | **19** |
| Symptomatic PAD | **13** |
| **Cardiovascular risk factor** (%) | |
| Hypertension | **80** |
| Diabetes mellitus | **37** |
| Current cigarette use | **28** |

**Median time from most recent event ~3 yrs**



Pooled data; no differences between treatment arms

# Lipid Lowering Therapy & Lipid Levels at Baseline

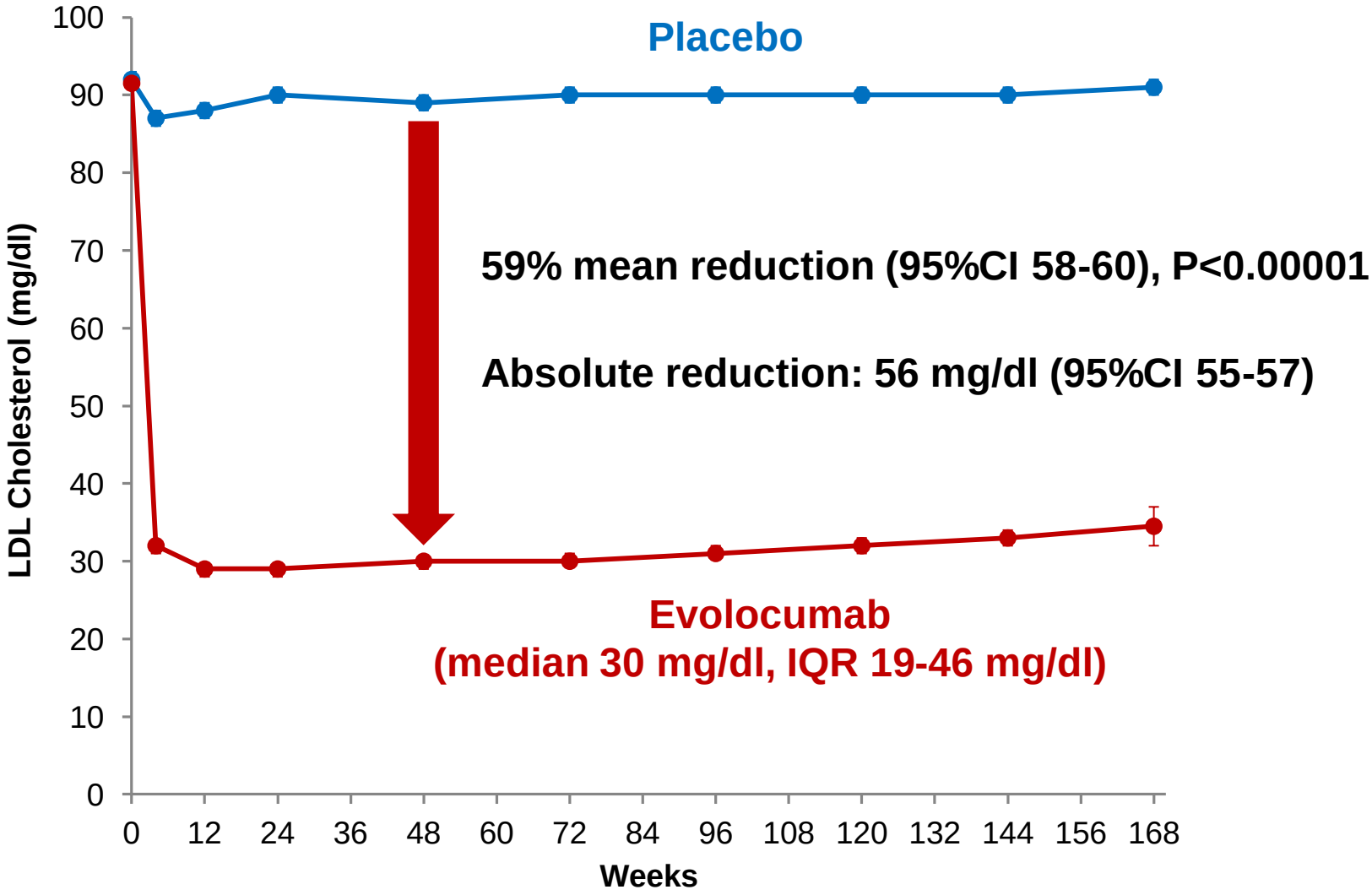
| Characteristic | Value |
|---|---|
| **Statin use** (%)* | |
| High-intensity | **69** |
| Moderate-intensity | **30** |
| **Ezetimibe use** (%) | **5** |
| **Median lipid measures** (IQR) – mg/dL | |
| LDL-C | **92 (80-109)** |
| Total cholesterol | **168 (151-189)** |
| HDL-C | **44 (37-53)** |
| Triglycerides | **133 (100-182)** |

