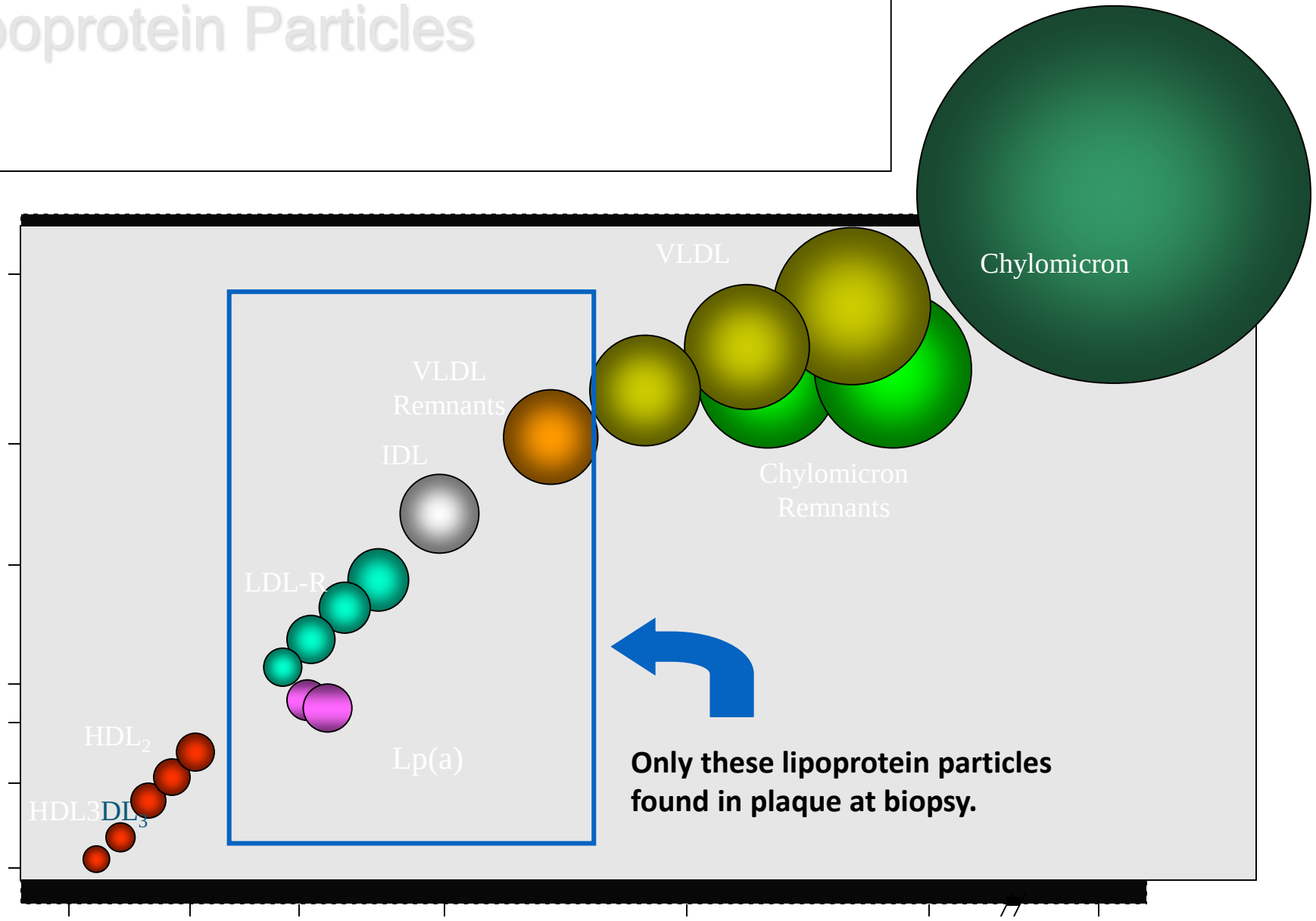
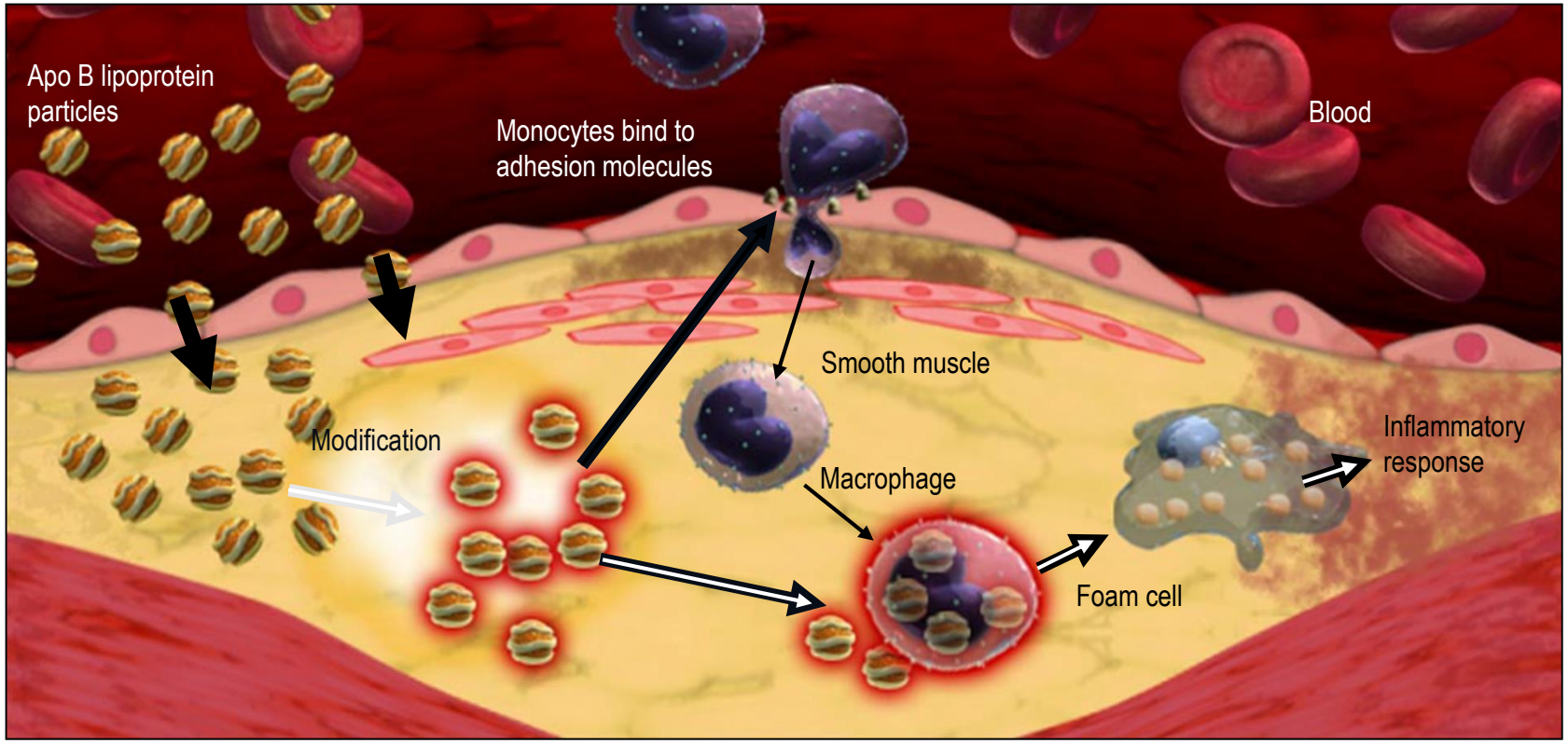
CHOLESTEROL MANAGEMENT UPDATE - 2019

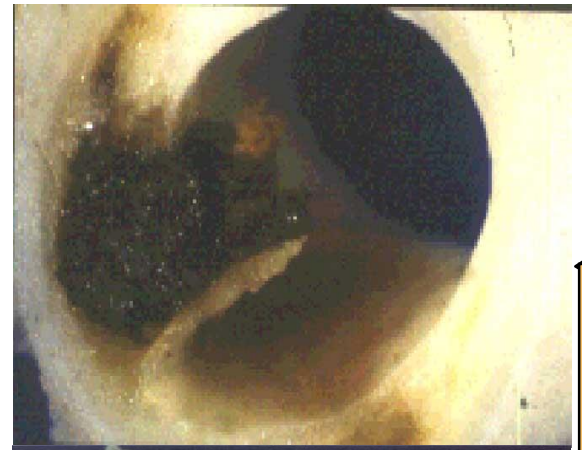
Franklin Handel, MD

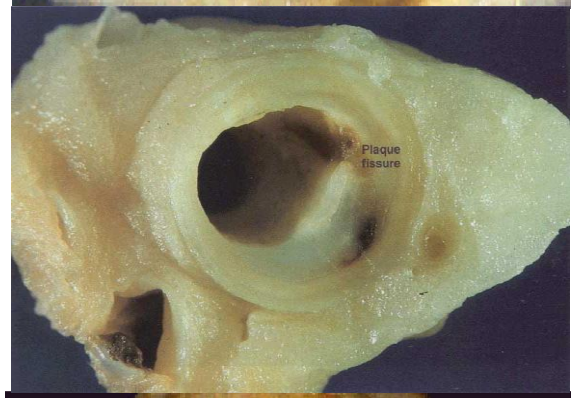
Lipoprotein Particles

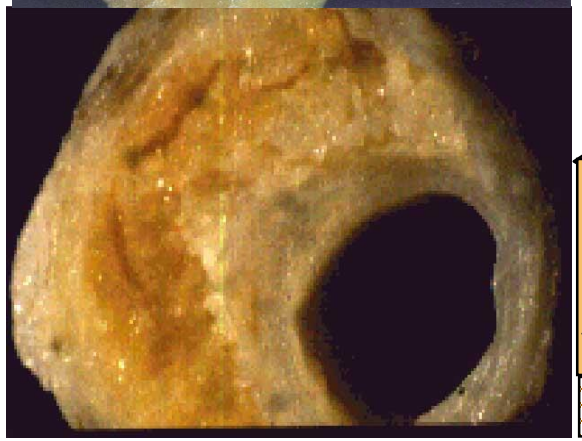


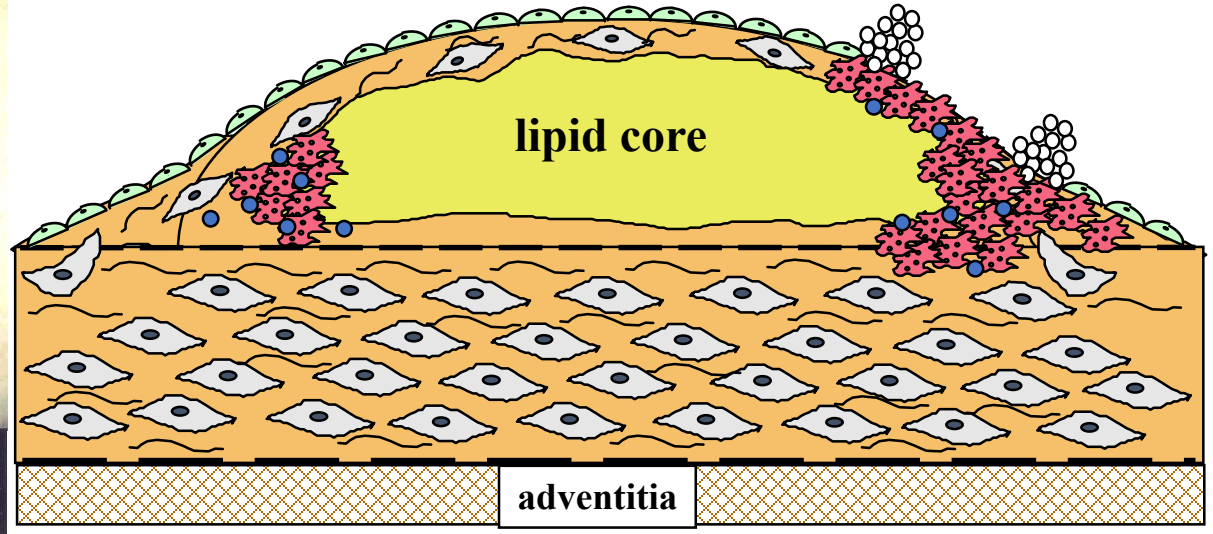
High Plasma Apo B Lipoprotein Levels Promote Atherogenesis

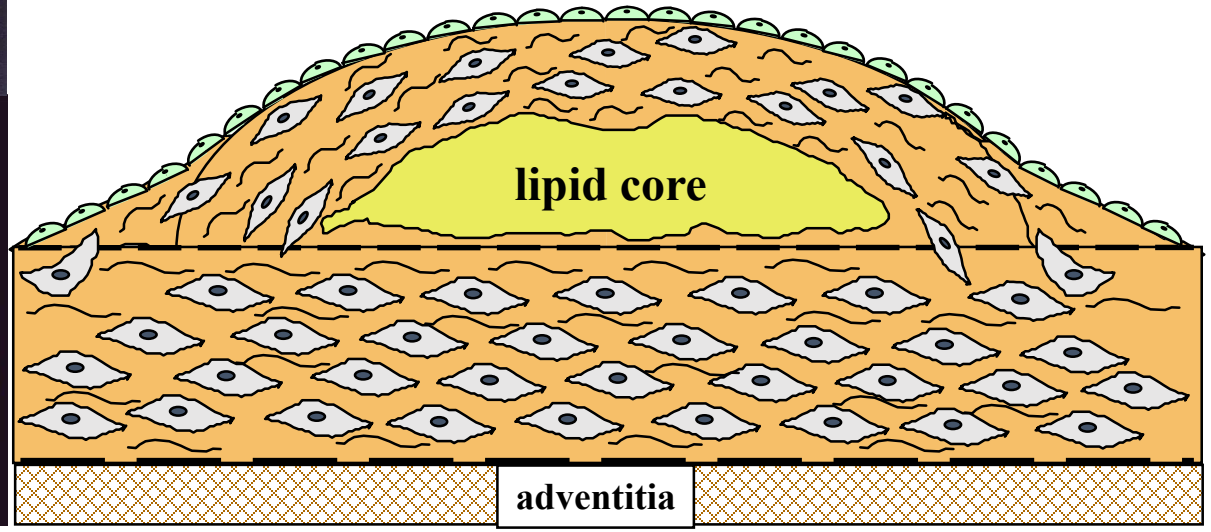




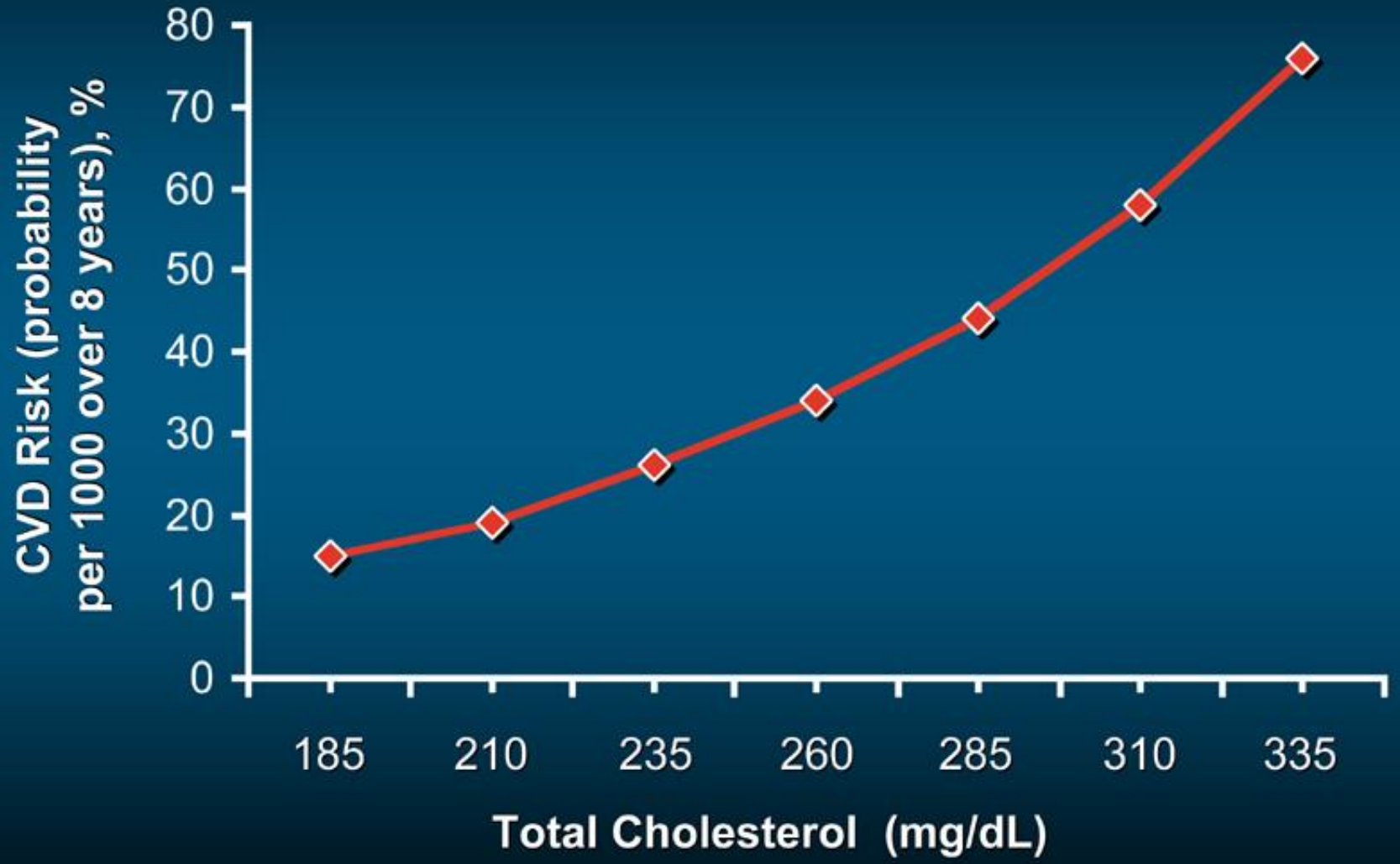

Plaque
fissure




lipid core
adventitia


lipid core
adventitia

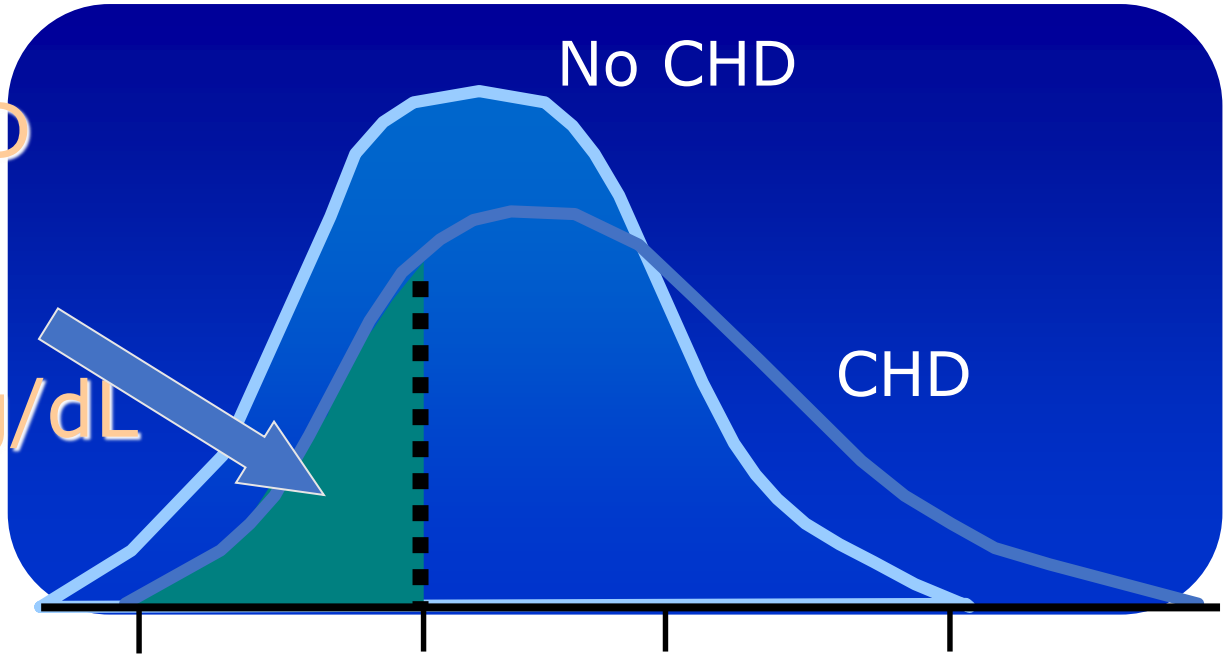
There Is a Strong Relationship Between CVD Risk and the Presence of Dyslipidemia: Framingham



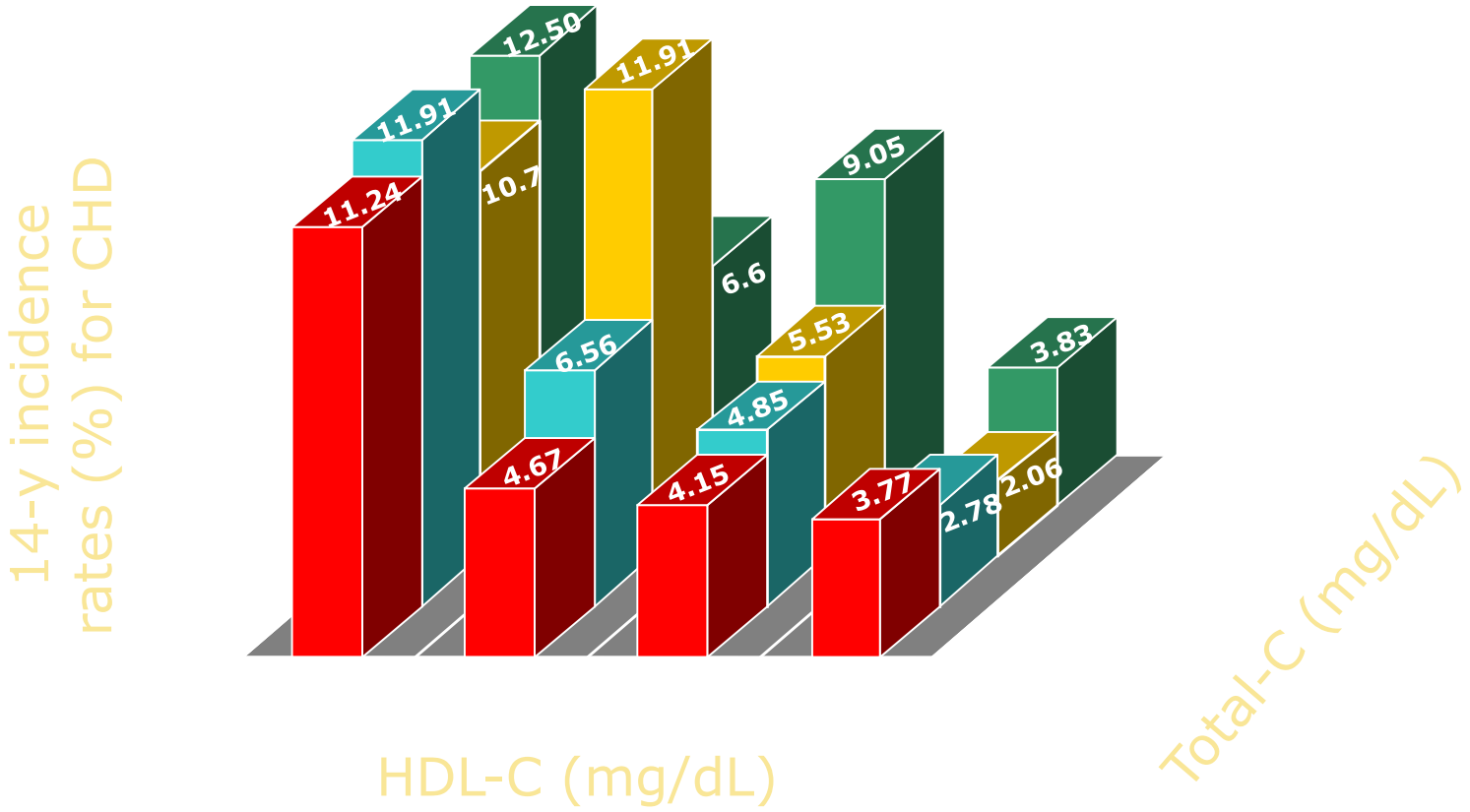
Kannel. *Hypertension*: *Physiopathology and Treatment.* 1977:888-910.

