LDL cholesterol

how low to go and how do we get there?

Dr Chan ka Chun Alan
Associate consultant
Queen Elizabeth hospital

Wisdom from Scientist decades before

A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

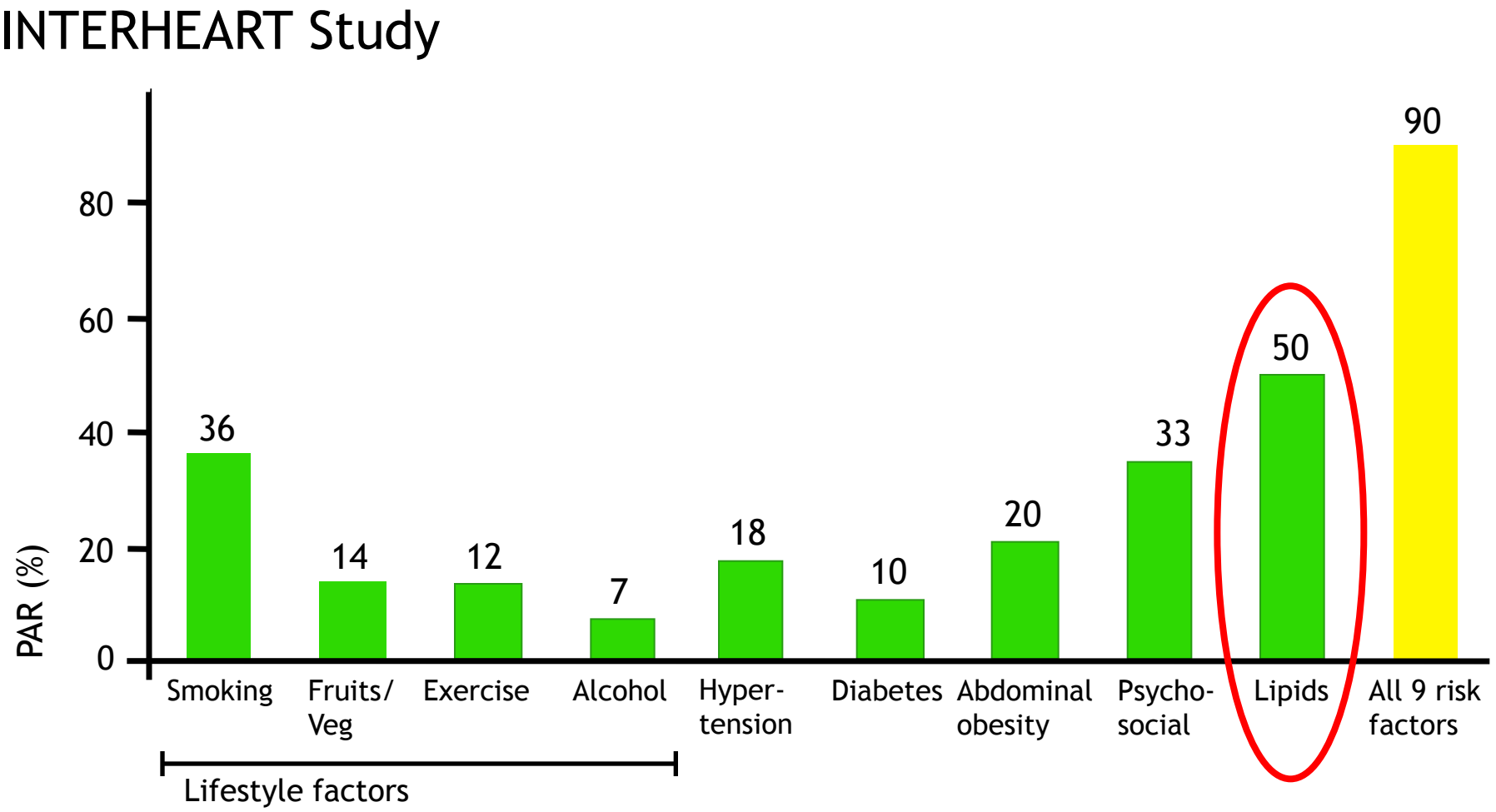
The LDL-receptor studies lend experimental support to the epidemiologists' suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (*9*). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (*28*). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (*118*). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (*119*). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.

Adapted from Nobel Prize Lecture, Stockholm, Sweden, 1985.
Science 1986;232:34.