*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

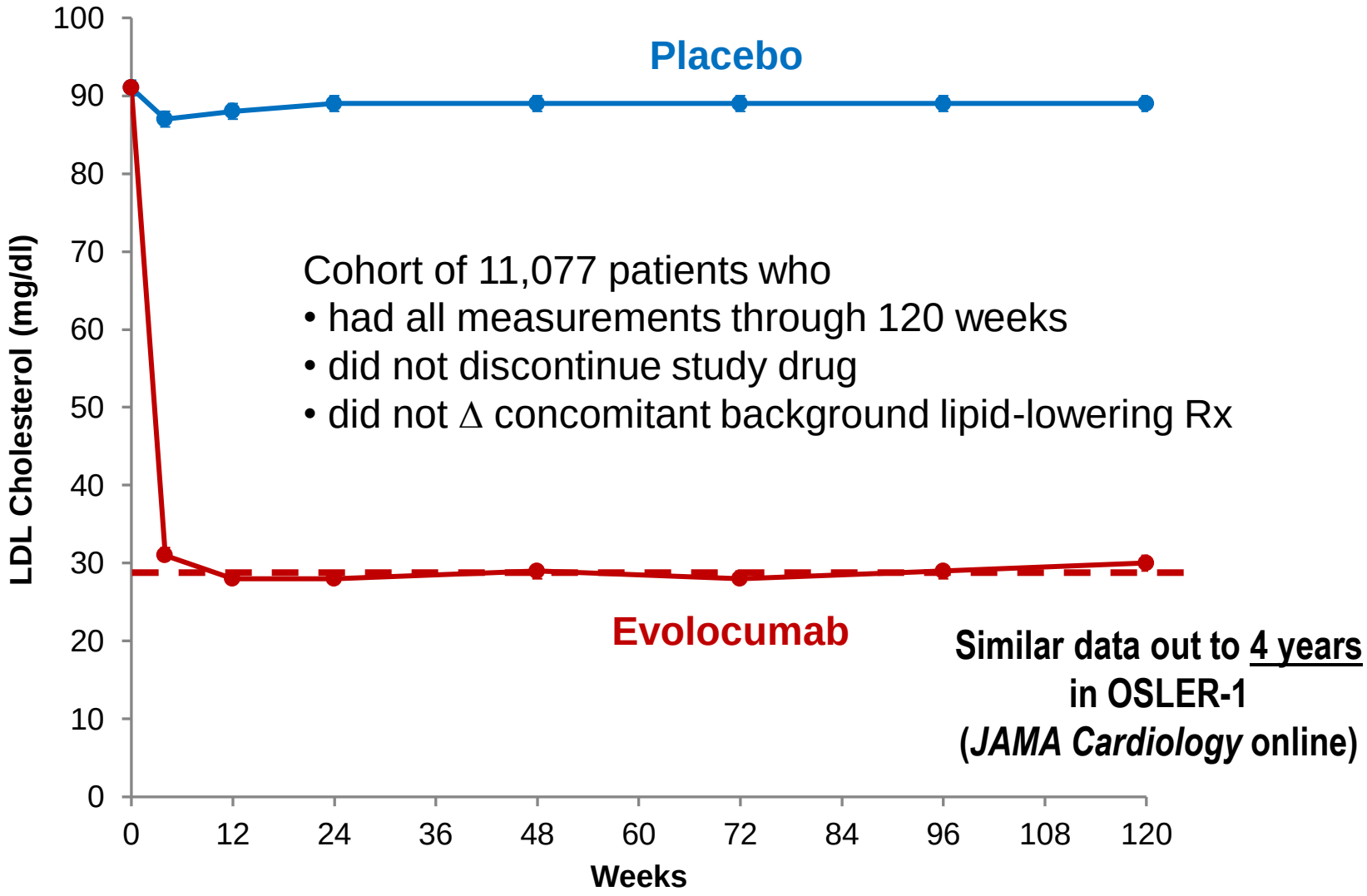


Pooled data; no differences between treatment arms

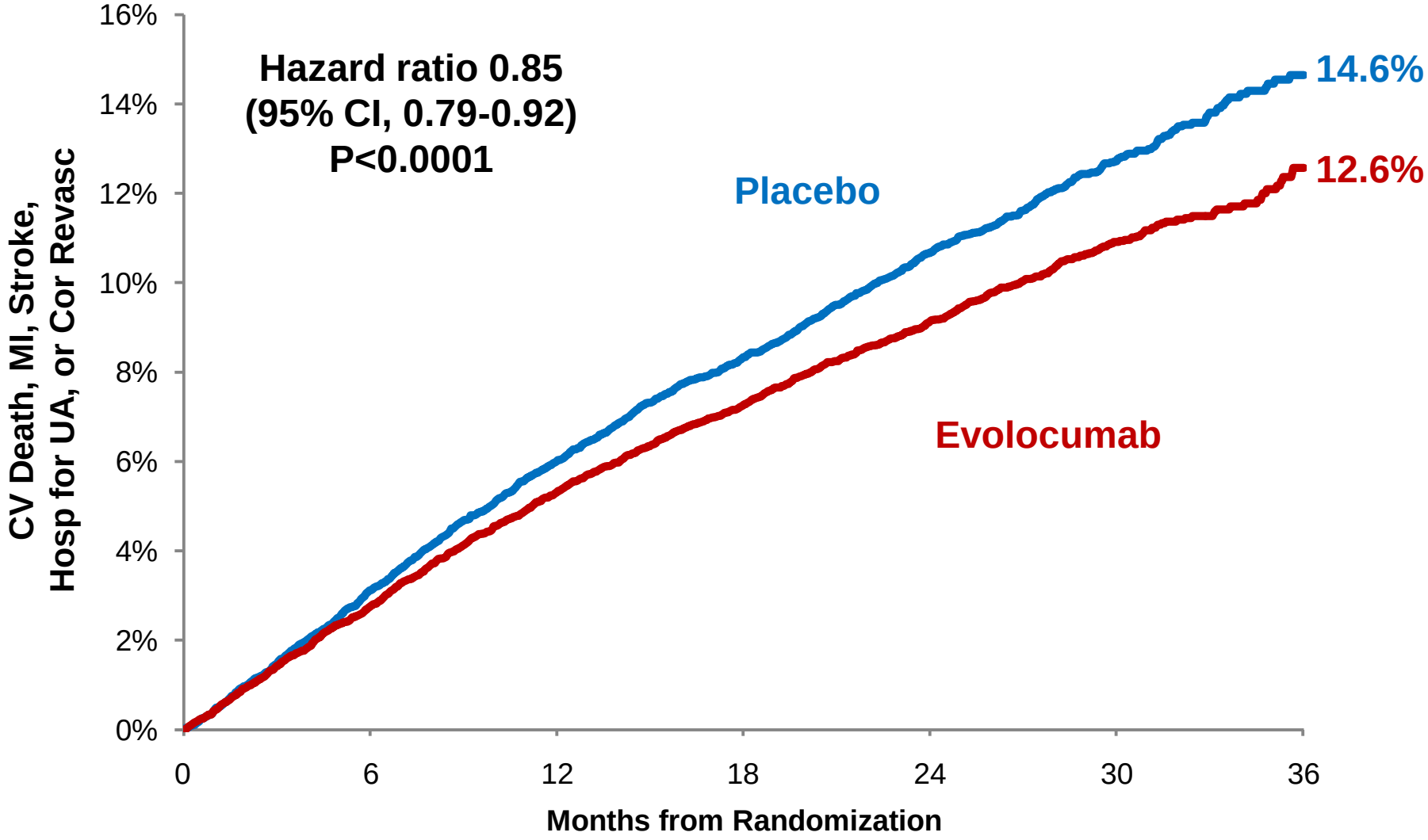
# LDL Cholesterol



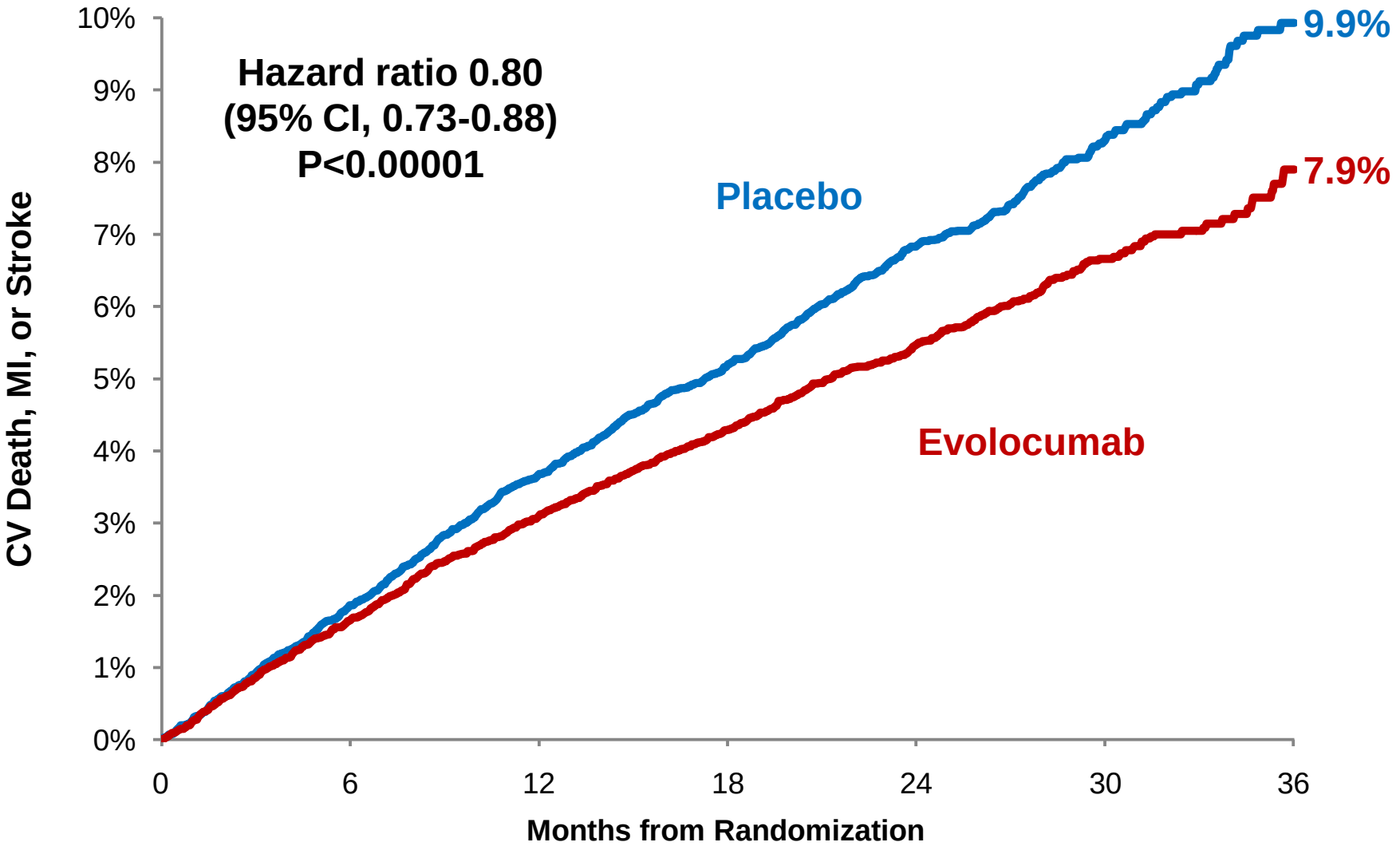