Total Cholesterol Distribution:
CHD vs Non-CHD Population

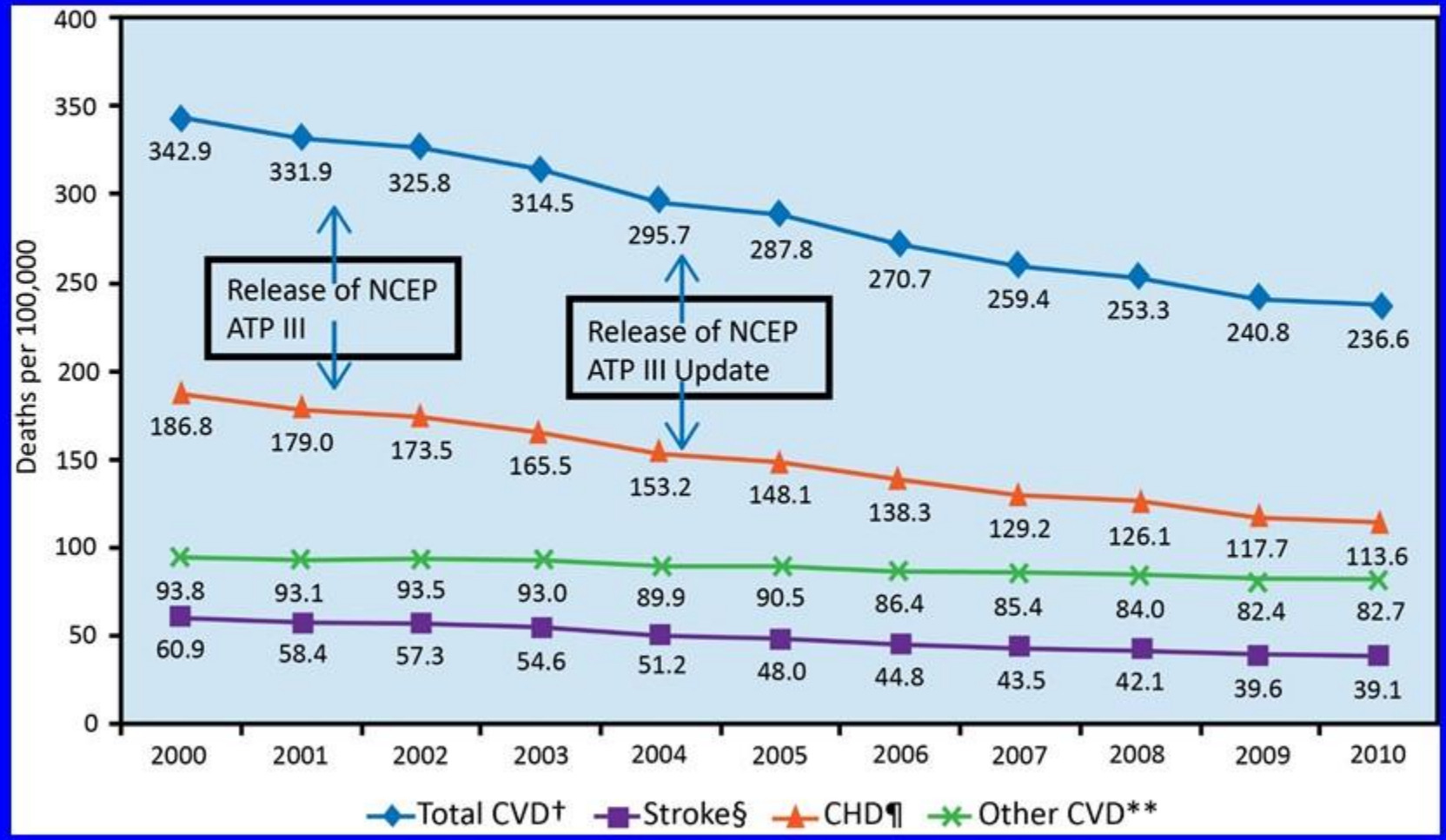
35% of CHD Occurs in People with TC<200 mg/dL



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

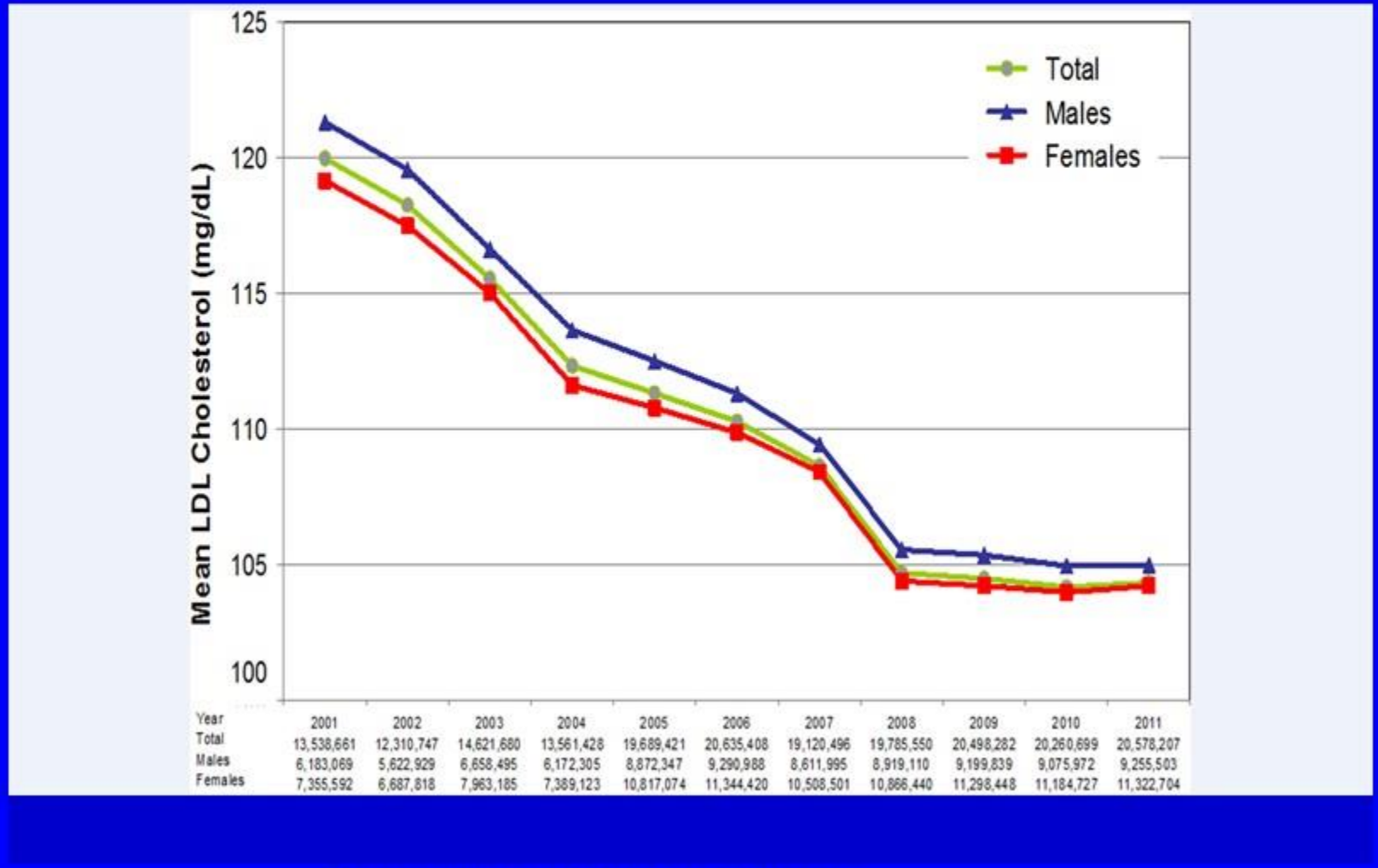


US age-standardized death rates attributable to CVD, 2000 to 2010



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

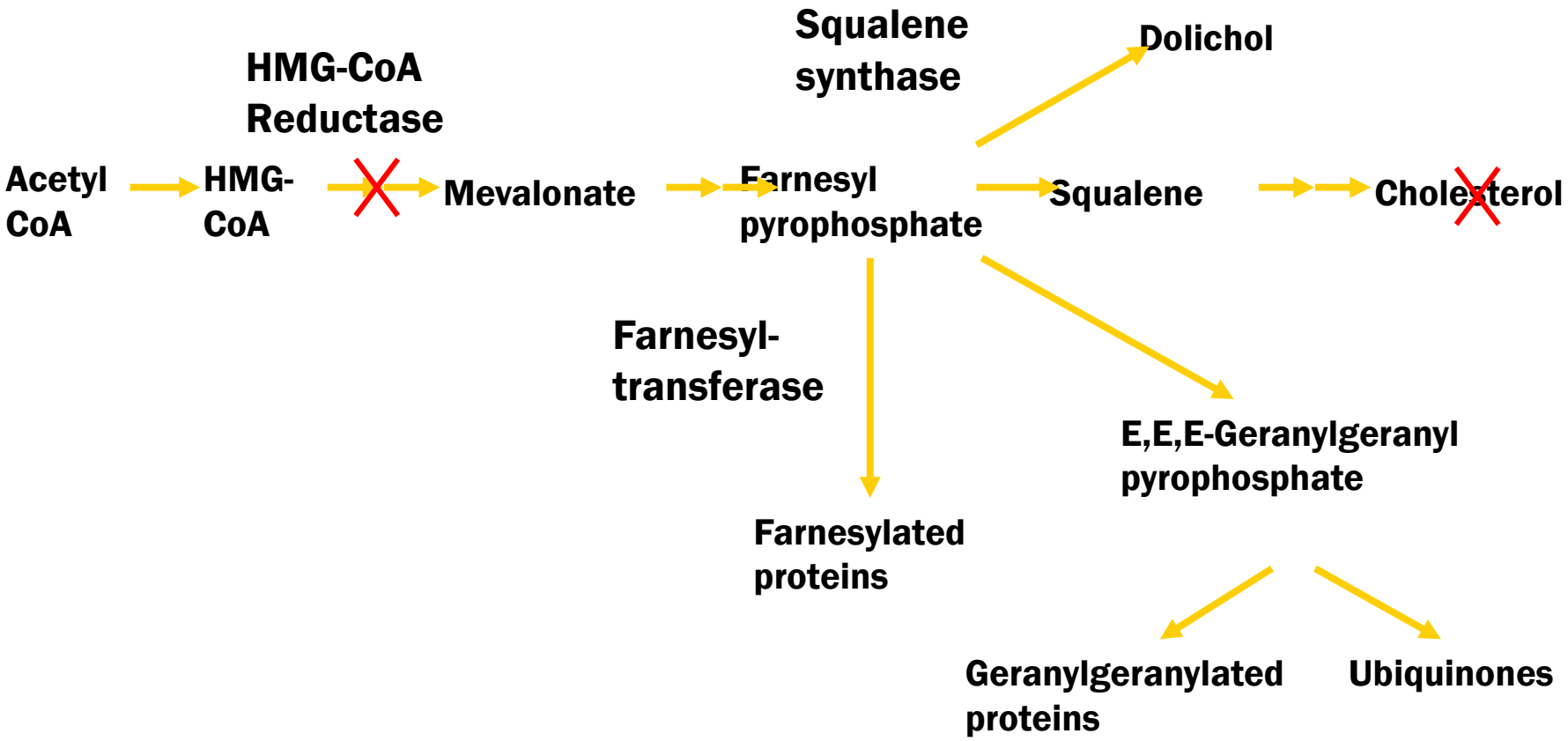


Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total	13,538,661	12,310,747	14,621,680	13,561,428	19,689,421	20,635,408	19,120,496	19,785,550	20,498,282	20,260,699	20,578,207
Males	6,183,069	5,622,929	6,658,495	6,172,305	8,872,347	9,290,988	8,611,995	8,919,110	9,199,839	9,075,972	9,255,503
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

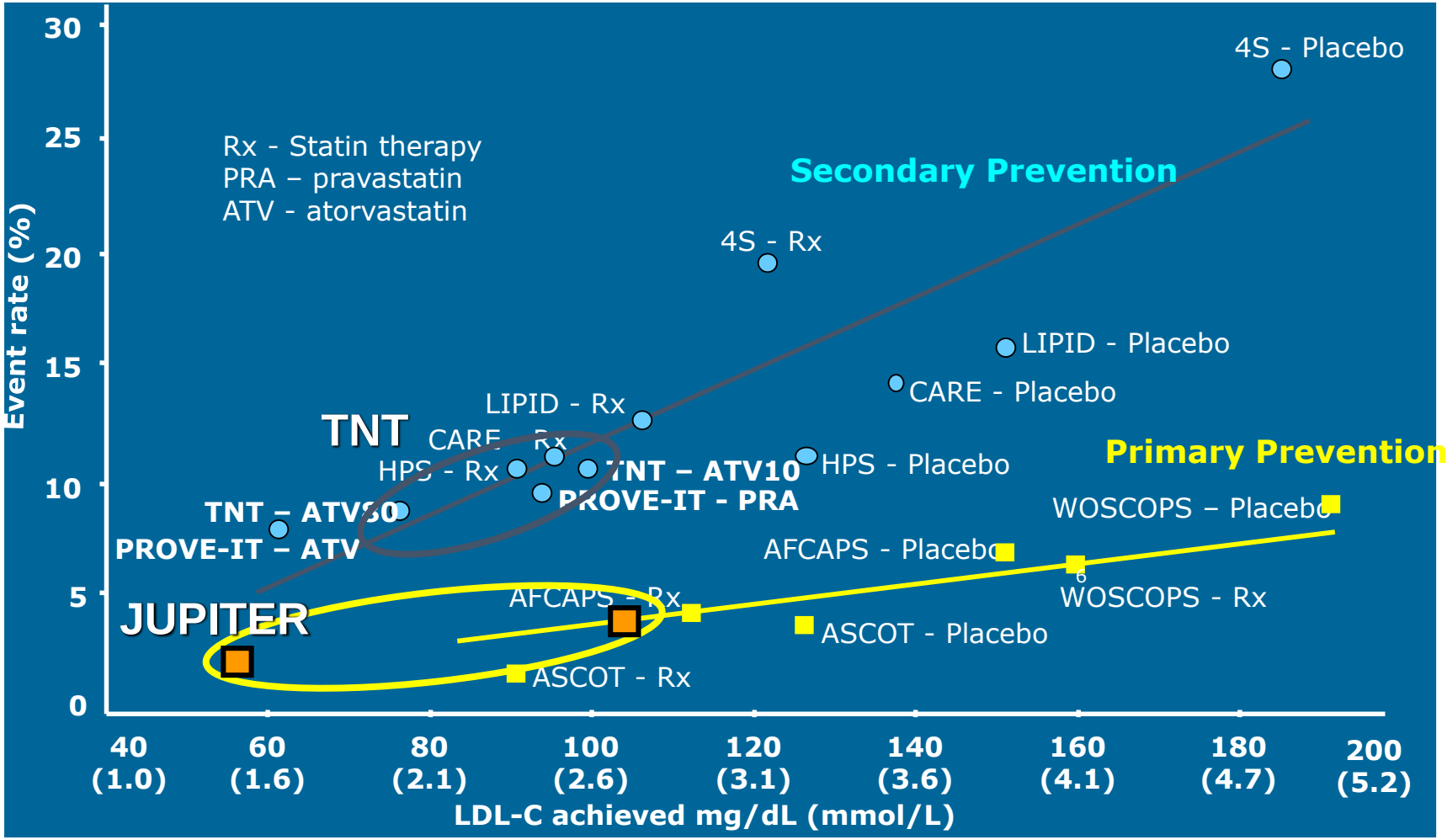
Kaufman HW, et al. PLoS ONE. 2013;8(5):e63416.

HMG-CoA Reductase Inhibitor: Mechanism of Action

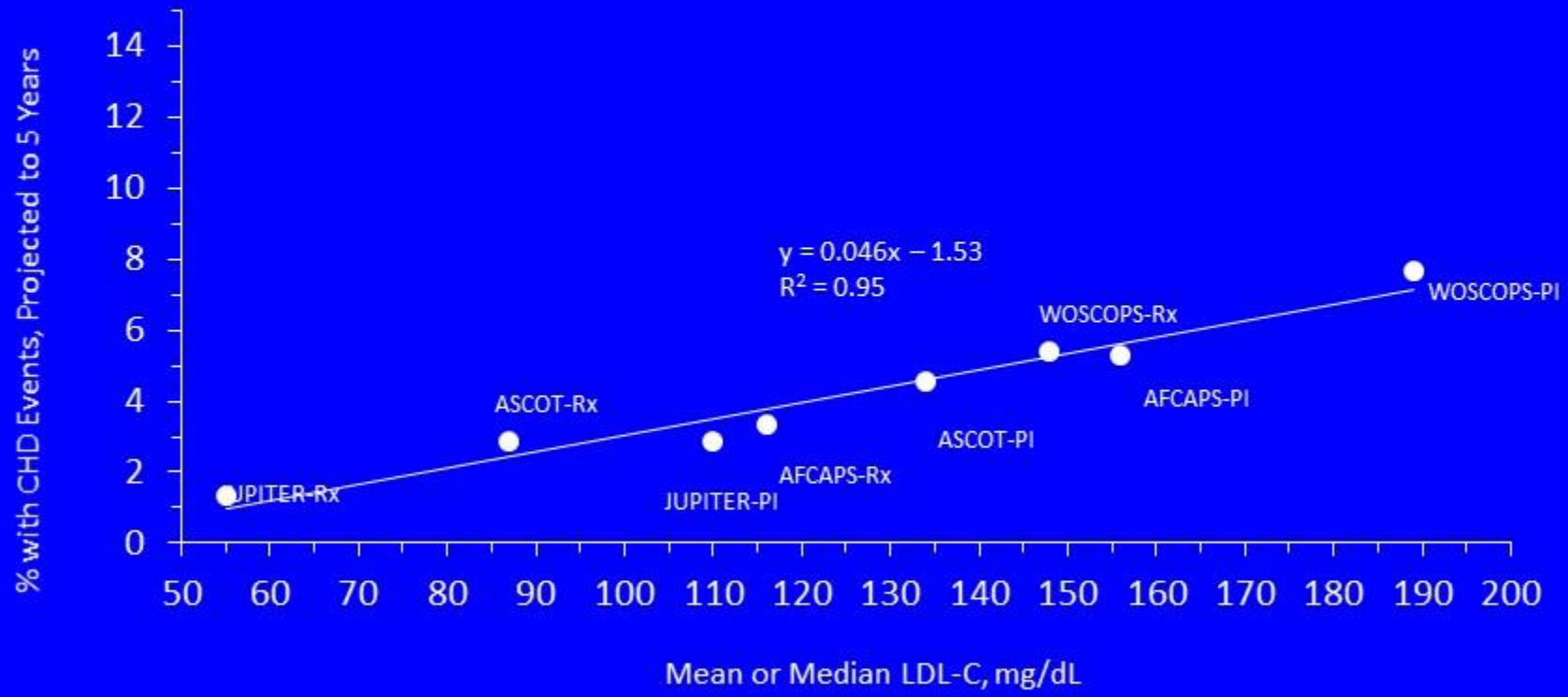
Inhibition of the cholesterol biosynthetic pathway



LDL cholesterol and benefit in clinical trials
Is lower better ?