4 major factor to consider

- Atherosclerotic cardiovascular disease (ASCVD)
- DM
- Predictive life time risk of ASCVD
- Baseline LDL-C level

Attributable Risk Factors for a First Myocardial Infarction

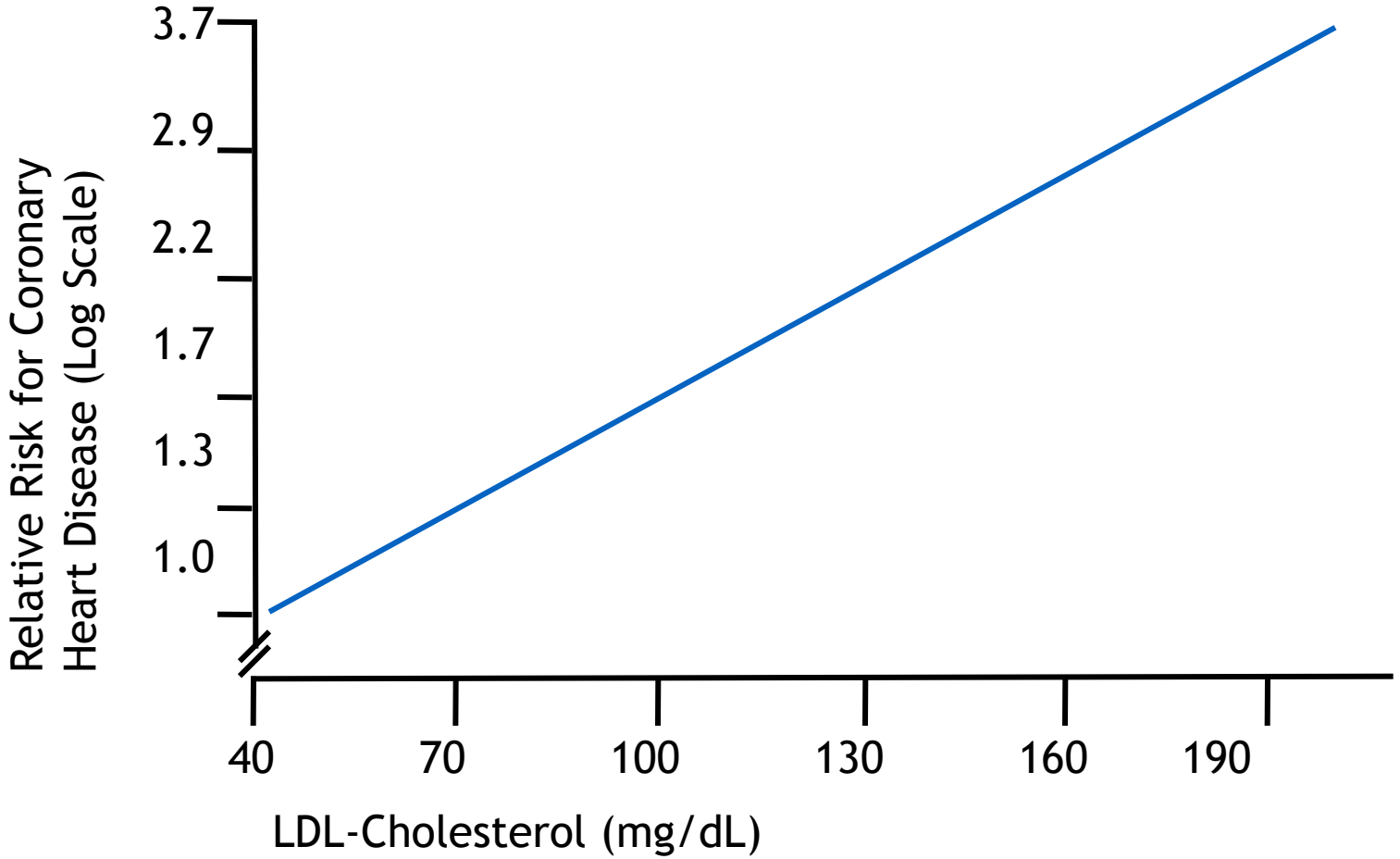


n=15,152 patients and 14,820 controls in 52 countries

MI=Myocardial infarction, PAR=Population attributable risk (adjusted for all risk factors)

Yusuf S et al. *Lancet*. 2004;364:937-952

Coronary Heart Disease Risk According to LDL-C Level



CHD=Coronary heart disease, LDL-C=Low-density lipoprotein cholesterol

Grundy S et al. *Circulation* 2004;110:227-239

2018 Guideline on the Management of Blood Cholesterol

GUIDELINES MADE SIMPLE

A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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Risk Stratification: Framingham Risk Score On Line Calculator