# LDL Cholesterol



# Primary Endpoint



# Key Secondary Endpoint



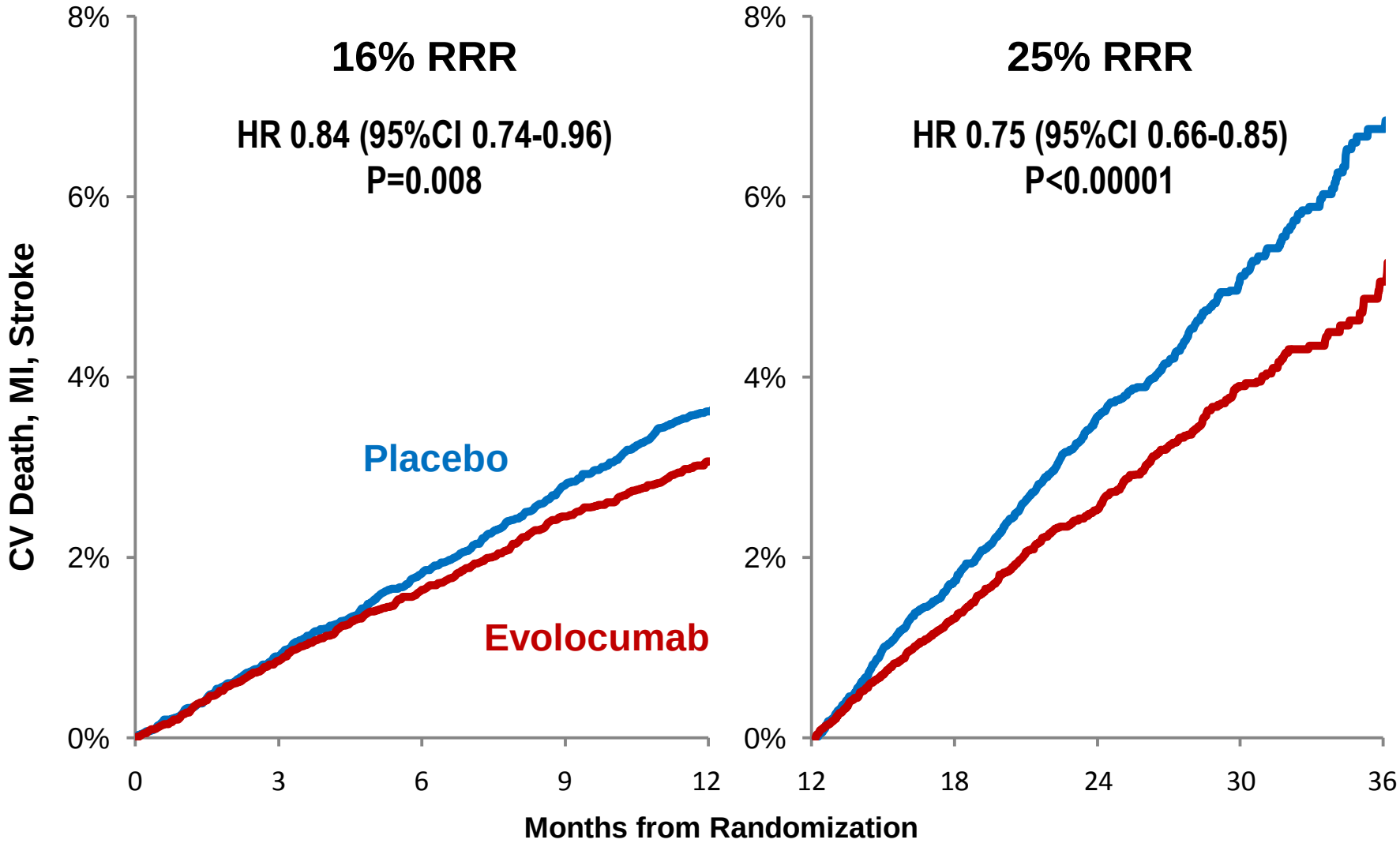
# Types of CV Outcomes

| Endpoint | Evolocumab (N=13,784) | Placebo (N=13,780) | HR (95% CI) |
|---|---|---|---|
| | *3-yr Kaplan-Meier rate* | | |
| **CV death, MI, or stroke** | **7.9** | **9.9** | **0.80 (0.73-0.88)** |
| **Cardiovascular death** | **2.5** | **2.4** | **1.05 (0.88-1.25)** |
| Death due to acute MI | 0.26 | 0.32 | 0.84 (0.49-1.42) |
| Death due to stroke | 0.29 | 0.30 | 0.94 (0.58-1.54) |
| Other CV death | 1.9 | 1.8 | 1.10 (0.90-1.35) |
| **MI** | **4.4** | **6.3** | **0.73 (0.65-0.82)** |
| **Stroke** | **2.2** | **2.6** | **0.79 (0.66-0.95)** |