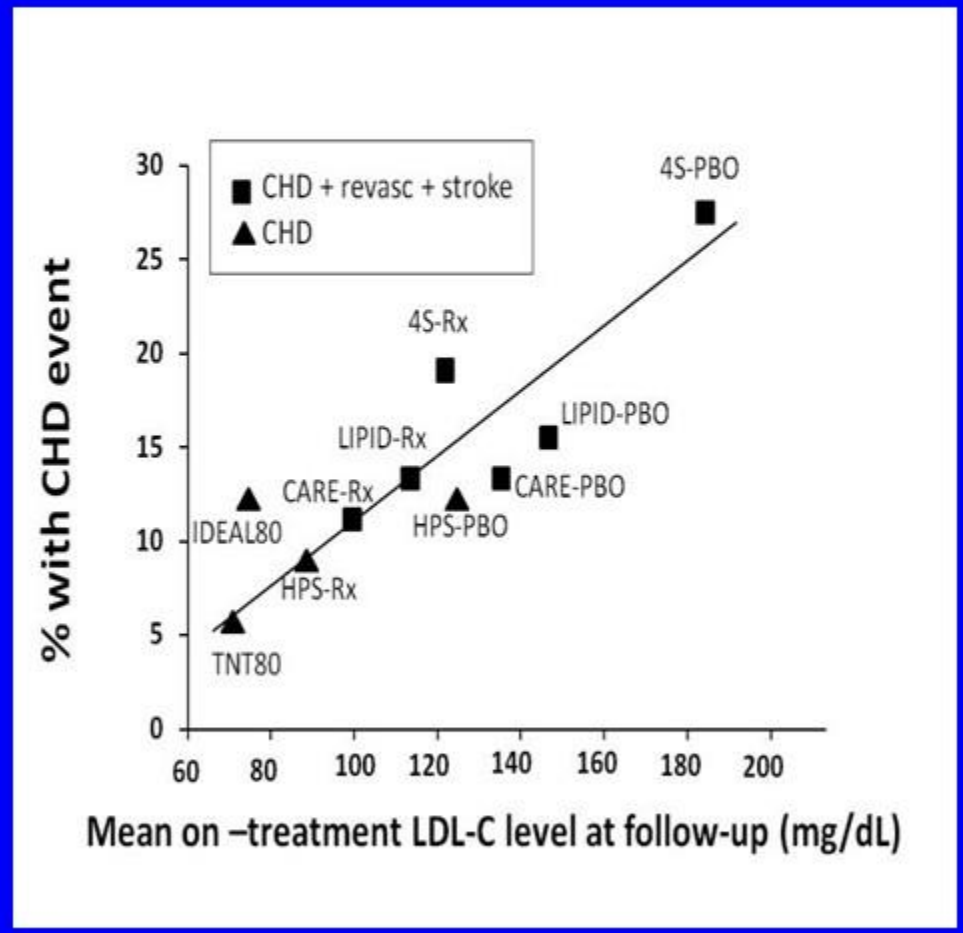


On-Treatment LDL-C and CHD Events in Primary Prevention



Data abstracted from original publications

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



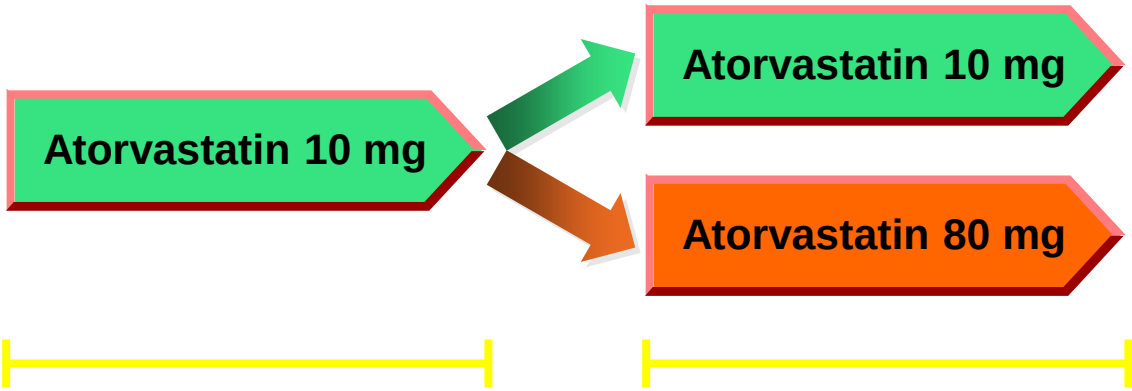
Expert Dyslipidemia Panel of IAS. J Clin Lipidol. 2014;8:29-60.

TNT: New data on intensive lipid lowering in stable CHD patients

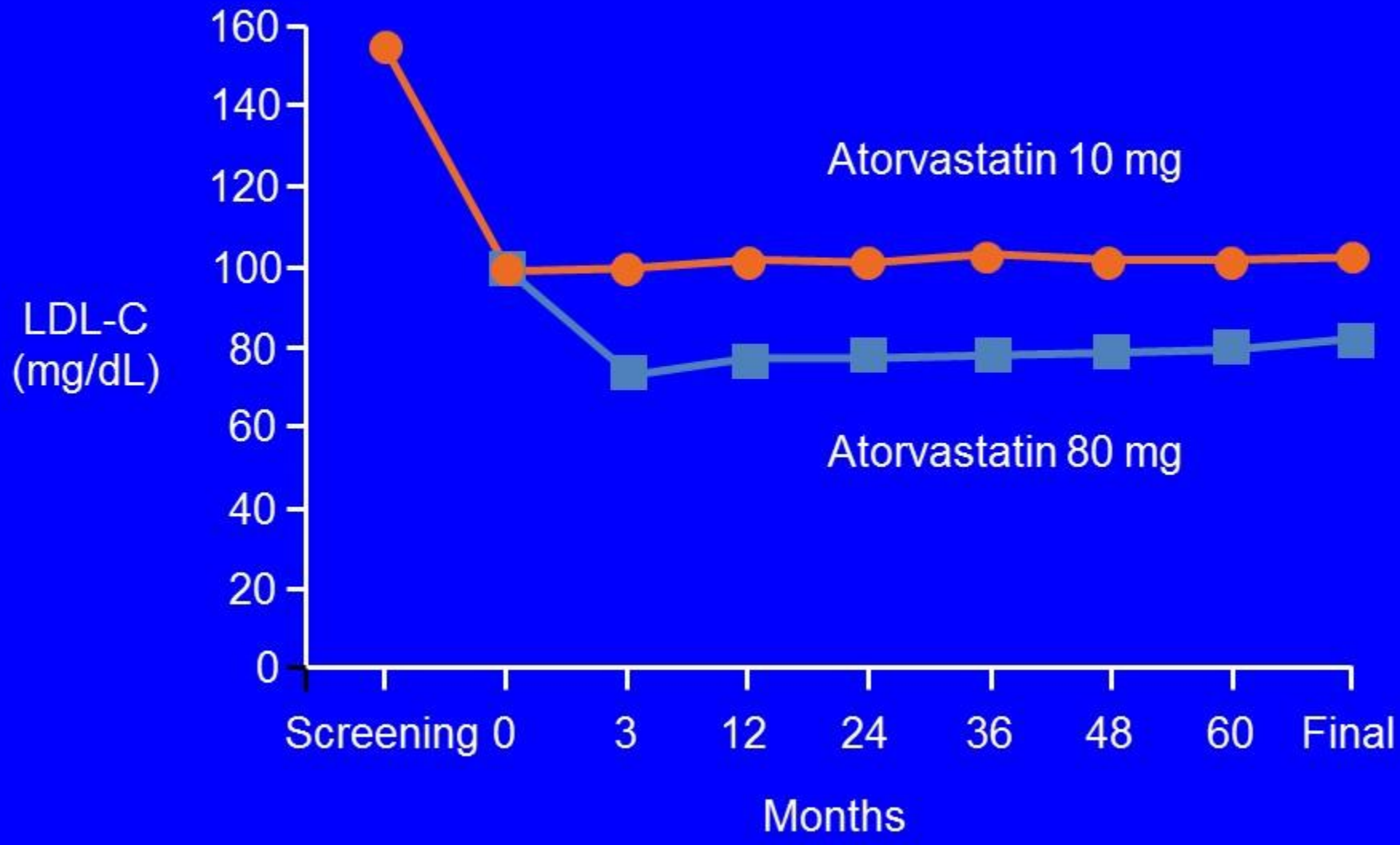
TNT: Design

Patient population

- **250 centers in 14 countries (N = 10,001)**
- **LDL 130–250 mg/dL**
- **TG <600 mg/dL**

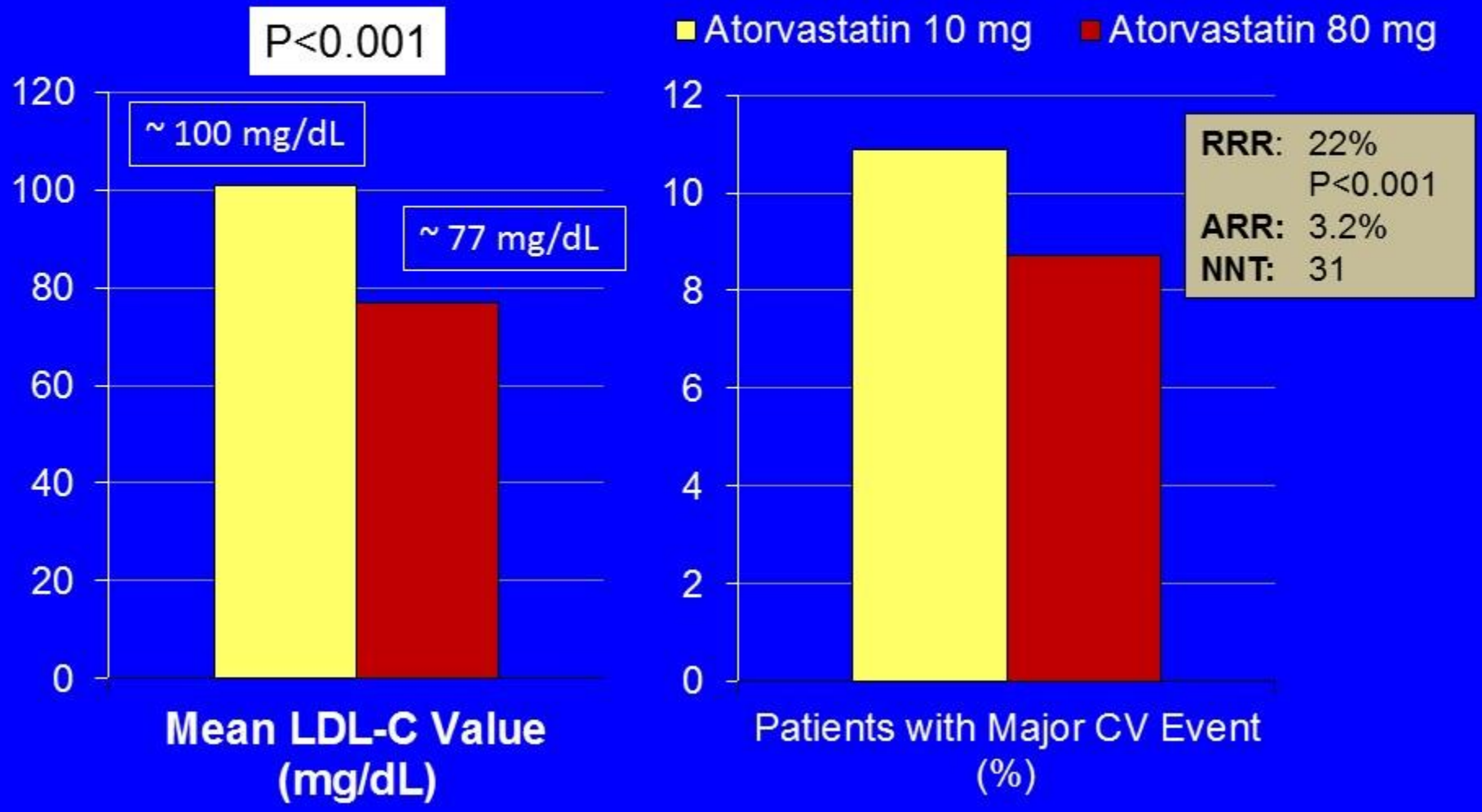


TNT: Treatment Effects on LDL-C



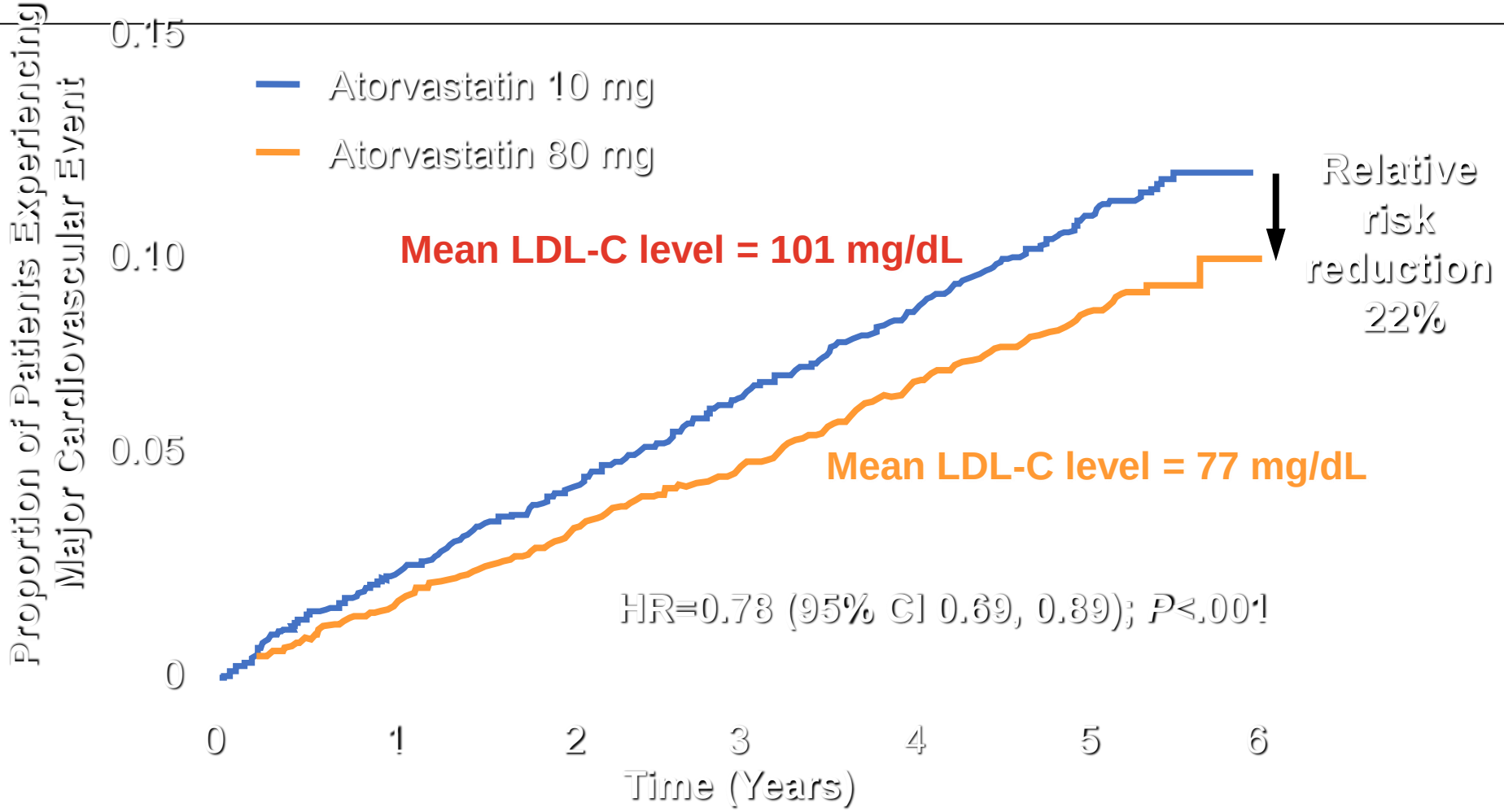
LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435.

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



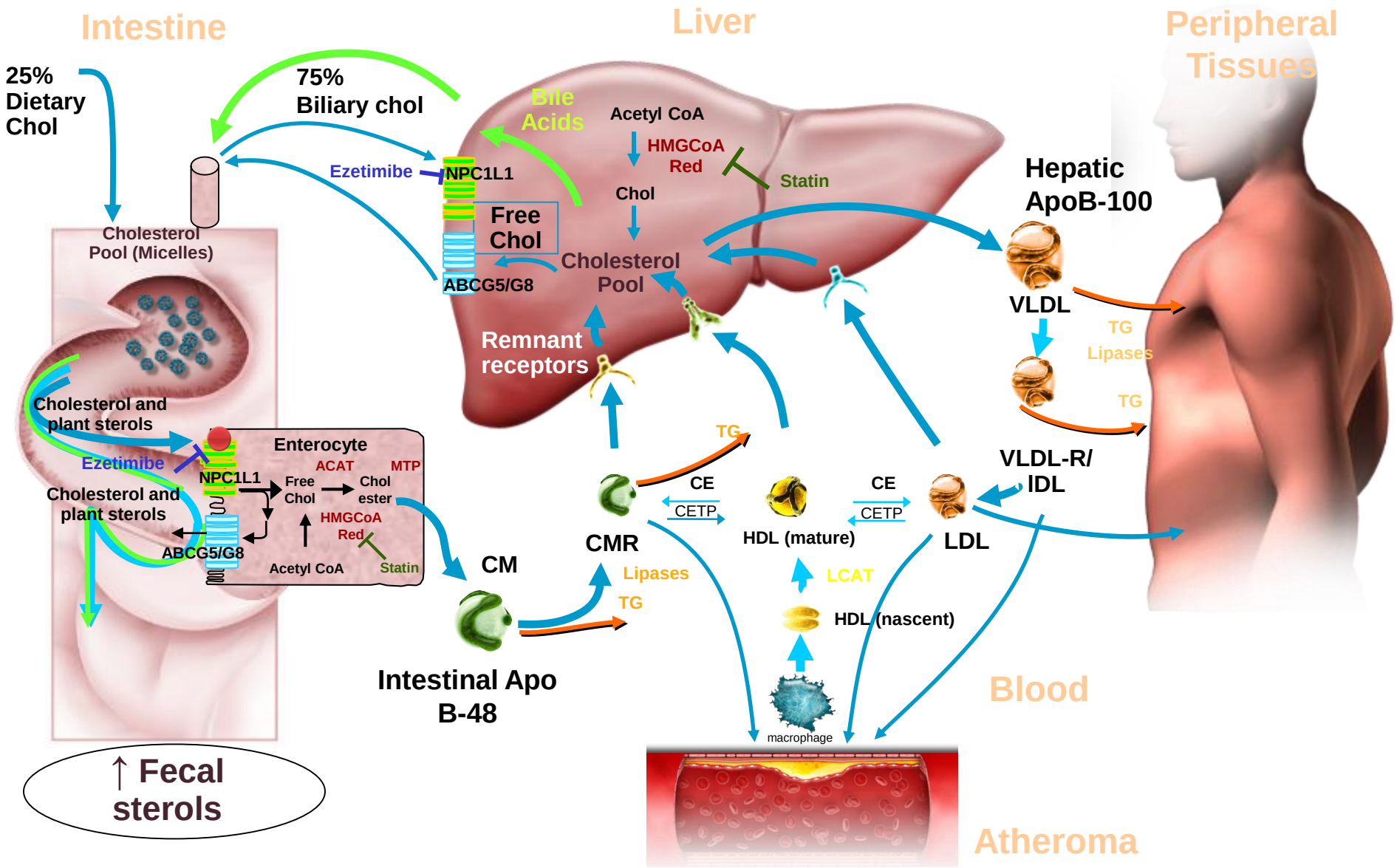
LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435.