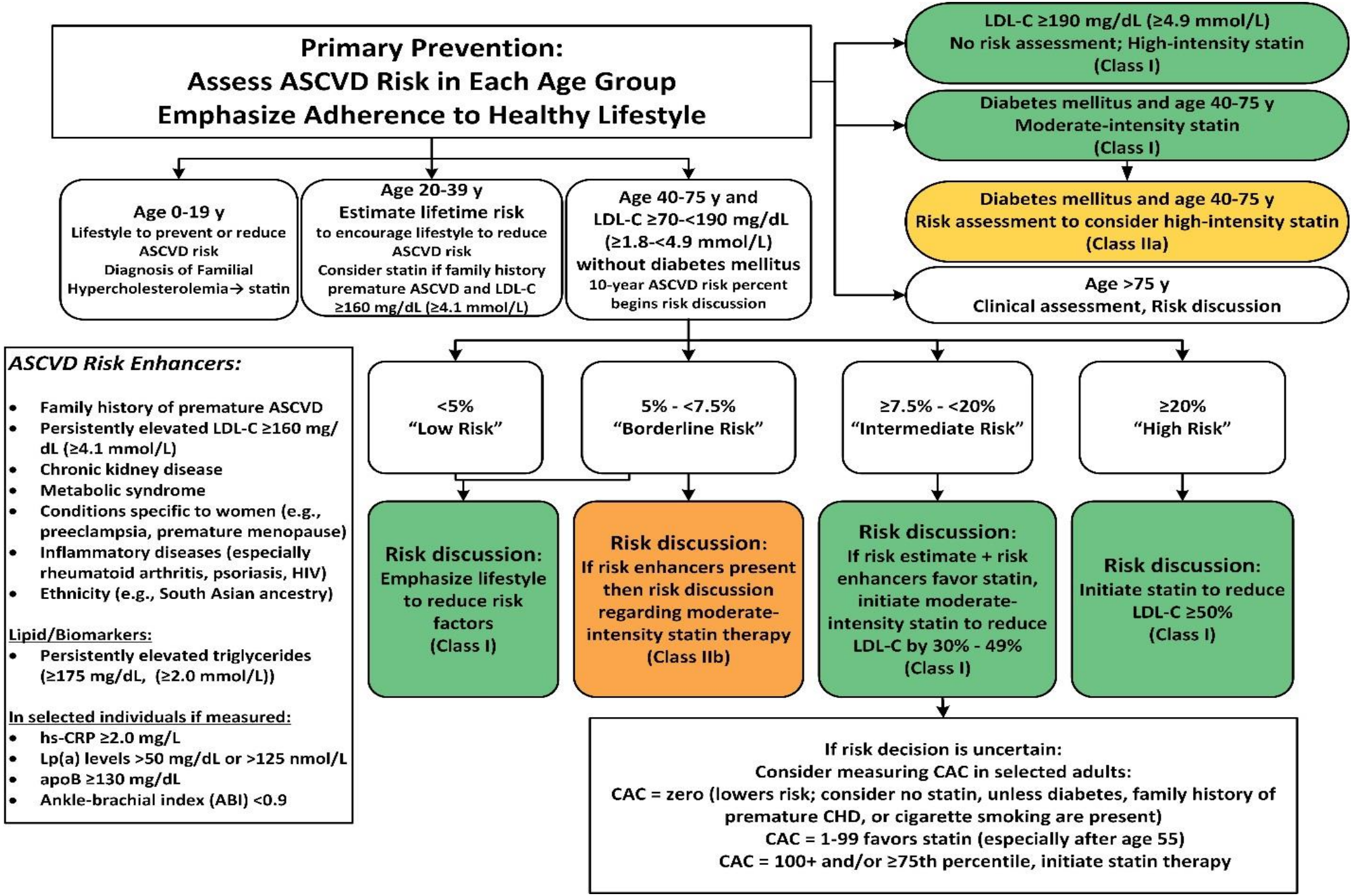
Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