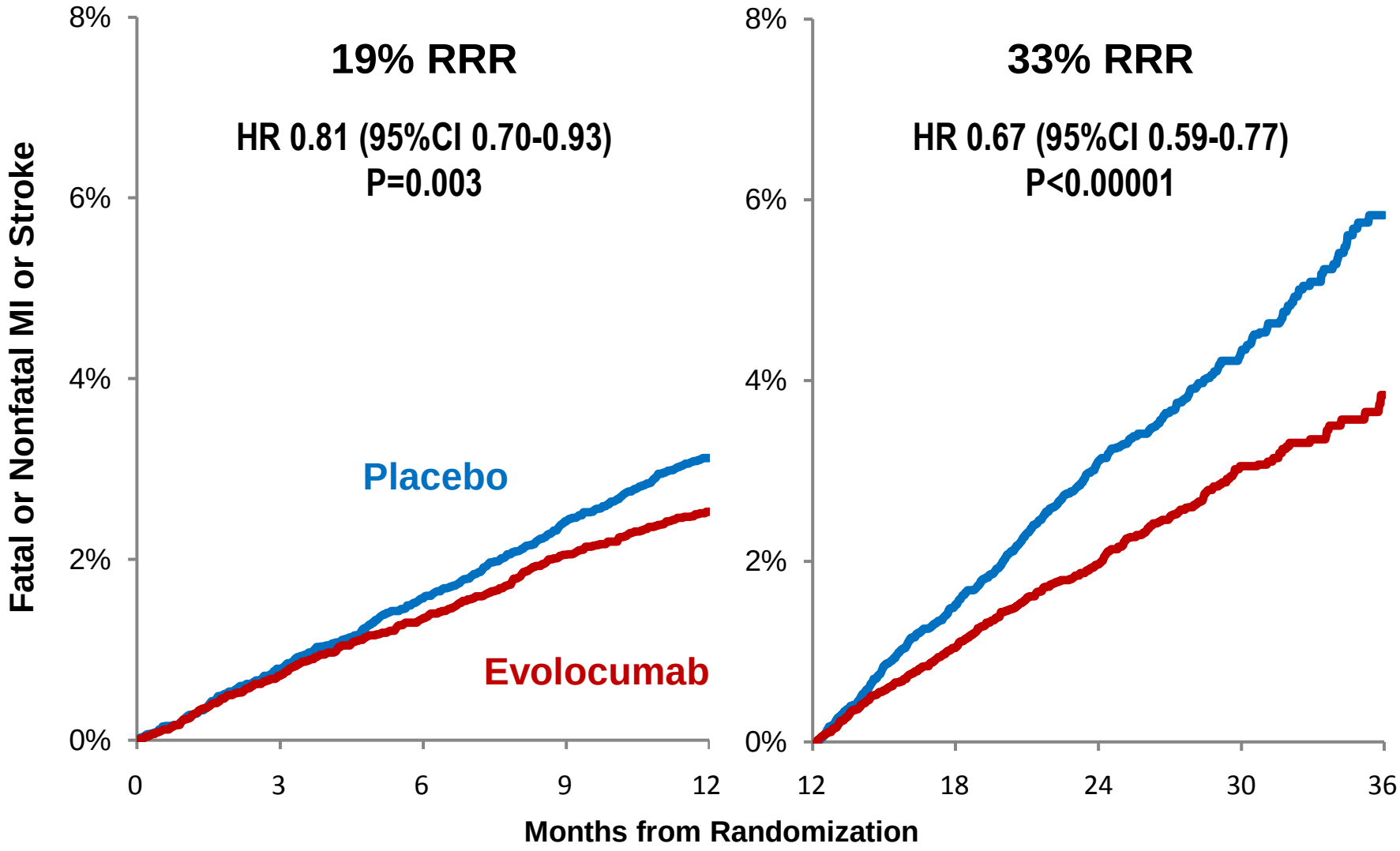
# Types of CV Outcomes

| Endpoint | Evolocumab (N=13,784) | Placebo (N=13,780) | HR (95% CI) |
|---|---|---|---|
| | *3-yr Kaplan-Meier rate* | | |
| **CVD, MI, stroke, UA, or revasc** | **12.6** | **14.6** | **0.85 (0.79-0.92)** |
| **CV death, MI, or stroke** | **7.9** | **9.9** | **0.80 (0.73-0.88)** |
| **Cardiovascular death** | **2.5** | **2.4** | **1.05 (0.88-1.25)** |
| **MI** | **4.4** | **6.3** | **0.73 (0.65-0.82)** |
| **Stroke** | **2.2** | **2.6** | **0.79 (0.66-0.95)** |
| **Hosp for unstable angina** | **2.2** | **2.3** | **0.99 (0.82-1.18)** |
| **Coronary revasc** | **7.0** | **9.2** | **0.78 (0.71-0.86)** |
| Urgent | 3.7 | 5.4 | 0.73 (0.64-0.83) |
| Elective | 3.9 | 4.6 | 0.83 (0.73-0.95) |
| **Death from any cause** | **4.8** | **4.3** | **1.04 (0.91-1.19)** |

# Landmark Analysis



# Fatal or Nonfatal MI or Stroke



# Safety

| | Evolocumab (N=13,769) | Placebo (N=13,756) |
|---|---|---|
| **Adverse events** (%) | | |
| Any | 77.4 | 77.4 |
| Serious | 24.8 | 24.7 |
| Allergic reaction | 3.1 | 2.9 |
| Injection-site reaction | 2.1 | 1.6 |
| Treatment-related and led to d/c of study drug | 1.6 | 1.5 |
| Muscle-related | 5.0 | 4.8 |
| Cataract | 1.7 | 1.8 |
| Diabetes (new-onset) | 8.1 | 7.7 |
| Neurocognitive | 1.6 | 1.5 |
| **Laboratory results** (%) | | |
| Binding Ab | 0.3 | n/a |
| Neutralizing Ab | *none* | n/a |

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

# Summary for Evolocumab

- **↓ LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- **↓ CV outcomes in patients already on statin therapy**
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1$^{st}$ year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C
- **Safe and well-tolerated**
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

# Conclusions

**In patients with known cardiovascular disease:**

1. **PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy**

2. **Benefit was achieved with lowering LDL cholesterol well below current targets**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1. Statins remain the cornerstone of risk reduction in patients with atherosclerotic cardiovascular disease and primary prevention.

2. Consider add-on therapy, i.e ezetimibe, for patients not at goal or not able to tolerate maximal statin therapy

3. PCSK9 inhibitors are now indicated for patients with familial heterozygous hyperlipidemia or clinical atherosclerotic cardiovascular disease on maximally tolerated statin therapy not at goal

4. All therapies are only indicated when patient are on low cholesterol diets