TNT: Primary Efficacy Outcome Measure: Major Cardiovascular Events*

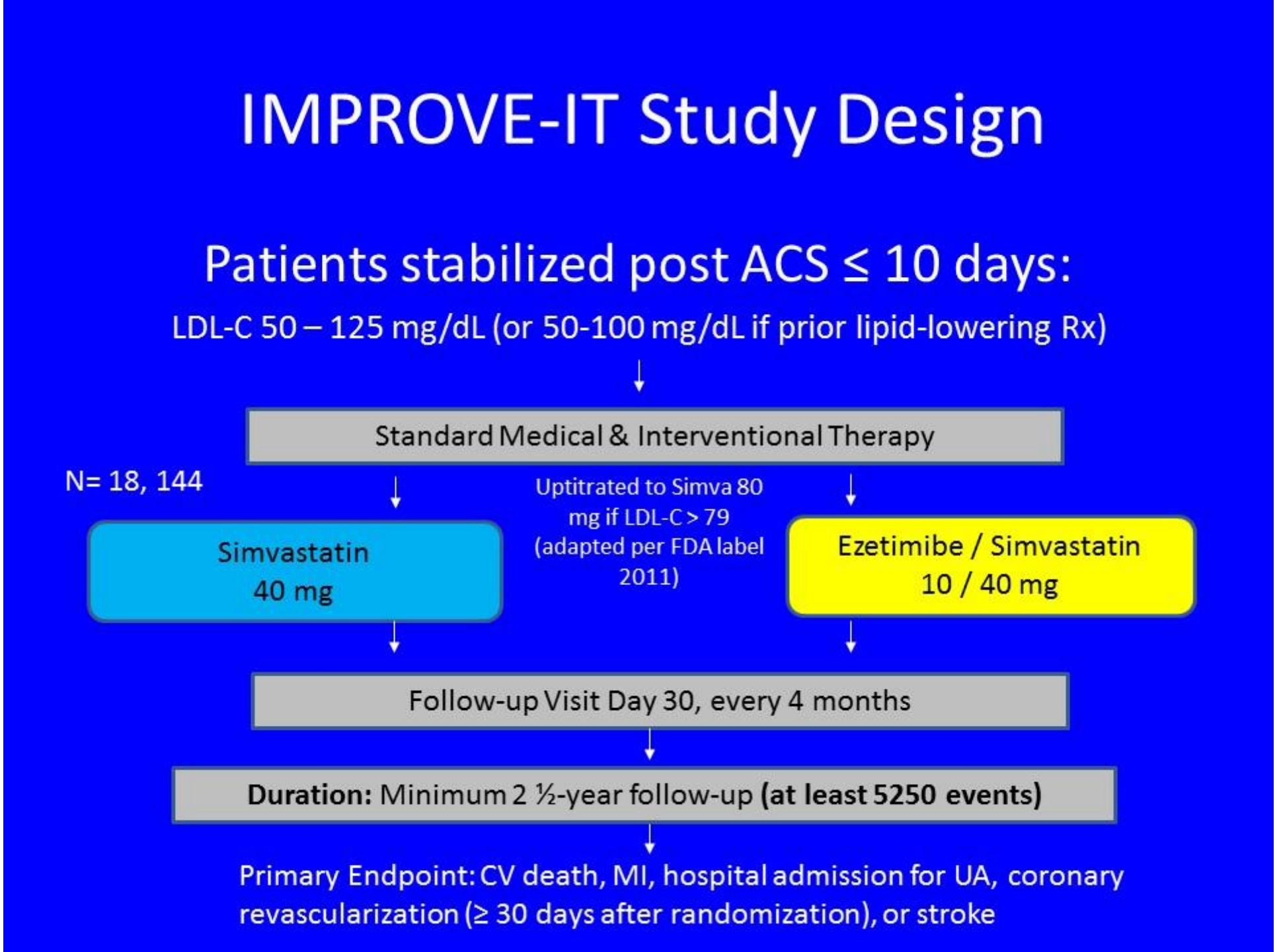


* CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

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

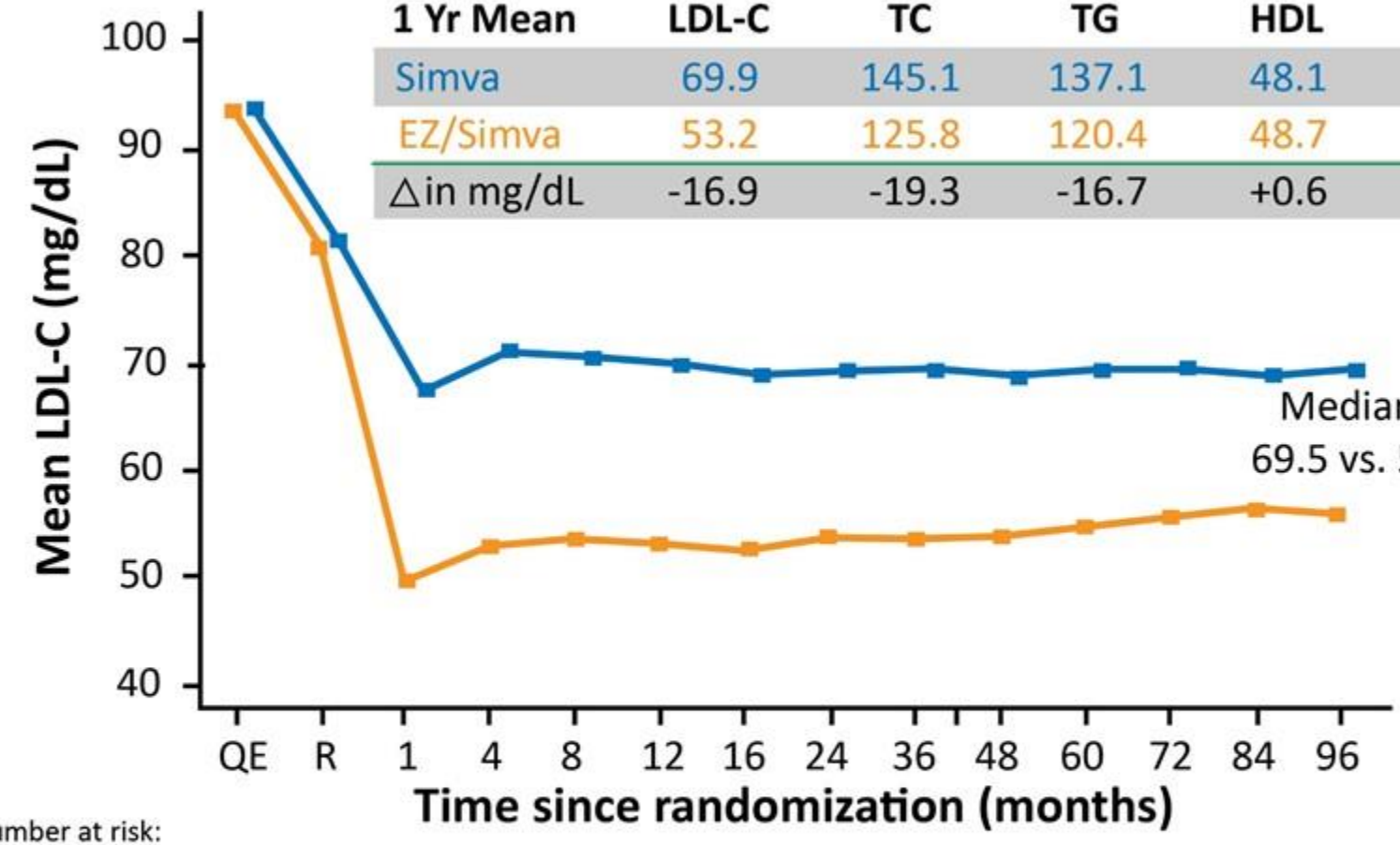

Intestine
Liver
Peripheral Tissues
25% Dietary Chol
75% Biliary chol
Bile Acids
Acetyl CoA
HMGCoA Red
Statin
Chol
Ezetimibe
NPC1L1
Free Chol
ABCG5/G8
Cholesterol Pool
Cholesterol Pool (Micelles)
Hepatic ApoB-100
VLDL
TG
Lipases
TG
Remnant receptors
Cholesterol and plant sterols
Enterocyte
ACAT
MTP
Free Chol
Chol ester
HMGCoA Red
Acetyl CoA
Statin
Ezetimibe
NPC1L1
Cholesterol and plant sterols
ABCG5/G8
TG
CE
CETP
CE
CETP
VLDL-R/ IDL
CMR
HDL (mature)
LDL
CM
Lipases
TG
LCAT
HDL (nascent)
Intestinal Apo B-48
Blood
macrophage
↑ Fecal sterols
Atheroma

IMPROVE-IT Study Design



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



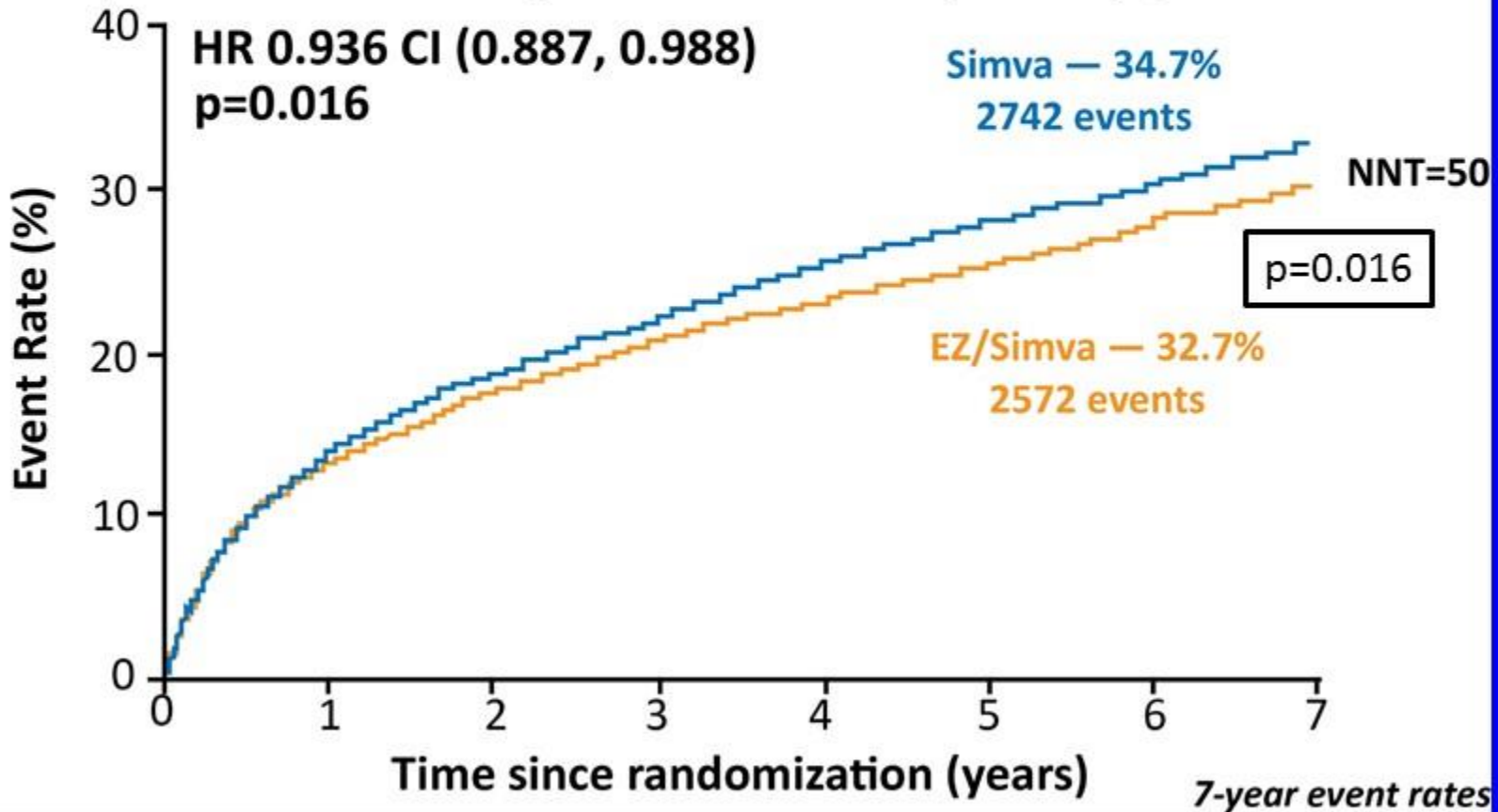
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

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

Primary Endpoint—ITT

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



7-year event rates

Conclusions

- IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:
  - **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
  - **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
  - **YES:** Confirms ezetimibe safety profile

- Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

- Results could be considered for future guidelines

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 LDL-C mg/dL	
Low	▪ 0-1 major ASCVD risk factors ▪ Consider other risk indicators, if known	<130 <100	≥190 ≥160
Moderate	▪ 2 major ASCVD risk factors ▪ Consider quantitative risk scoring ▪ Consider other risk indicators	<130 <100	≥160 ≥130

High	▪ ≥3 major ASCVD risk factors
	▪ Diabetes mellitus* (Type 1 or 2)
	  ▪ 0-1 other major ASCVD risk factors, and
	  ▪ No evidence of end organ damage
	▪ Chronic kidney disease stage 3B or 4
	▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)
	▪ Quantitative risk score reaching the high-risk threshold
		<130
		<100
			≥130
			≥100

Very High	▪ ASCVD*
	▪ Diabetes mellitus* (Type 1 or 2)
	  ▪ ≥2 other major ASCVD risk factors or
	  ▪ Evidence of end organ damage
		<100
		<70
			≥100
			≥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.

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,

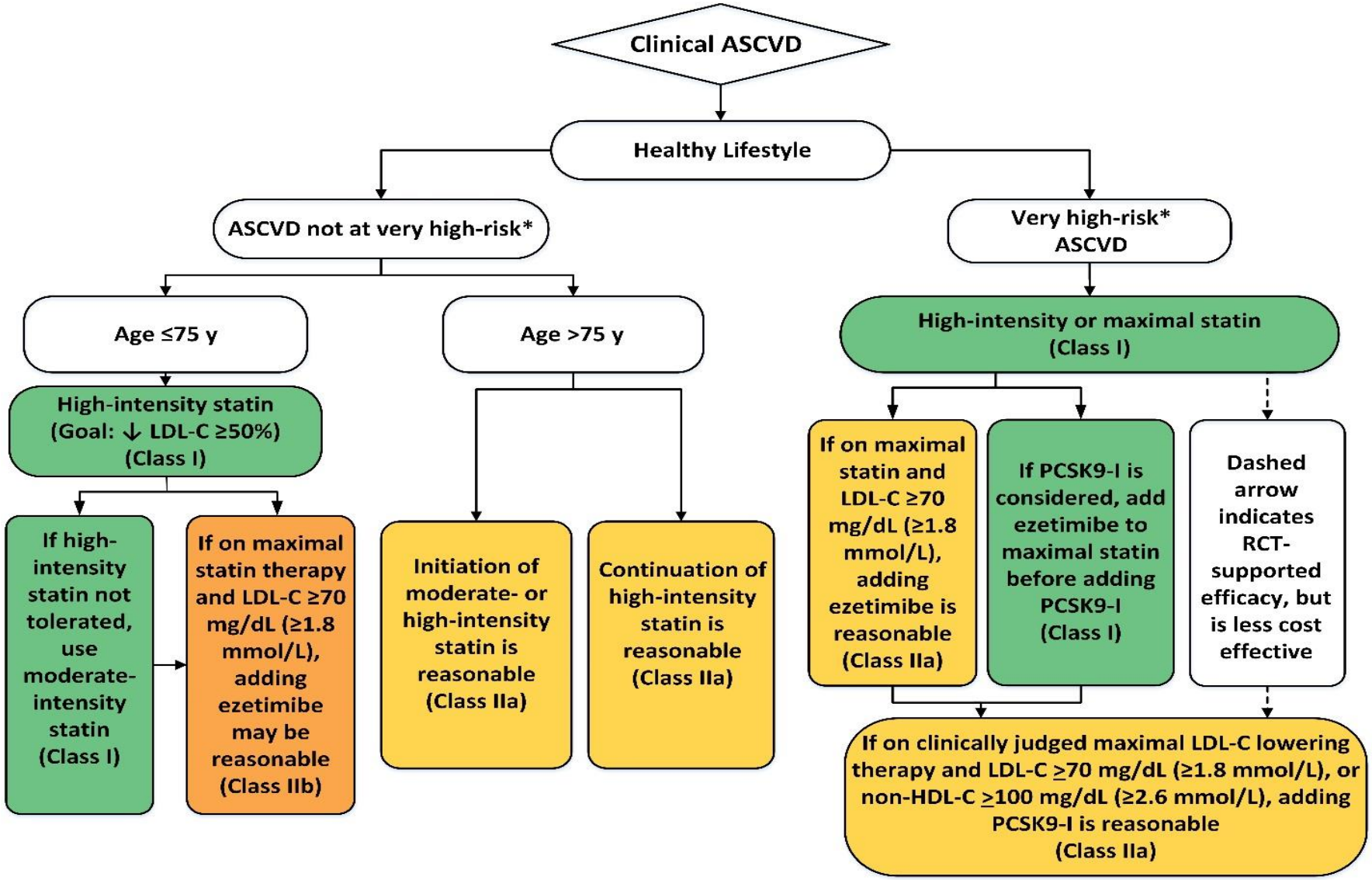
Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

Table 4 continued

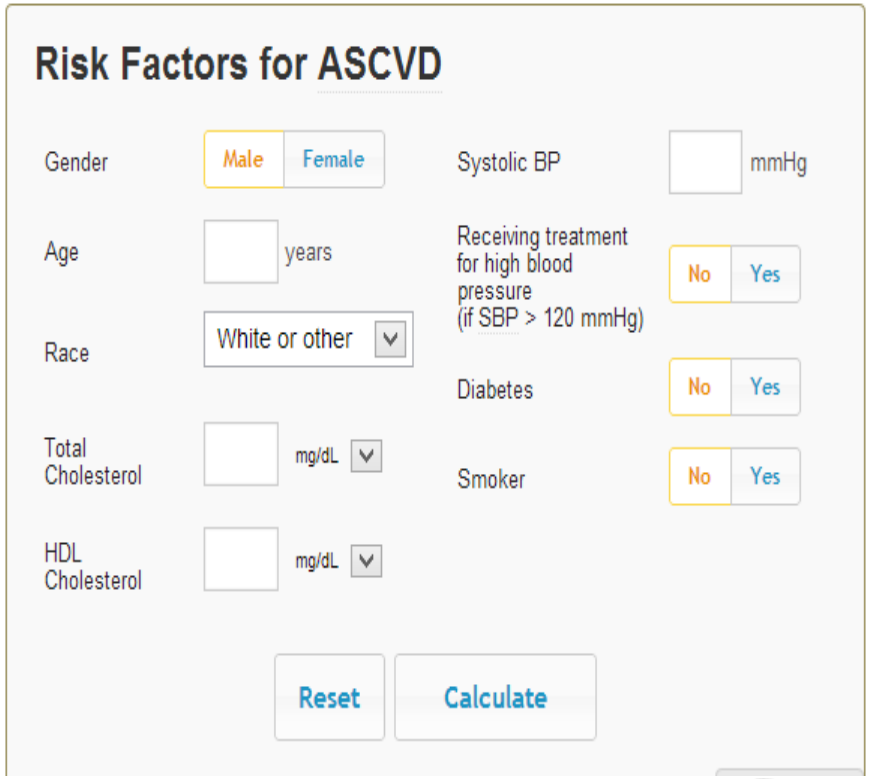
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Secondary Prevention

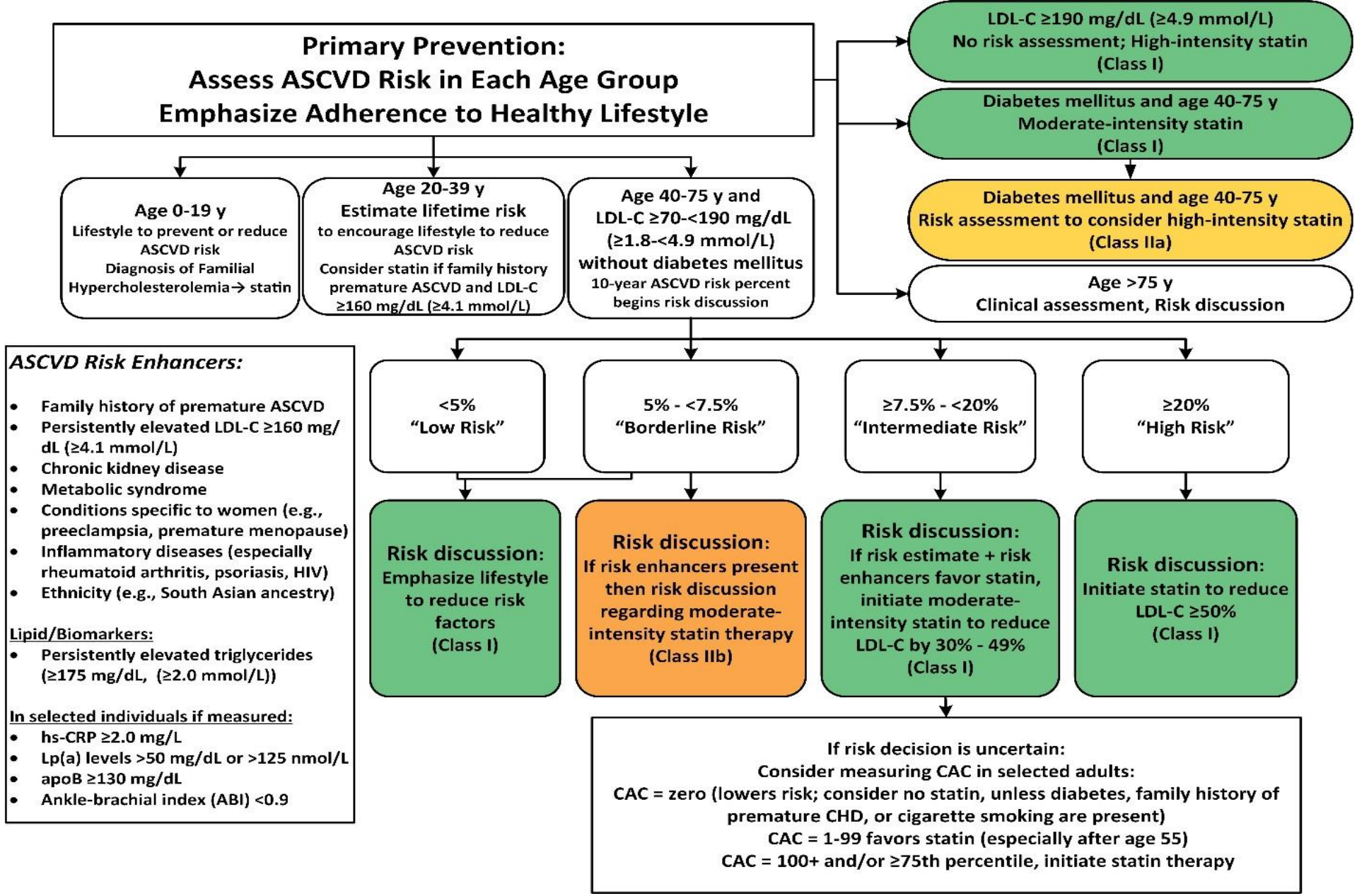


Pooled Cohort Risk Assessment Equations

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



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


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

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 **Rosuvastatin 20** *(40)* **mg**	**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*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry)

Table 6 continued

Risk-Enhancing Factors

• **Lipid/biomarkers**: Associated with increased ASCVD risk
  ○ Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  ○ If measured:
  ▪ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
  ▪ **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
  ▪ **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
  ▪ **ABI** <0.9

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

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:

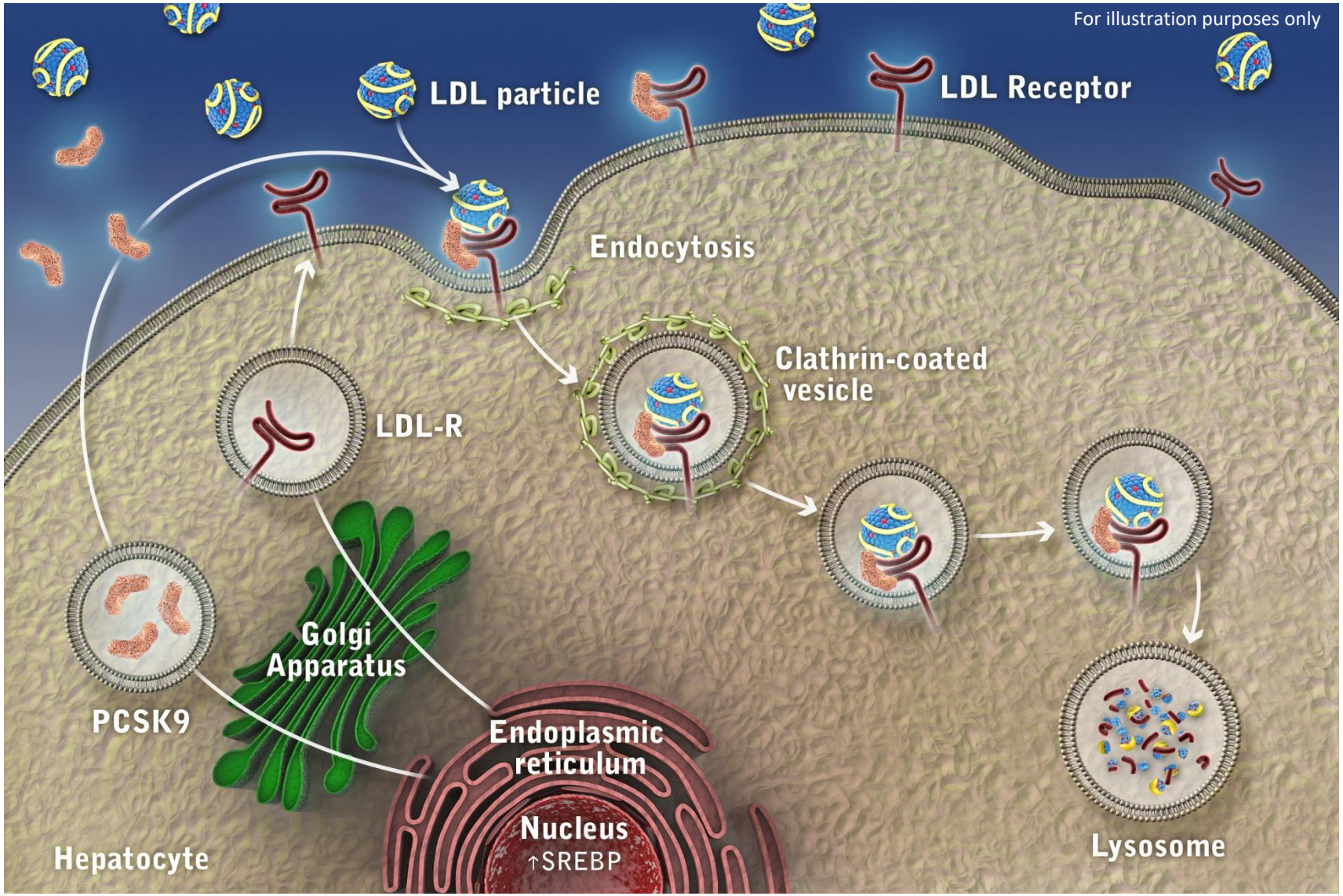
- Discontinue the statin until the symptoms are evaluated
- Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
- If after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms

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

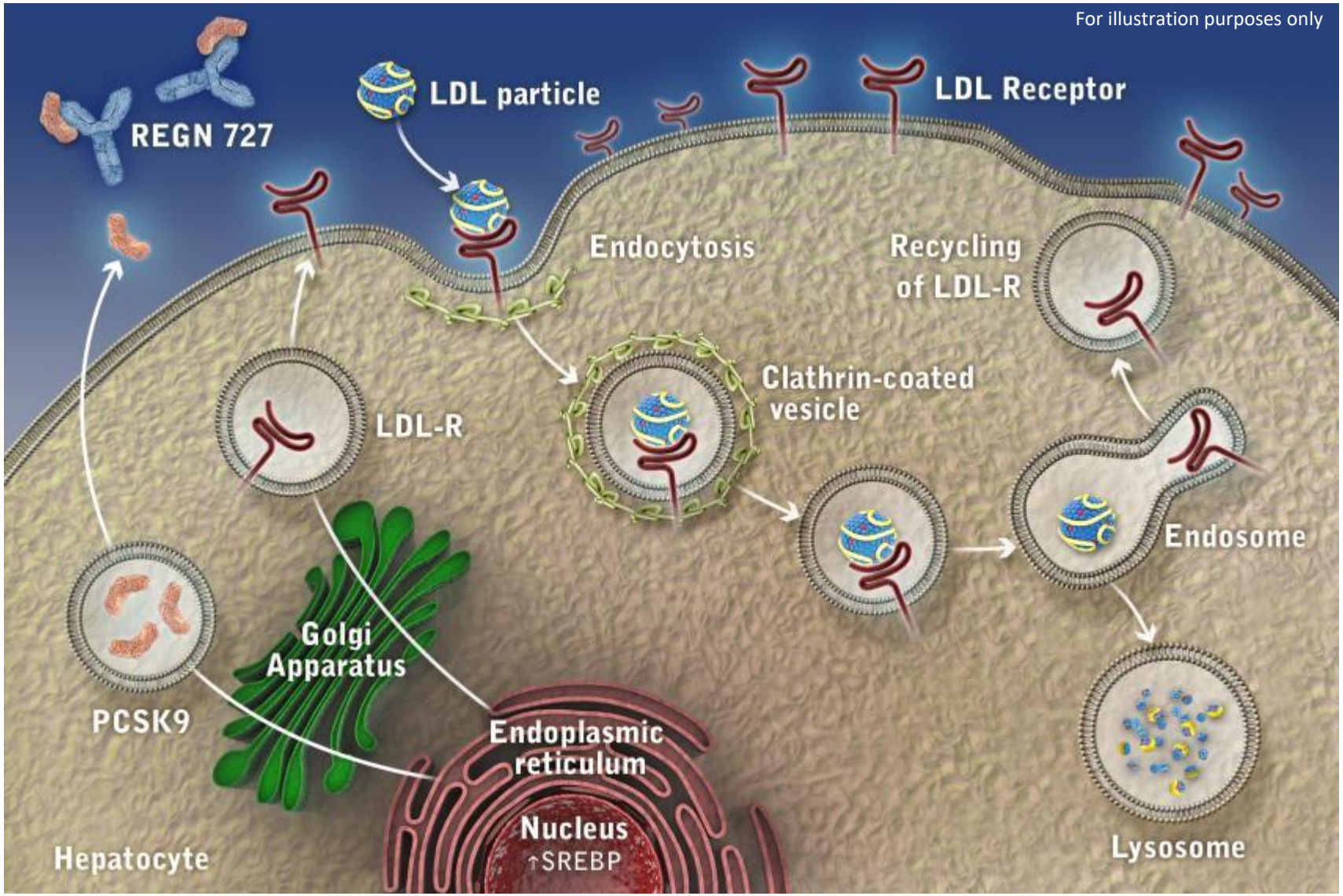
Statin-Treated Individuals
Nonstatin Therapy Considerations

- 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

The Role of PCSK9 in the Regulation of LDL Receptor Expression



Impact of an PCSK9 mAb on LDL Receptor Expression



The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,

Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402

Residual Risk After Acute Coronary Syndrome

- Remains high despite evidence-based preventive therapies
- Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
- Is reduced when LDL-C is lowered by
  - Statin therapy, compared with placebo[1]
  - High-intensity, compared with moderate-intensity statin therapy[2]
  - Ezetimibe, compared with placebo, added to statin[3]

1. Schwartz GG, et al. JAMA 2001;285:1711-8. 2. Cannon CP, et al. NEJM 2004;350:1495-504.
3. Cannon CP, et al. NEJM 2015;372:2387-97.

Alirocumab

- PCSK9 is a validated target for risk reduction in stable atherosclerotic cardiovascular disease[1–3]
- A fully human monoclonal antibody against PCSK9
- Produces substantial and sustained reductions in LDL-C and other atherogenic lipoproteins[2]
- Has been safe and well-tolerated in studies to date[4]

PCSK9, proprotein convertase subtilisin/kexin type 9

1. Sabatine et al, NEJM 2017;376:713-22. 2. Robinson JG et al. NEJM 2015;372:1489-99.
3. Ridker PM et al. NEJM 2017;376:1527-39. 4. Robinson JG et al. JACC 2017;69:471-82.

Study Hypothesis

Alirocumab, versus placebo, reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Schwartz GG, et al. Am Heart J2014;168:682-689.e1.

Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented
Schwartz GG, et al. Am Heart J2014;168:682-689.e1.

Primary Efficacy Outcome

Time of first occurrence of:

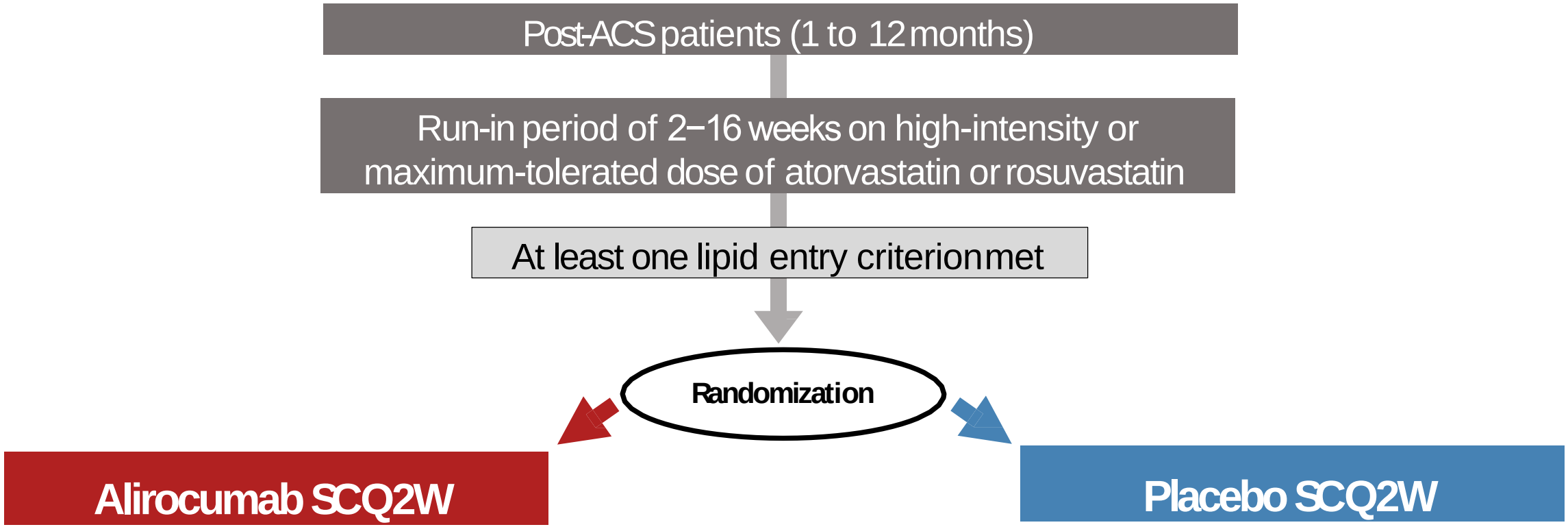
- **Coronary heart disease (CHD) death, or**
- **Non-fatal MI, or**
- **Fatal or non-fatal ischemic stroke, or**
- **Unstable angina requiring hospitalization***

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the Duke Clinical Research Institute (DCRI). Members were unaware of treatment assignment and lipid levels

*Required all of the following:
1. Hospital admission >23 h for MI symptoms, ↑ tempo in prior 48 hours and/or ≥20 min of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

Schwartz GG, et al. Am Heart J2014;168:682-689.e1.

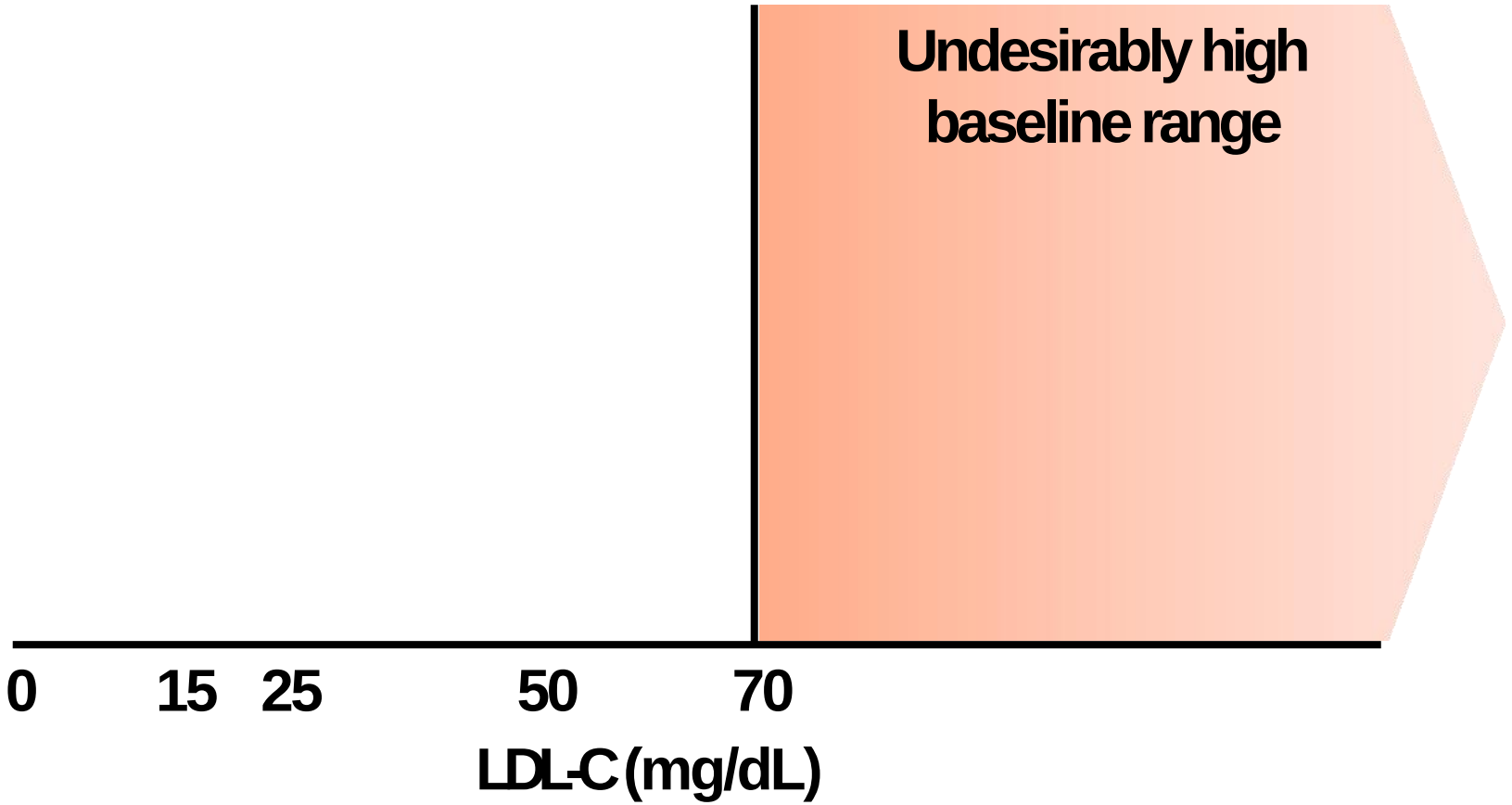
Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

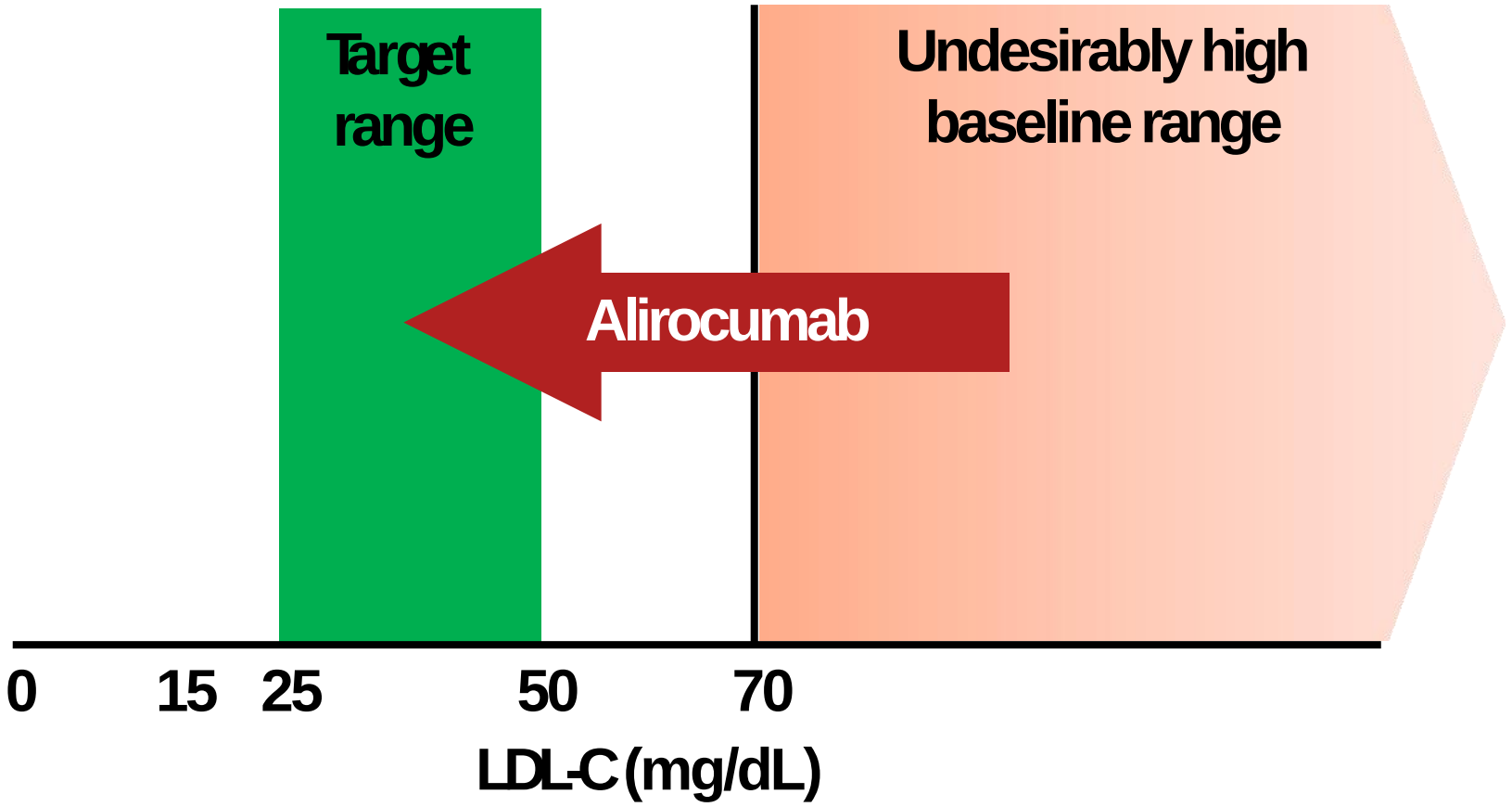
Schwartz GG, et al. Am Heart J2014;168:682-689.e1.

A Target Range for LDL-C



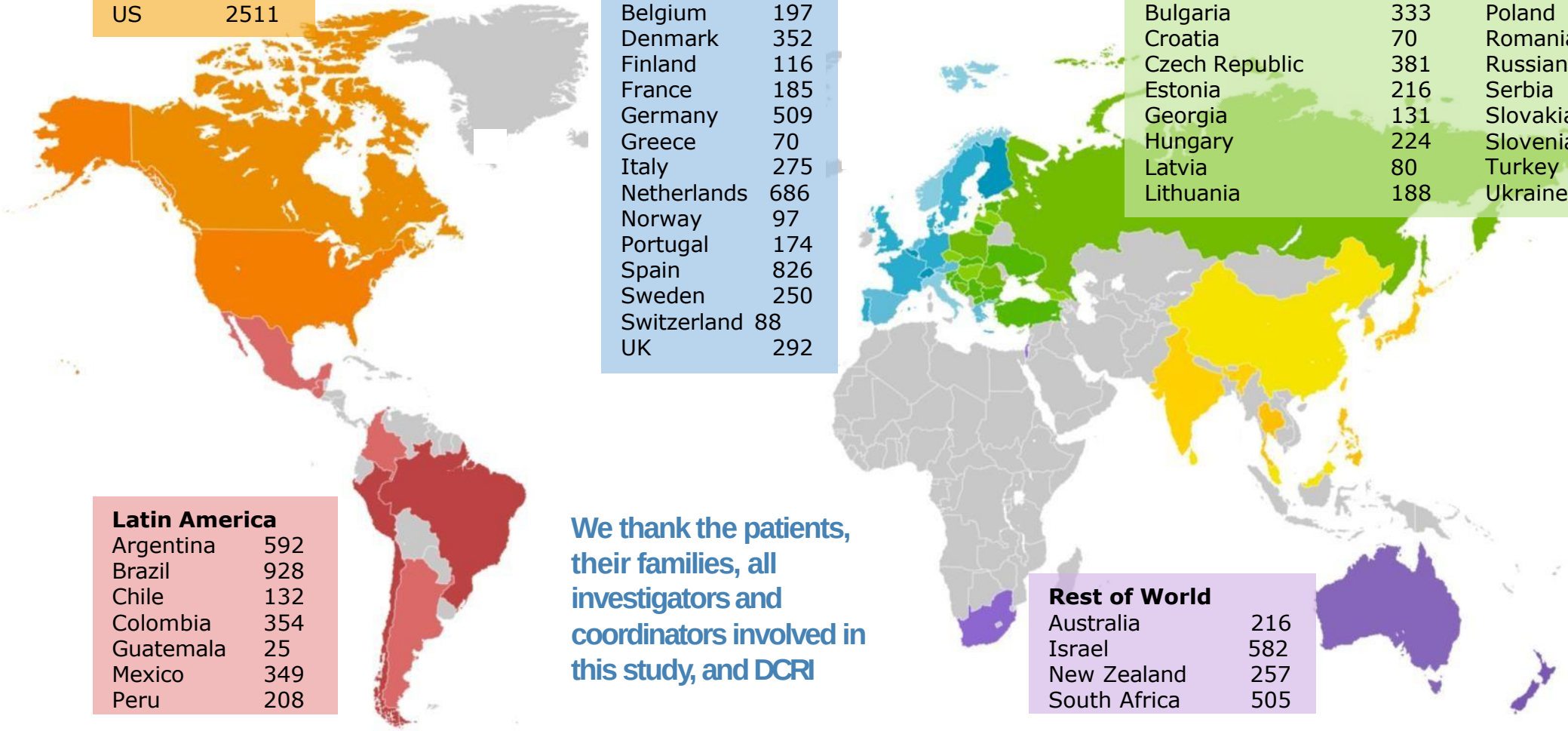
Schwartz GG, et al. Am Heart J2014;168:682-689.e1.