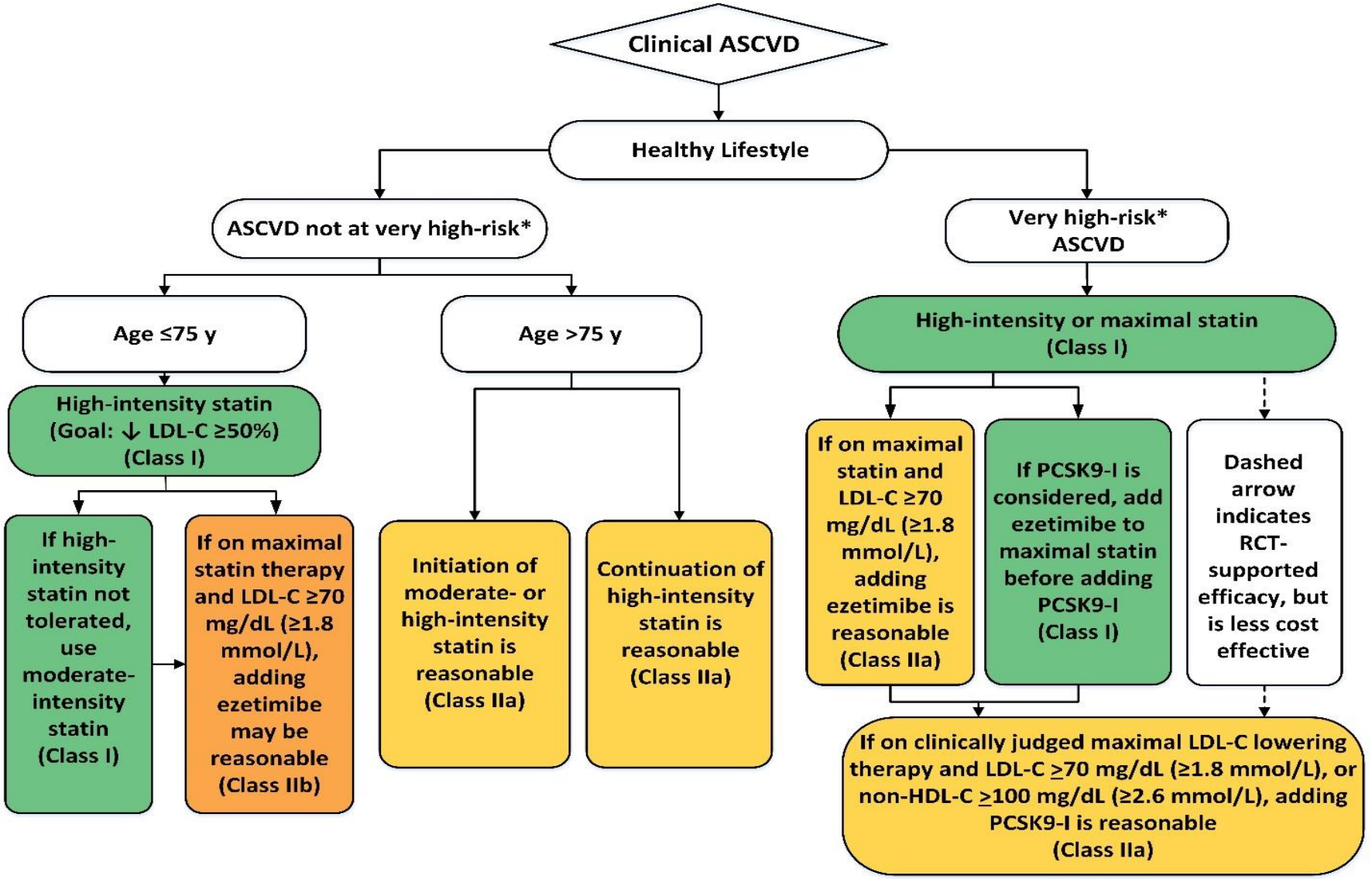
Age:	☐ years
Gender:	○ Female ○ Male
Total Cholesterol:	☐ mg/dL
HDL Cholesterol:	☐ mg/dL
Smoker:	○ No ○ Yes
Systolic Blood Pressure:	☐ mm/Hg
Are you currently on any medication to treat high blood pressure.	○ No ○ Yes

Calculate Your 10-Year Risk

Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Risk Assessment Tool. http://hp2010.nhlbihin.net/atpiii/calculator.asp


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
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
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
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

Secondary Prevention



ESC/EAS 2016 Dyslipidemia Guidelines: Lipid Targets[1]

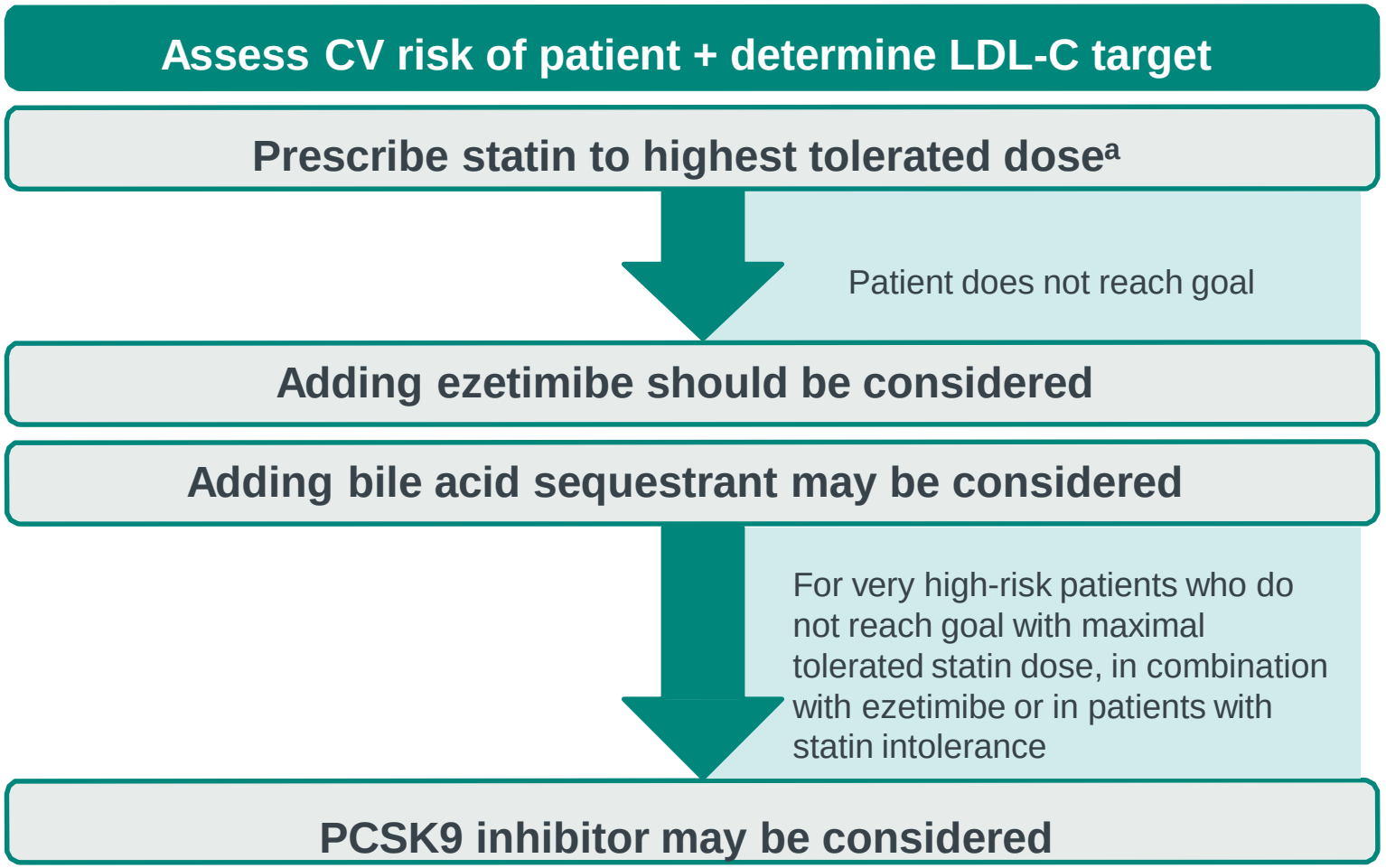
Risk Category	LDL-C (Primary Treatment Target)	
	On LLT	NOT on LLT
Very high risk Documented CVD,[a] clinical or unequivocal on imaging; **DM with target organ damage or with a major risk factor**[c]; severe CKD (GFR <30 mL/min/1.73 m^2); or a calculated SCORE ≥10%	<1.8 mmol/L (<70 mg/dL)	<1.8 mmol/L (<70 mg/dL) or a ≥50% reduction if untreated baseline[b] LDL-C is 1.8–3.5 mmol/L (70–135 mg/dL)
High risk Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) or BP ≥180/110 mmHg; most other people with DM (except young people with type 1 DM and without very high levels of individual risk factors, who may be at low or moderate risk); moderate CKD (GFR 30–59 mL/min/1.73 m^2); or a calculated SCORE ≥5% and <10%	<2.6 mmol/L (<100 mg/dL)	<2.6 mmol/L (<100 mg/dL) or a ≥50% reduction if untreated baseline[b] LDL-C is 2.6–5.2 mmol/L (100–200 mg/dL)
Moderate risk SCORE is ≥1% and <5% at 10 years	<3.0 mmol/L (<115 mg/dL)	

- ApoB (secondary target) <80 mg/dL for very high-risk individuals and <100 mg/dL for high-risk subjects
- Non–HDL-C (secondary target) <2.6 mmol/L (100 mg/dL) and <3.4 mmol/L (130 mg/dL) for very high-risk and high-risk individuals, respectively

[a]Documented clinical CVD includes previous MI, ACS, coronary revascularization (percutaneous coronary intervention , coronary artery bypass graft surgery) and other arterial revascularization procedures, stroke and transient ischemic attack , and peripheral arterial disease. Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
[b]Untreated baseline LDL-C is defined as not taking any lipid-lowering medication.
[c]Such as smoking, hypertension, and dyslipidemia.
ESC = European Society of Cardiology; EAS = European Artherosclerosis Society; CVD = cardiovascular disease; DM = diabetes mellitus; CKD = chronic kidney disease; GFR = glomerular filtration rate; SCORE = Systematic Coronary Risk Evaluation [SCORE estimates the 10-yr risk of a first fatal atherosclerotic event]; LLT = lipid-lowering therapy; BP = blood pressure; MI = myocardial infarction; ACS = acute coronary syndrome.