A Target Range for LDL-C



Schwartz GG, et al. Am Heart J2014;168:682-689.e1.

ODYSSEY OUTCOMES: 18,924 patients randomized at 1315 sites in 57 countries, Nov 2, 2012 – Nov 11, 2017



Canada/USA	
Canada	361
US	2511

Western Europe	
Austria	58
Belgium	197
Denmark	352
Finland	116
France	185
Germany	509
Greece	70
Italy	275
Netherlands	686
Norway	97
Portugal	174
Spain	826
Sweden	250
Switzerland	88
UK	292

Central/Eastern Europe			
Bosnia–Herzegovina	156	Macedonia	132
Bulgaria	333	Poland	926
Croatia	70	Romania	145
Czech Republic	381	Russian Federation	1109
Estonia	216	Serbia	255
Georgia	131	Slovakia	340
Hungary	224	Slovenia	36
Latvia	80	Turkey	78
Lithuania	188	Ukraine	639

Asia	
China	614
Hong Kong	17
India	521
Japan	204
Korea	94
Malaysia	110
Philippines	116
Singapore	49
Sri Lanka	314
Taiwan	93
Thailand	161

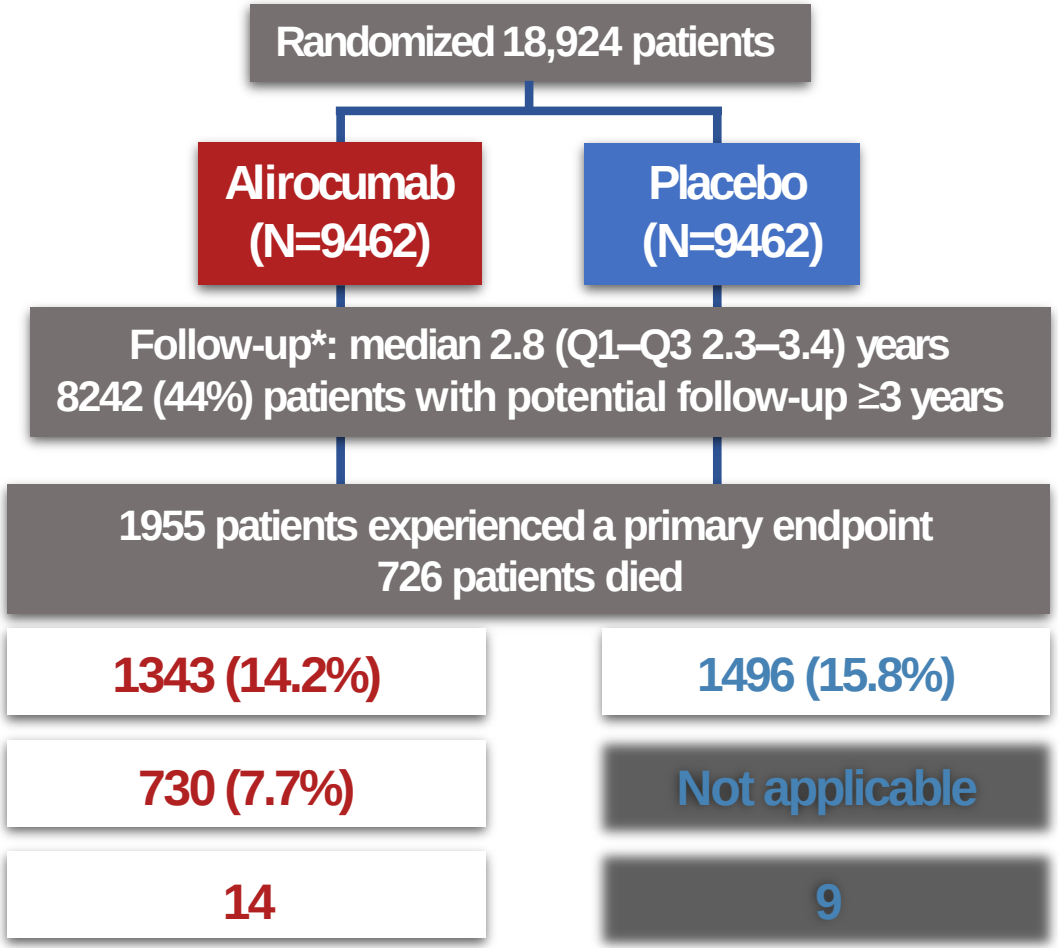
Latin America	
Argentina	592
Brazil	928
Chile	132
Colombia	354
Guatemala	25
Mexico	349
Peru	208

Rest of World	
Australia	216
Israel	582
New Zealand	257
South Africa	505

We thank the patients, their families, all investigators and coordinators involved in this study, and DCRI

ODYSSEY OUTCOMES

Patient Disposition



*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

Baseline Demographics

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age, years, median (Q1–Q3)	58 (52–65)	58 (52–65)
Female, n (%)	2390 (25.3)	2372 (25.1)
Medical history, n (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Prior MI	1790 (18.9)	1843 (19.5)

Baseline Index Events

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Time from index ACS to randomization, months, median (Q1−Q3)	2.6 (1.7−4.4)	2.6 (1.7−4.3)
ACS type, n (%)		
NSTEMI	4574 (48.4)	4601 (48.7)
STEMI	3301 (35.0)	3235 (34.2)
Unstable angina	1568 (16.6)	1614 (17.1)
Revascularization for index ACS, n (%)	6798 (71.8)	6878 (72.7)

Baseline Lipid Characteristics

Characteristic, mg/dL, median (Q1–Q3)	Alirocumab (N=9462)	Placebo (N=9462)
LDL-C	87 (73–104)	87 (73–104)
Non-HDL-C	115 (99–136)	115 (99–137)
Apolipoprotein B	79 (69–93)	80 (69–93)
HDL-C	43 (37–50)	42 (36–50)
Triglycerides	129 (94–181)	129 (95–183)
Lipoprotein(a)	21 (7–59)	22 (7–60)

92.5% of patients qualified on the basis of LDL-C≥70 mg/dL

Baseline Lipid-Lowering Therapy

Therapy, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
High-dose atorvastatin/rosuvastatin	8380 (88.6)	8431 (89.1)
Low-/moderate-dose atorvastatin/rosuvastatin	830 (8.8)	777 (8.2)
Other statin	19 (0.2)	27 (0.3)
Ezetimibe, with or without statin	269 (2.8)	285 (3.0)
No lipid-lowering therapy*	87 (0.9)	91 (1.0)

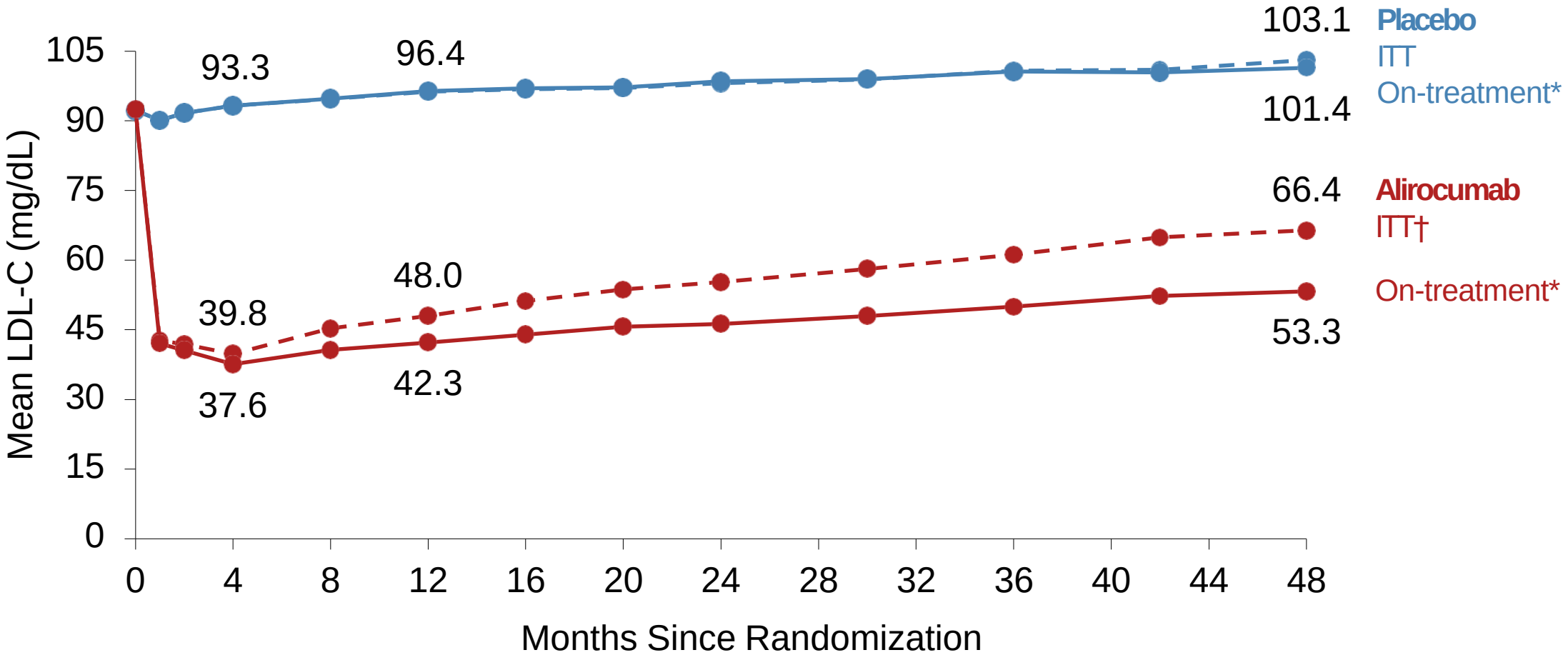
*Patients not on statins were authorized to participate if tolerability issues were present and documented

Guideline-Recommended Post-ACS Medications

Medication, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
Aspirin	9050 (95.6)	9036 (95.5)
$P2Y_{12}$ antagonist	8296 (87.7)	8245 (87.1)
ACE-I/ARB	7356 (77.7)	7360 (77.8)
Beta-blocker	7998 (84.5)	7992 (84.5)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

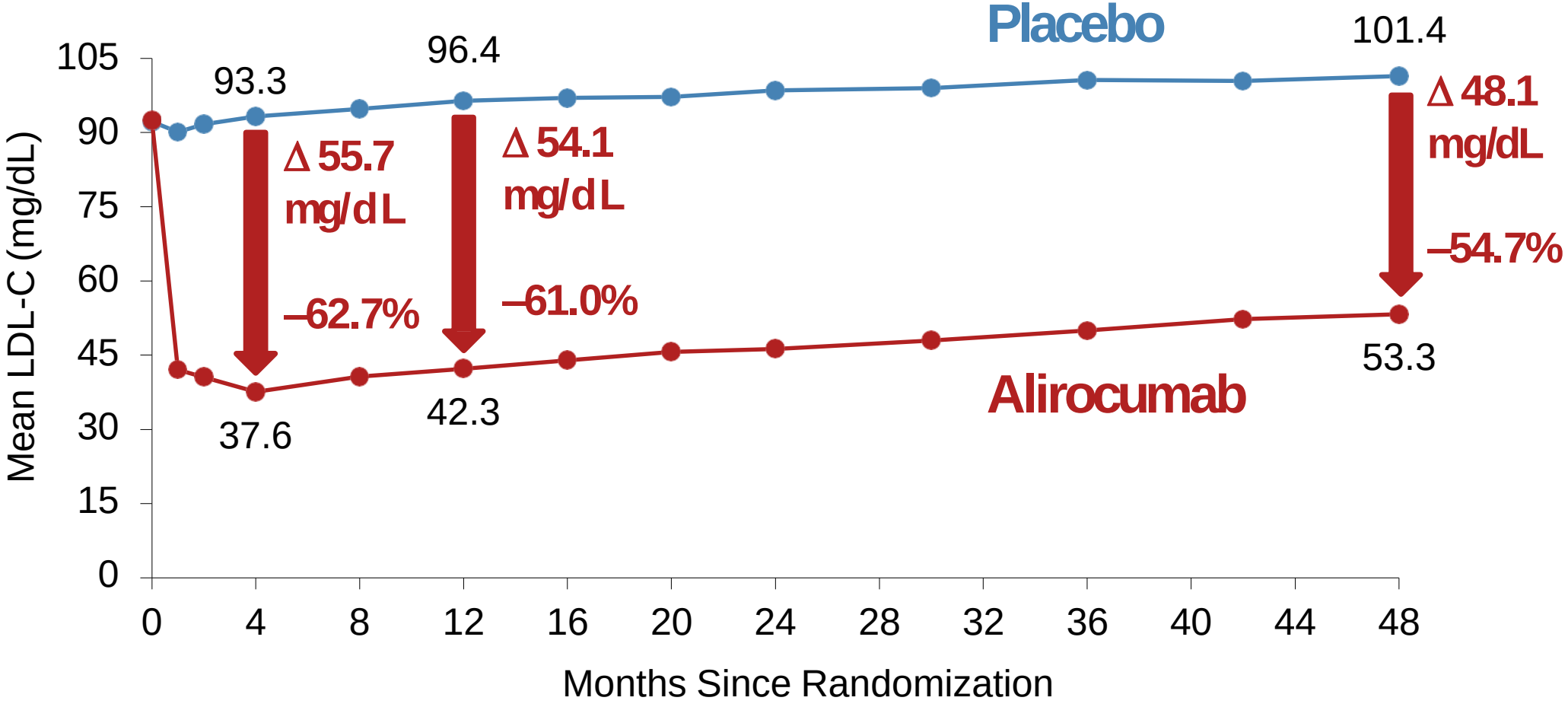
LDL-C: ITT and On-Treatment Analyses



*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

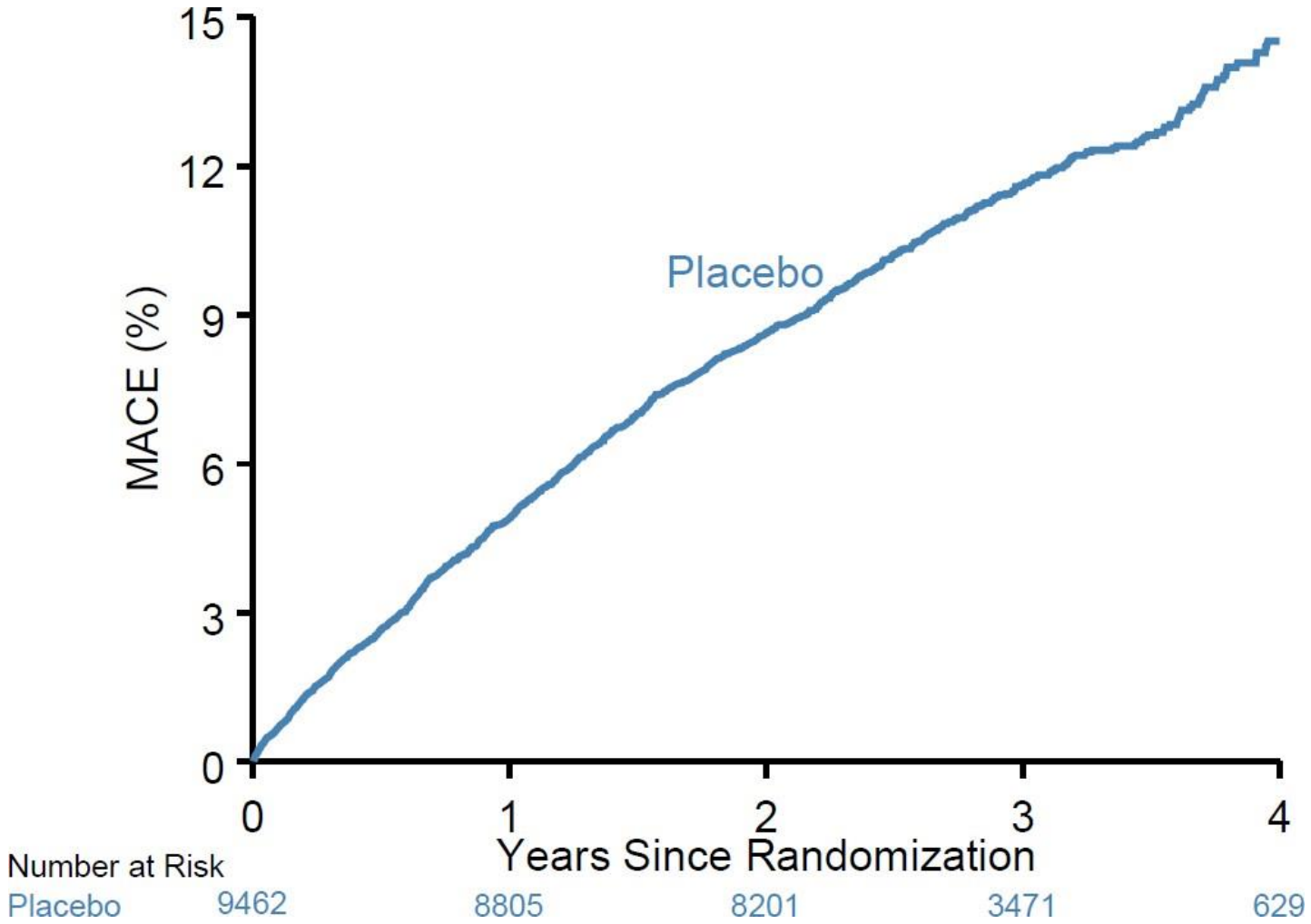
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

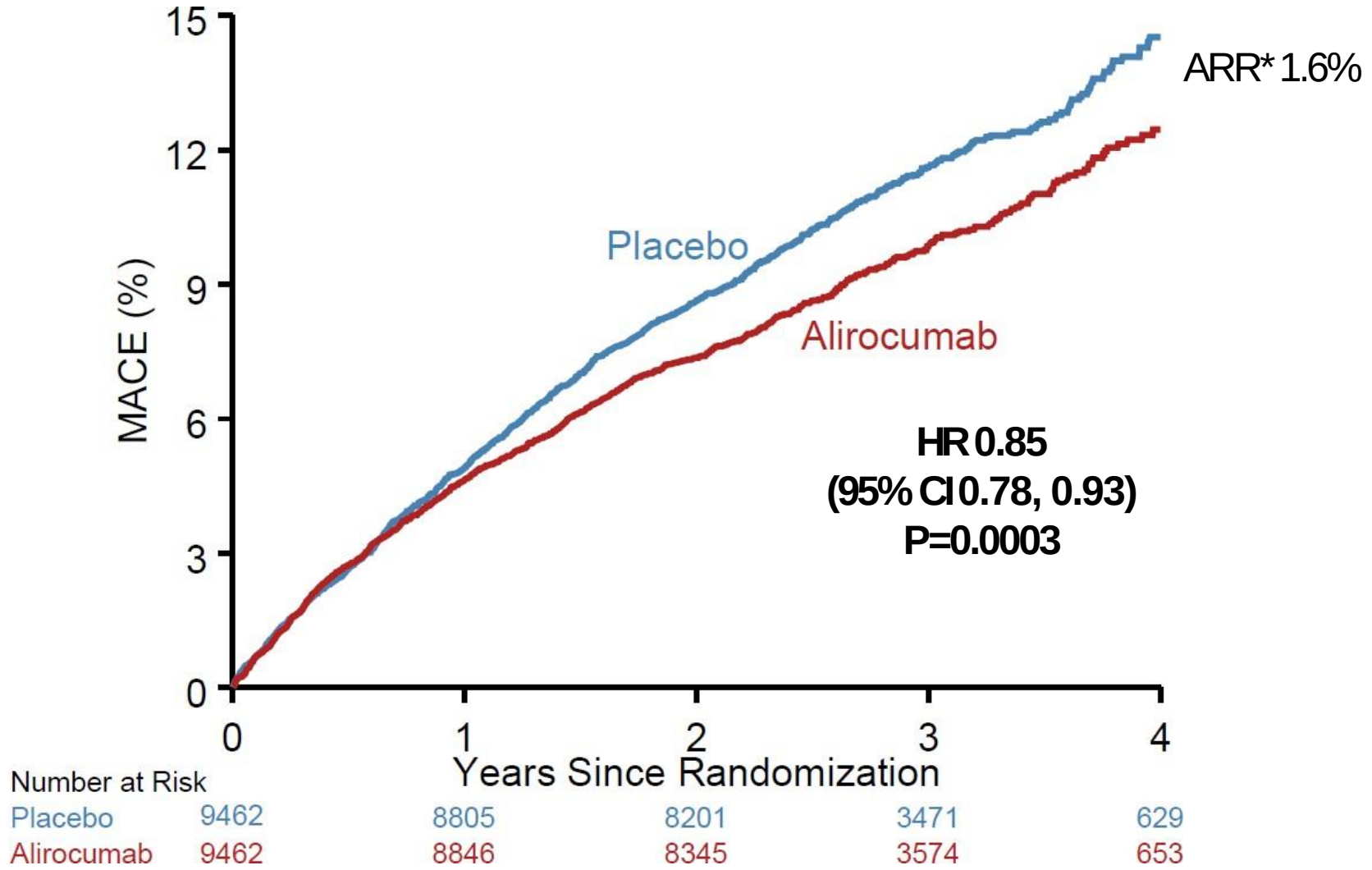
Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