1. Catapano AL et al. *Atherosclerosis*. 2016;253:281–344.

ESC/EAS 2016 Dyslipidemia Guidelines: Pharmacological Treatment Pathway for Lowering LDL-C[1]



[a]For statin intolerance, ezetimibe and bile acid sequestrants (or combination of these 2 therapies) should be considered.

ESC = European Society of Cardiology; EAS = European Artherosclerosis Society; CV = cardiovascular; PCSK9 = proprotein convertase subtilisin/kexin type 9.

1. Catapano AL et al. *Atherosclerosis*. 2016;253:281–344.

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

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering†	≥50%	30% to 49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 (40 mg)**	**Atorvastatin 10 mg (20 mg)** **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg**§	Simvastatin 10 mg
	–	**Pravastatin 40 mg (80 mg)** **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

HMG-CoA Reductase Inhibitor: Chronological Order of Event Driven Trials

Study populations:

Primary prevention

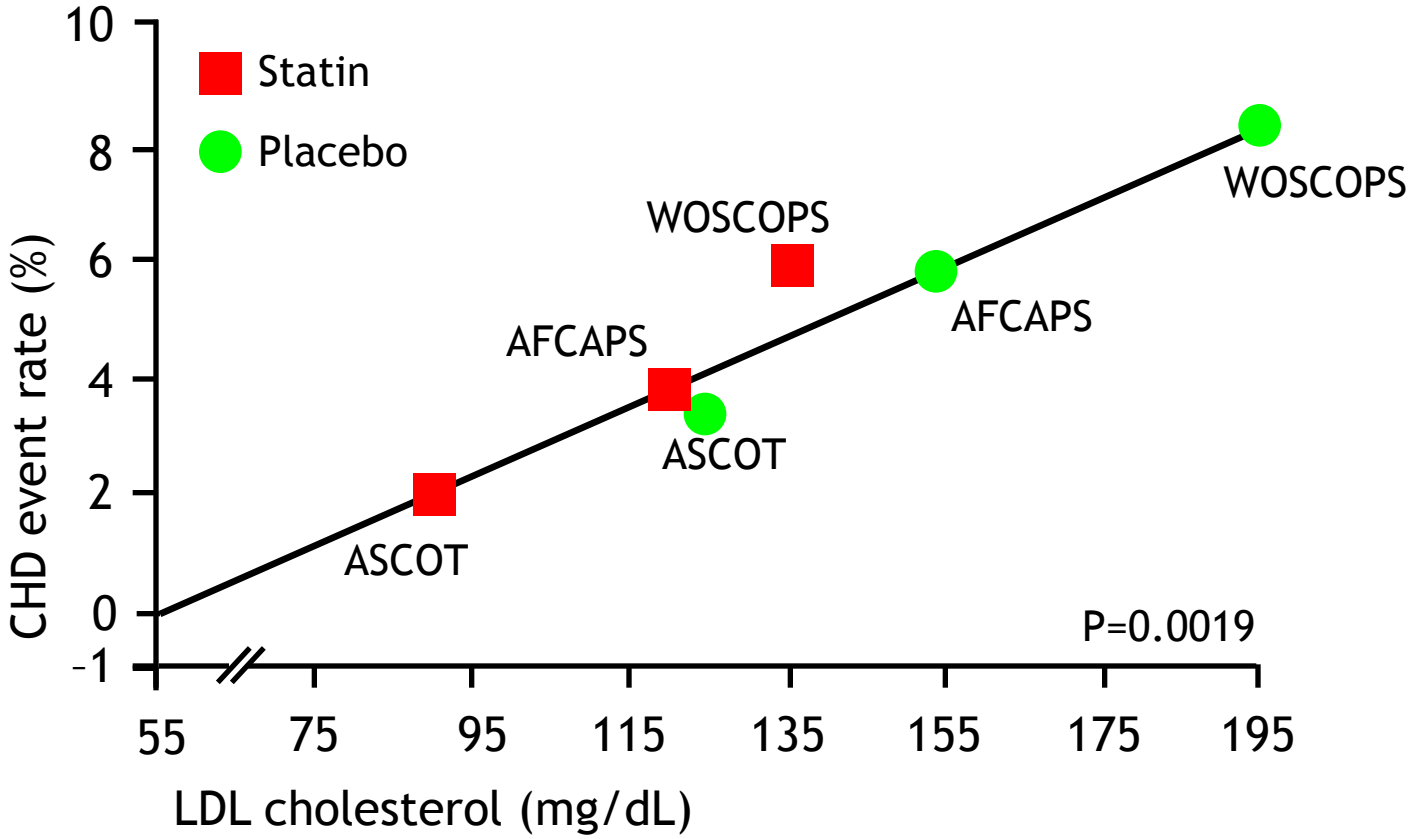
Acute coronary syndromes (Secondary prevention)

Chronic coronary heart disease (Secondary prevention)

1994	4S
1995	WOSCOPS
1996	CARE
1998	AFCAPS/TEXCAPS
1998	LIPID
2001	MIRACL
2002	HPS
2002	PROSPER
2002	ALLHAT-LLA
2002	ASCOT-LLA
2004	PROVE- IT
2004	A to Z
2005	TNT
2005	IDEAL
2008	JUPITER
2010	SEARCH

HMG-CoA Reductase Inhibitor Evidence: Primary Prevention

Relationship between LDL-C levels and event rates in select primary prevention statin trials

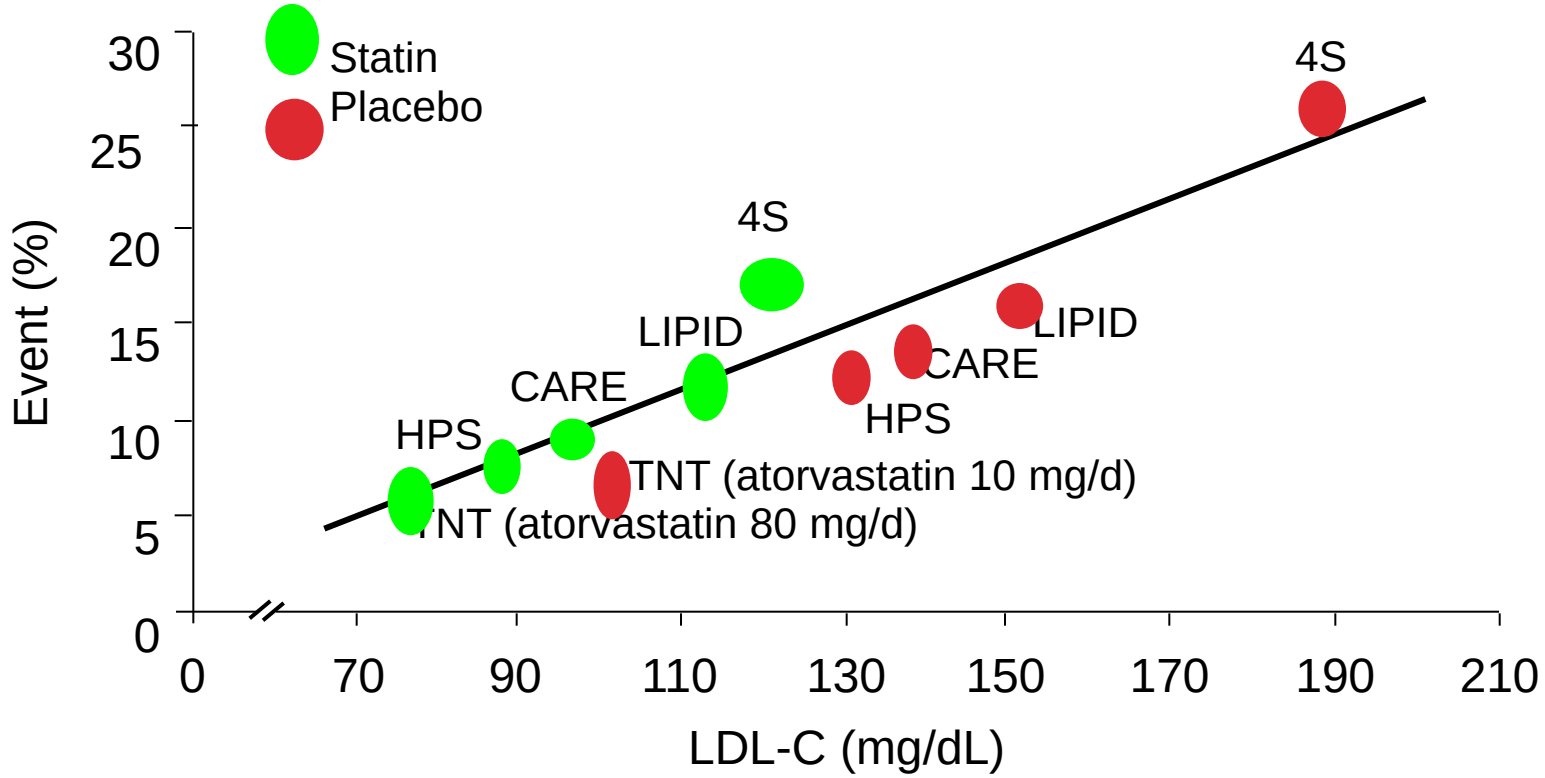


AFCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study, ASCOT= Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, LDL-C=Low density lipoprotein cholesterol, WOSCOPS= West of Scotland Coronary Prevention Study

O'Keefe JH Jr et al. *JACC* 2004;43:2142-2146