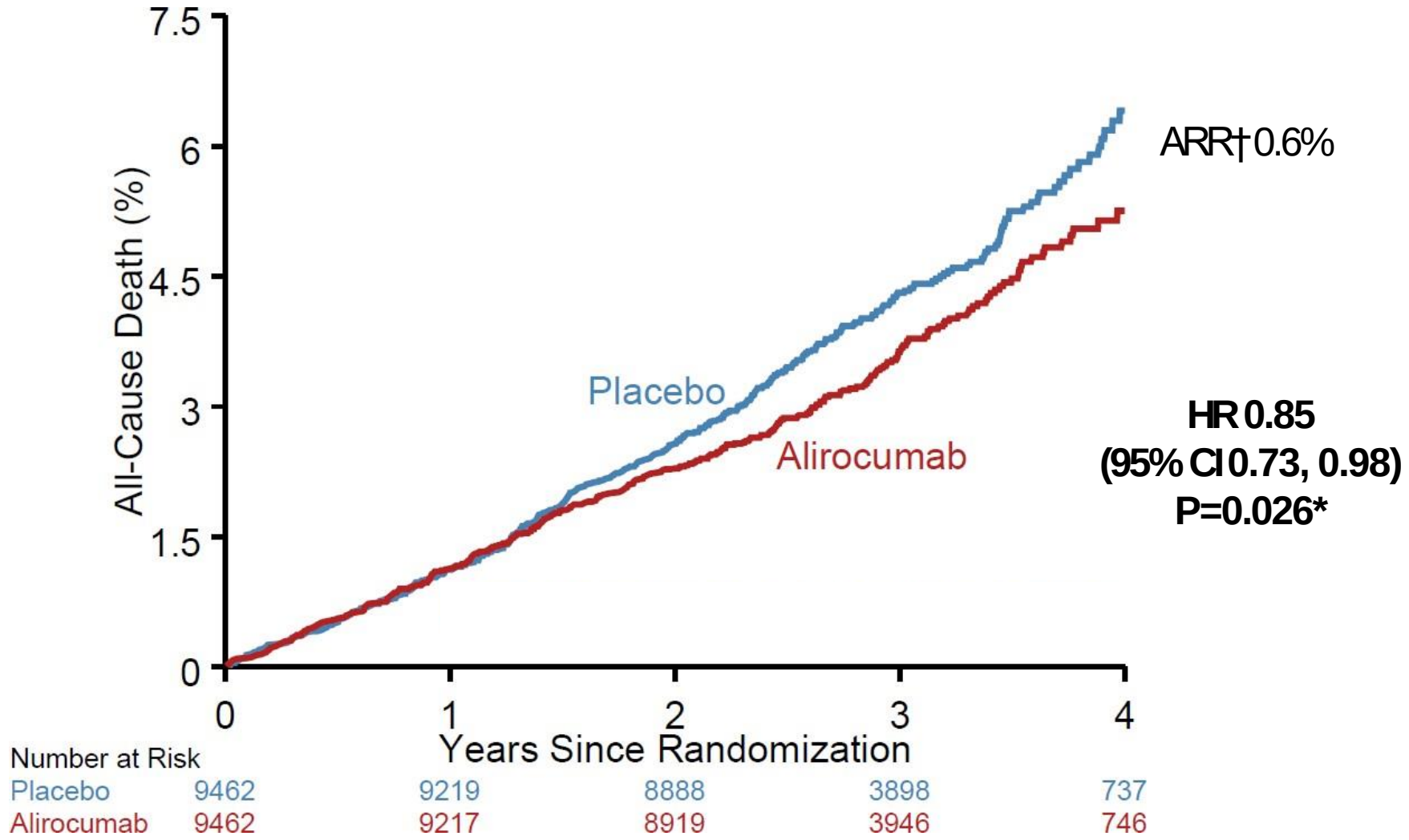


*Based on cumulative incidence

Primary Efficacy and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

All-Cause Death



*Nominal P-value
†Based on cumulative incidence

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions

Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢ These are the patients who may benefit most from treatment

ARR, absolute risk reduction

Results of the GLAGOV Trial

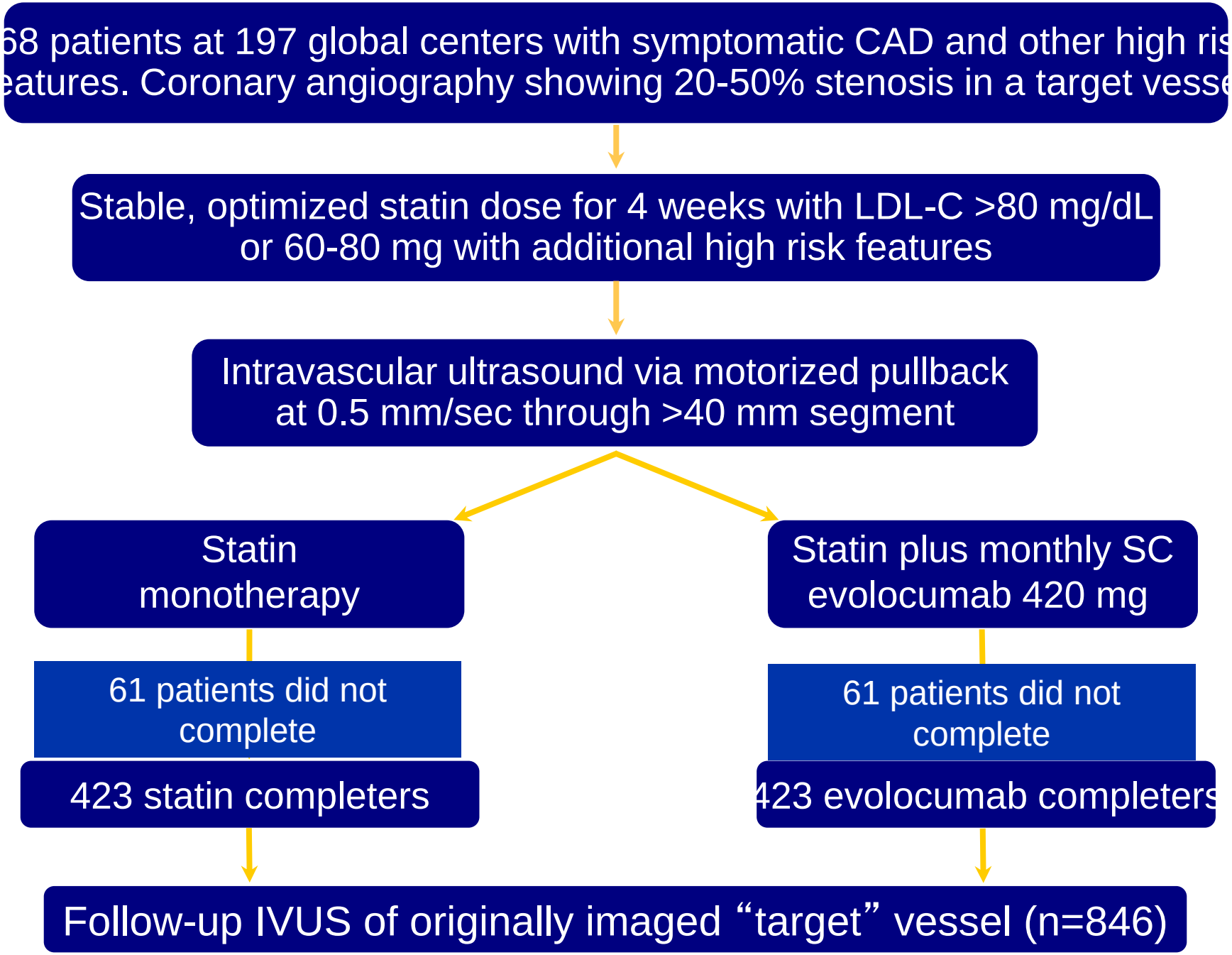
Steven E. Nissen MD
Stephen J. Nicholls MBBS PhD

Disclosure

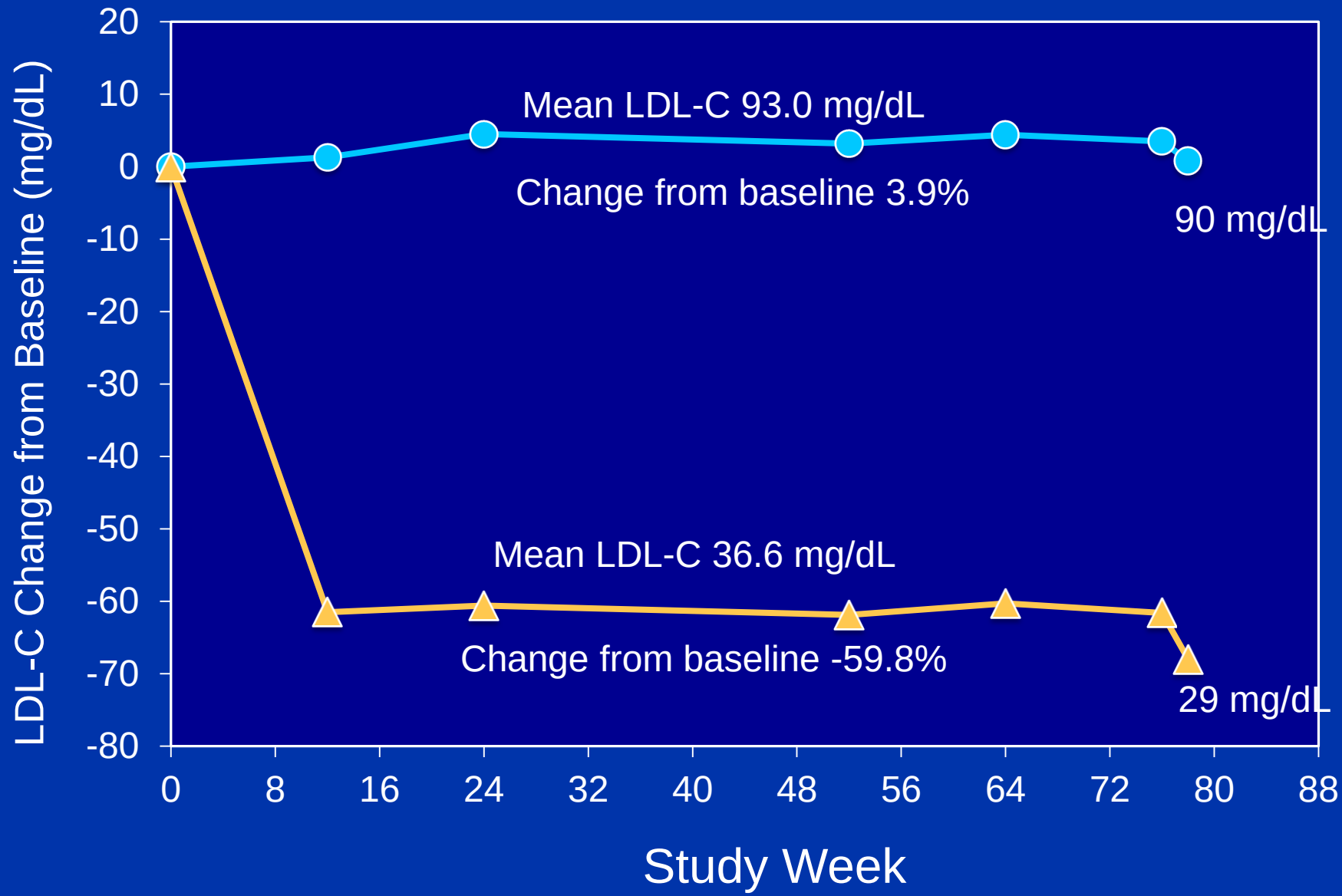
Sponsor: Amgen

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

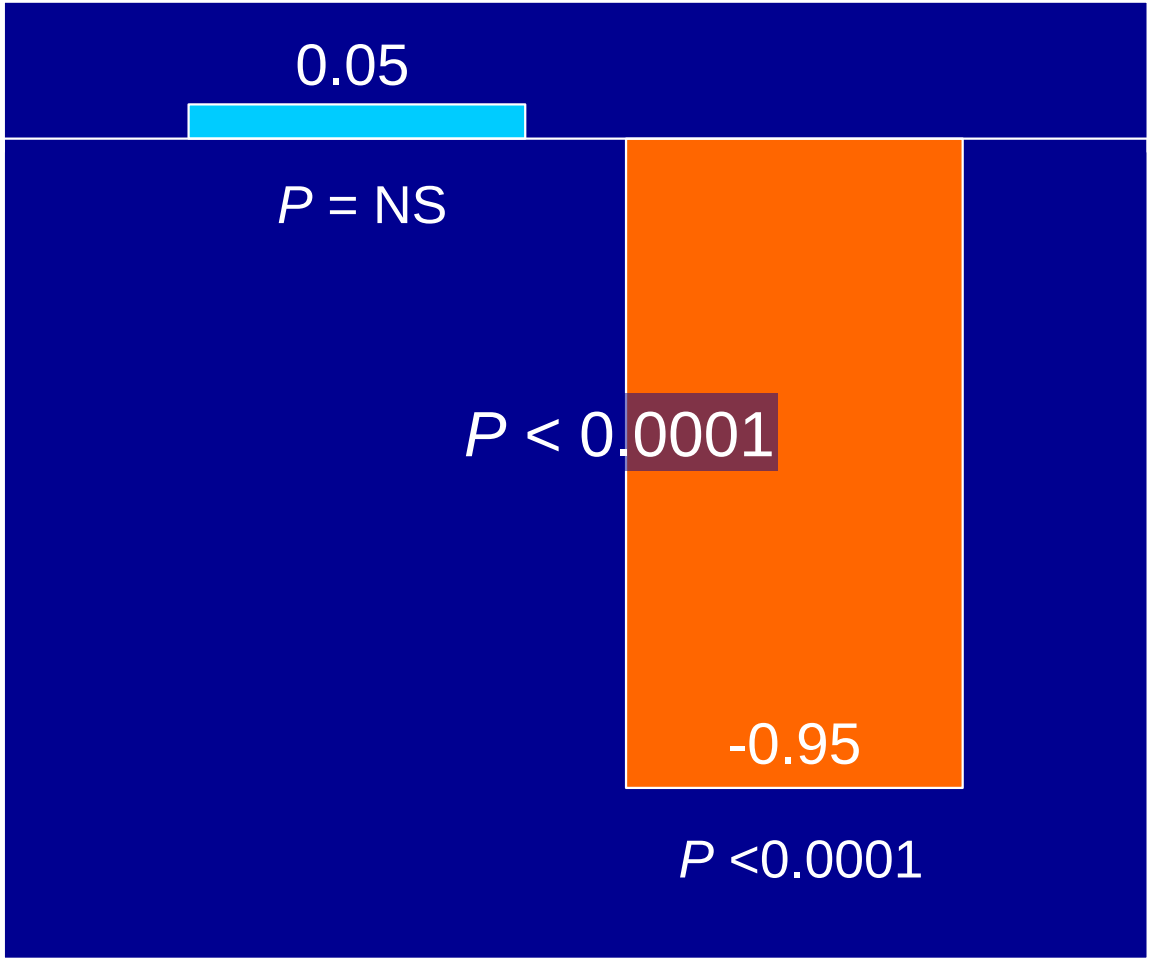
Companies are directed to pay any honoraria directly to charity. No personal reimbursement is accepted for directing or participating in clinical trials.


68 patients at 197 global centers with symptomatic CAD and other high ris
eatures. Coronary angiography showing 20-50% stenosis in a target vesse
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
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)

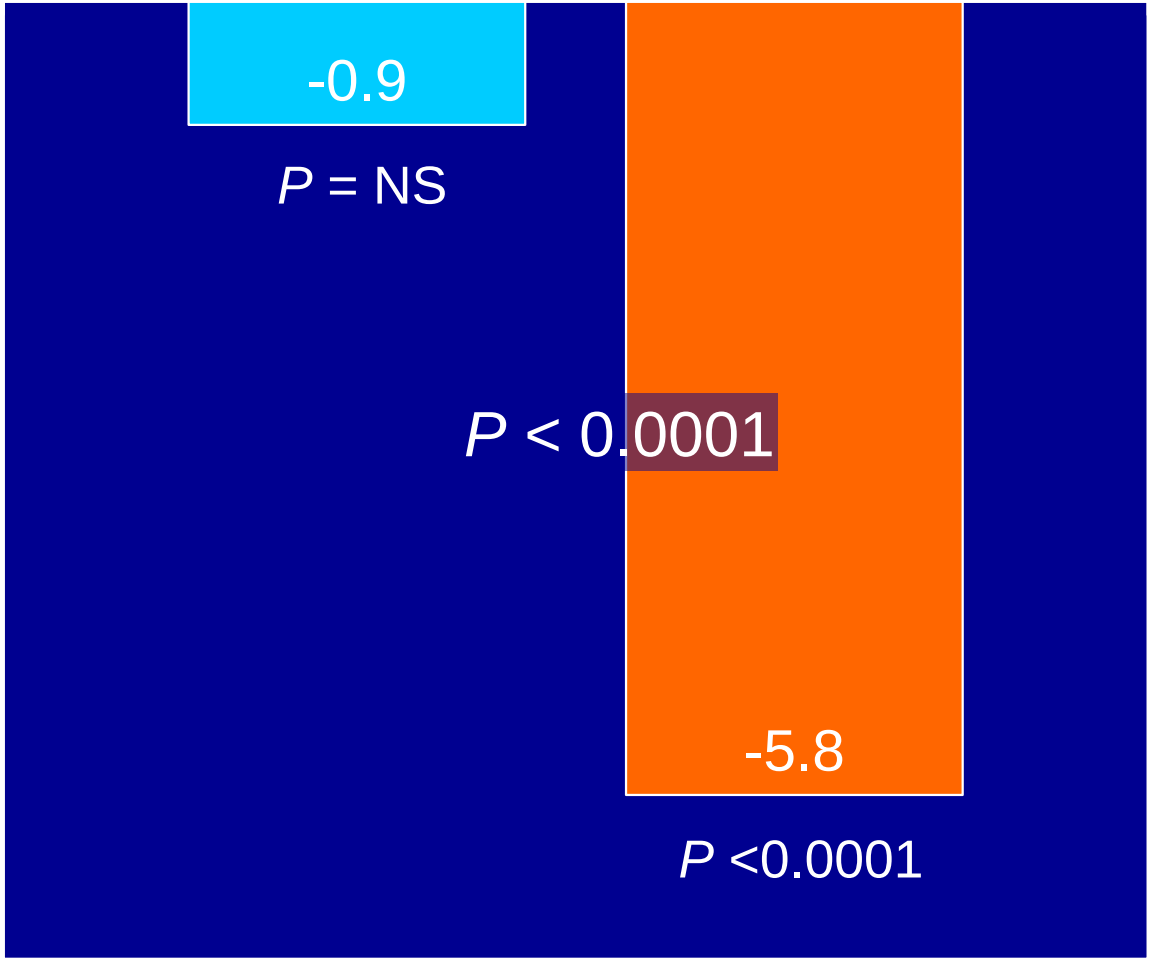
Change in LDL-Cholesterol During Treatment



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

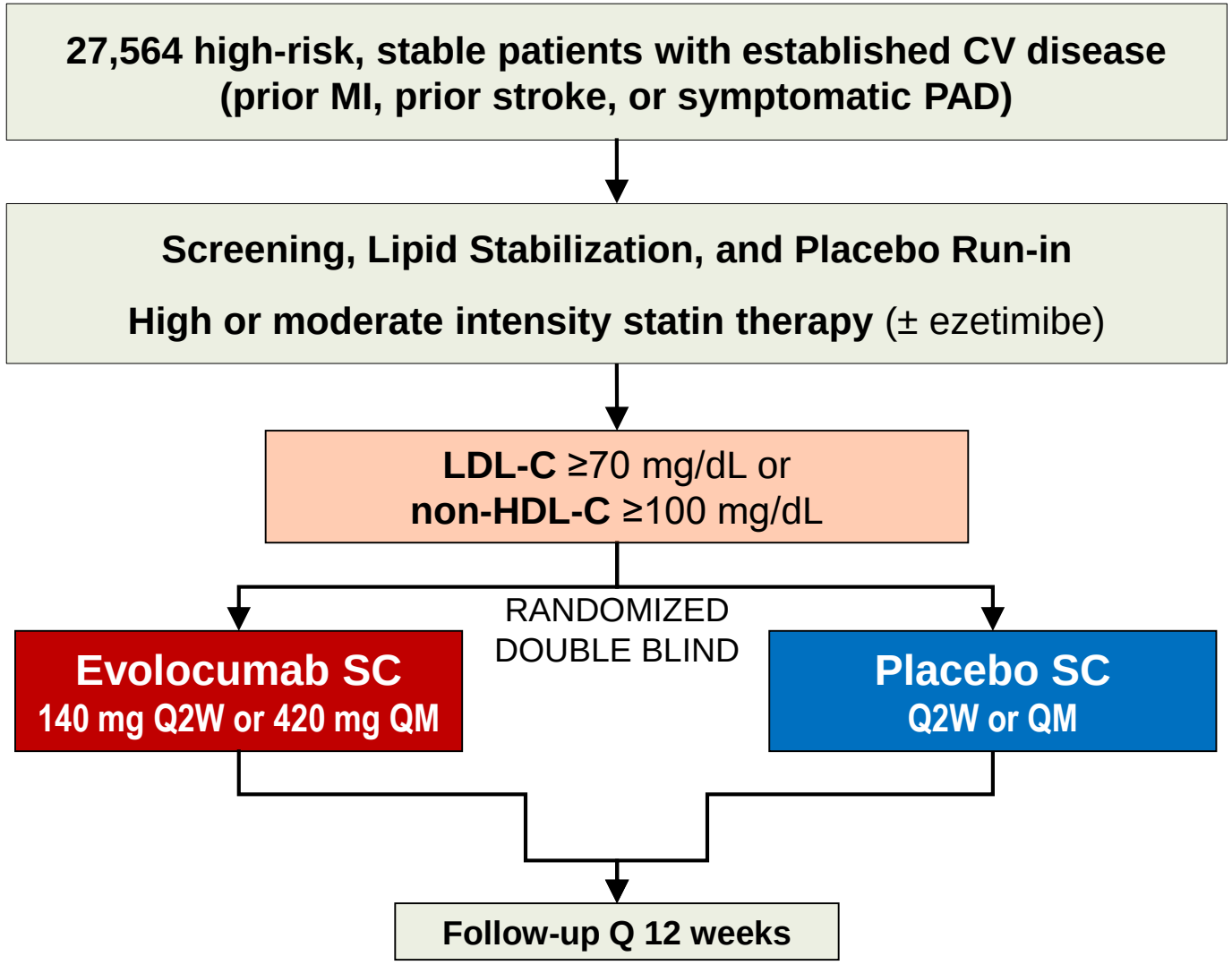
Objectives

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



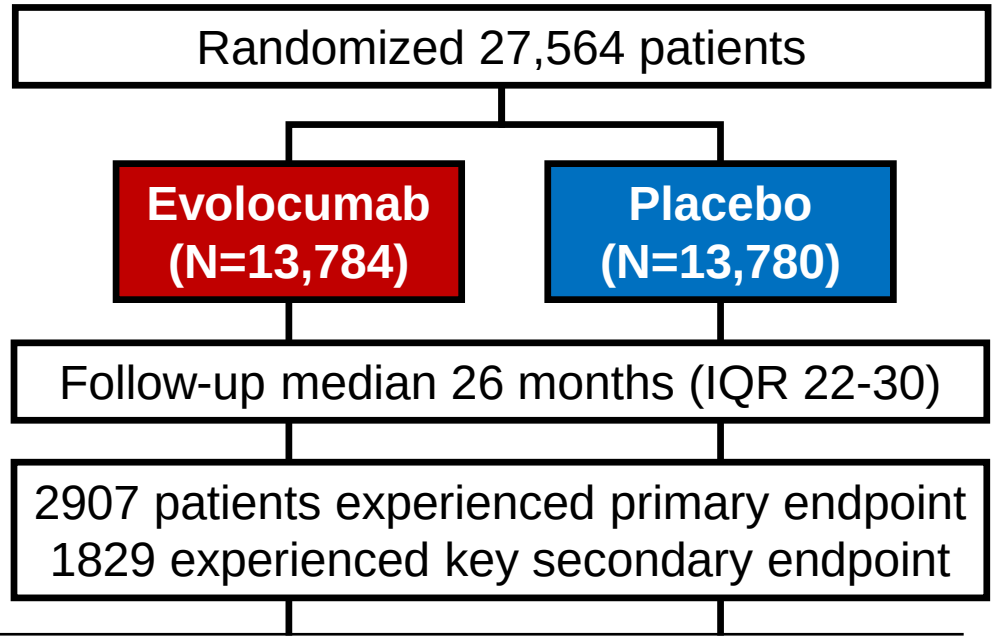
Sabatine MS et al. *Am Heart J* 2016;173:94-101

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

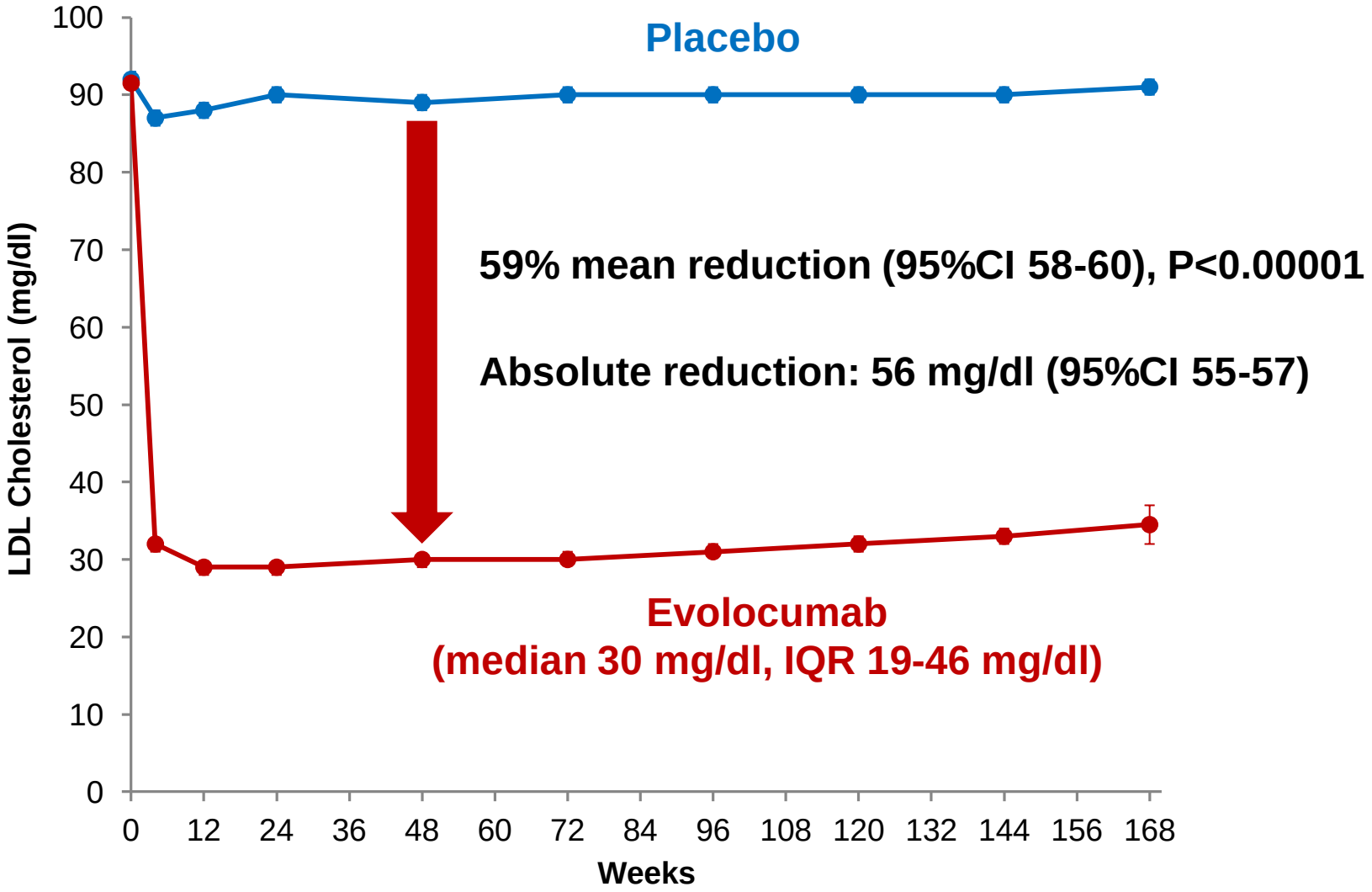
Lipid Lowering Therapy & Lipid Levels at Baseline

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)**

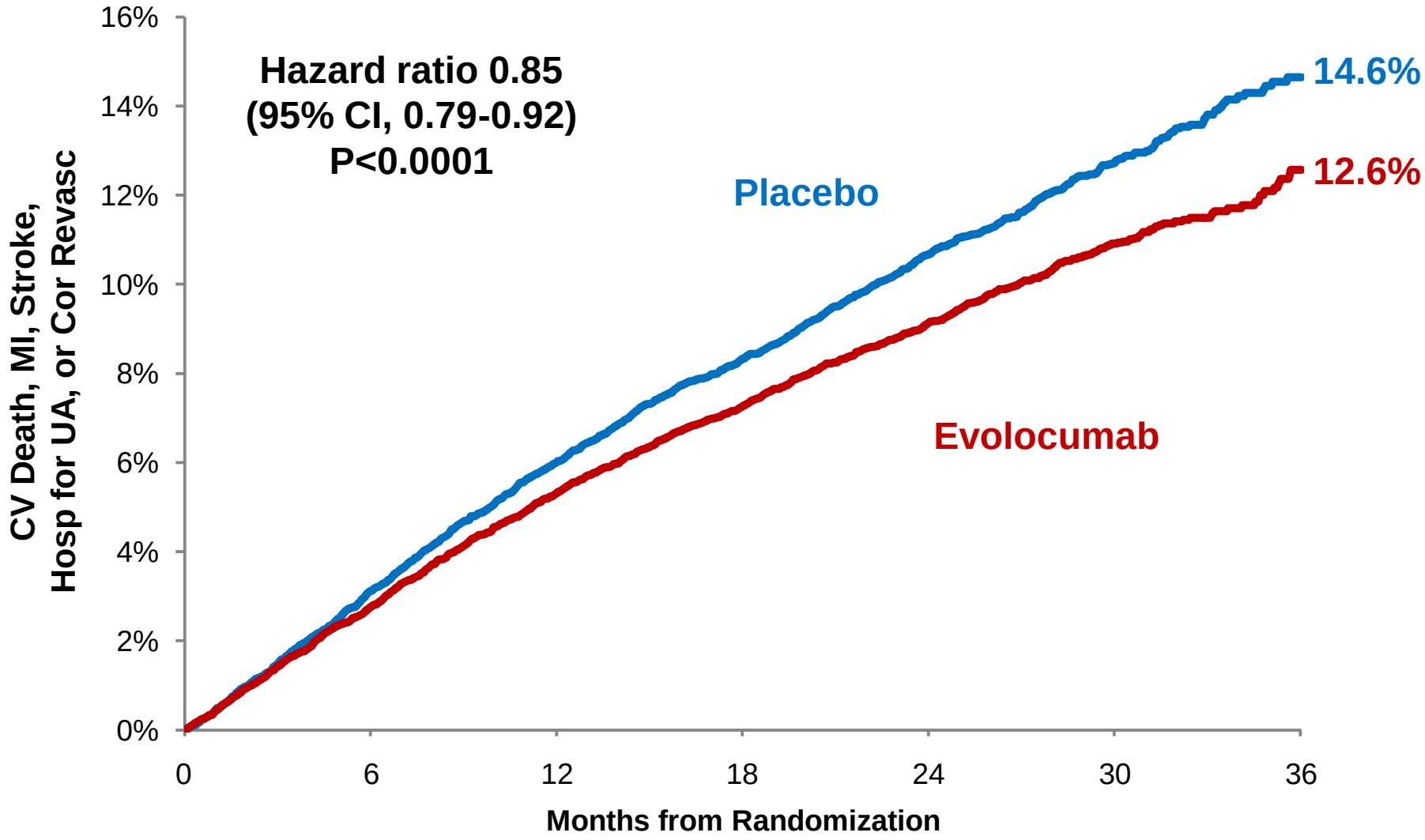
*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms

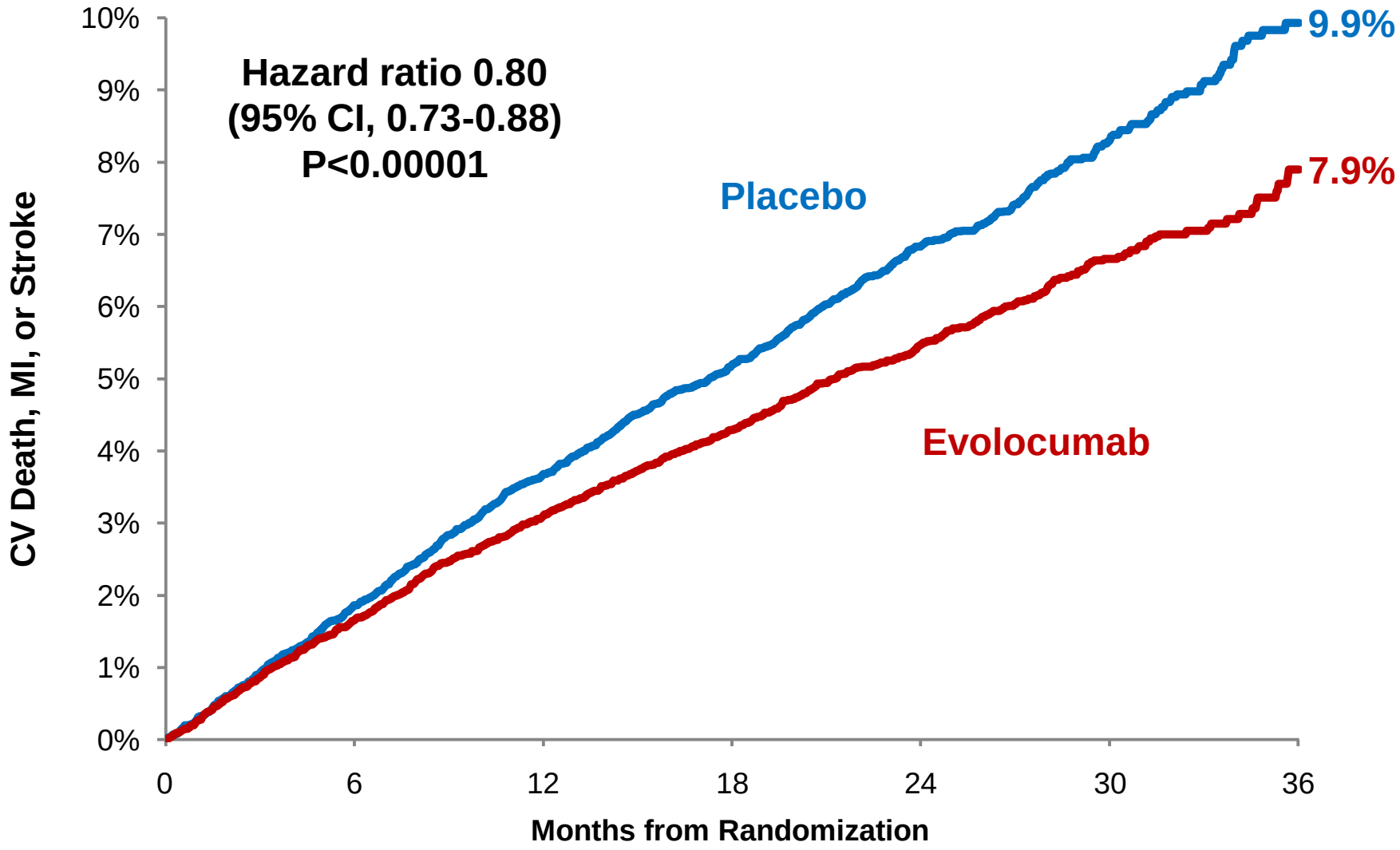
LDL Cholesterol



Primary Endpoint



Key Secondary Endpoint



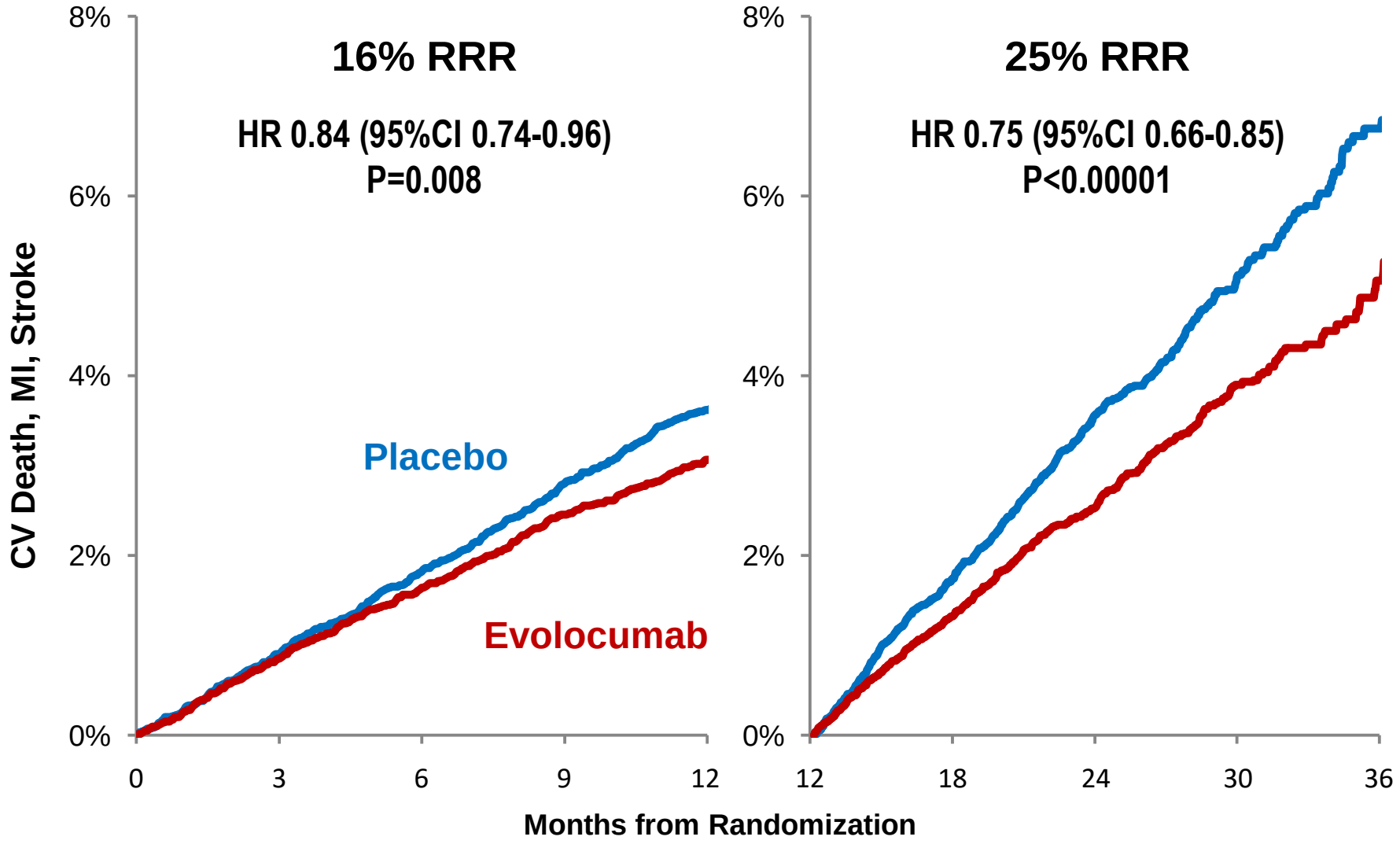
Types of CV Outcomes

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)

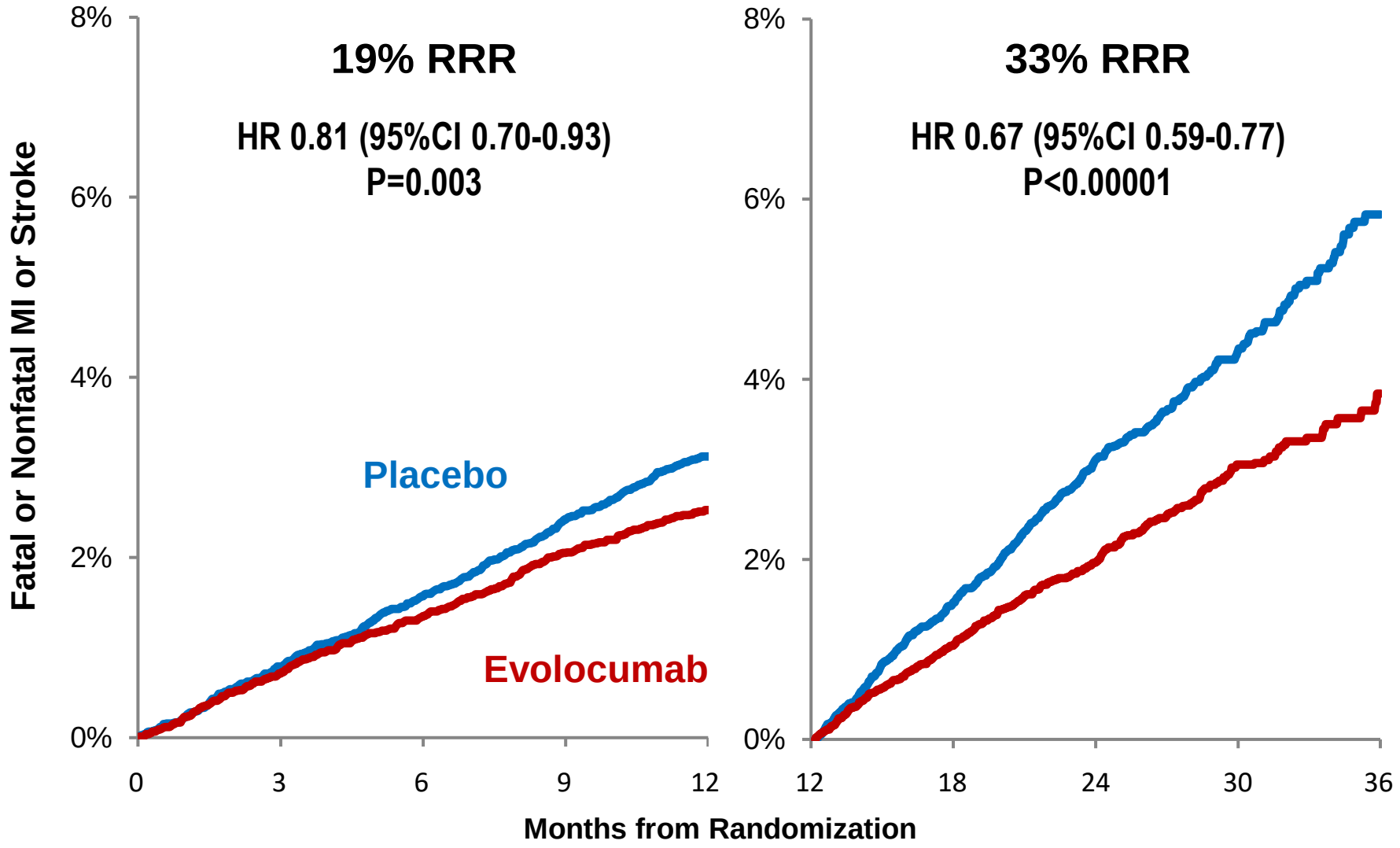
Types of CV Outcomes

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

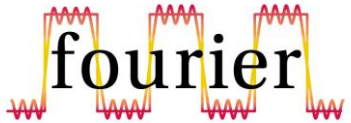
	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	**77.4**	**77.4**
Serious	**24.8**	**24.7**
Allergic reaction	**3.1**	**2.9**
Injection-site reaction	**2.1**	**1.6**
Treatment-related and led to d/c of study drug	**1.6**	**1.5**
Muscle-related	**5.0**	**4.8**
Cataract	**1.7**	**1.8**
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 1st 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


FIVE GUYS
BURGERS and FRIES
OPEN


ORDER
HERE

Top 10 Take-Home Messages

2018 Cholesterol Guidelines

Top 10 Take Home Messages

1. **In all individuals, emphasize a heart-healthy lifestyle across the life course**.

   A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

   In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Top 10 Take Home Messages

2. **In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.**

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

Top 10 Take Home Messages

Top 10

3. **In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.**

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable,
  although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.

Top 10 Take Home Messages

4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.**

   - If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable

   - If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered,
     although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.

Top 10 Take Home Messages

5. **In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.**

   In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

Top 10 Take Home Messages

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.

Top 10 Take Home Messages

7. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.**

   Risk-enhancing factors favor statin therapy (see No. 8).

   If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

Top 10 Take Home Messages

8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).**

Risk-enhancing factors include

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;

- history of preeclampsia or premature menopause (age <40 yrs)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);

Top 10 Take Home Messages

8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).**

Risk-enhancing factors include

and, if measured in selected individuals

- apolipoprotein B ≥130 mg/dL
- high-sensitivity C-reactive protein ≥2.0 mg/L
- ankle-brachial index <0.9 and l
- lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk)

Top 10 Take Home Messages

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

Top 10 Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

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