HMG-CoA Reductase Inhibitor Evidence: Secondary Prevention

Relationship between LDL-C levels and event rates in secondary prevention statin trials of patients with stable CHD



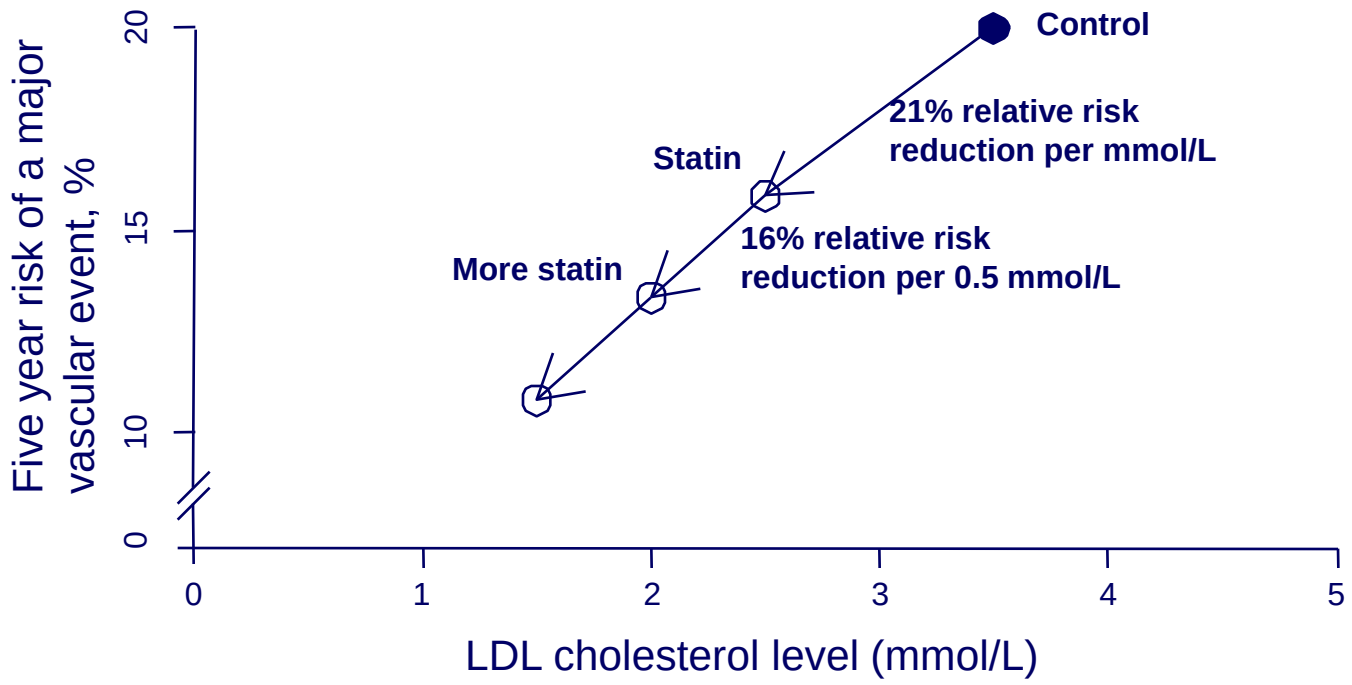
CARE=Cholesterol and Recurrent Events Trial, CHD=Coronary heart disease, HPS=Heart Protection Study, LDL-C=Low density lipoprotein cholesterol, LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease, 4S=Simvastatin Survival Study, TNT=Treating to New Targets

LaRosa JC et al. *NEJM* 2005;352:1425-1435

HMG-CoA Reductase Inhibitor Evidence: Effect of Intensive Therapy

Cholesterol Treatment Trialists' (CTT) Collaboration

Meta-analysis of 169,138 patients randomized to at least 2 years of statin therapy



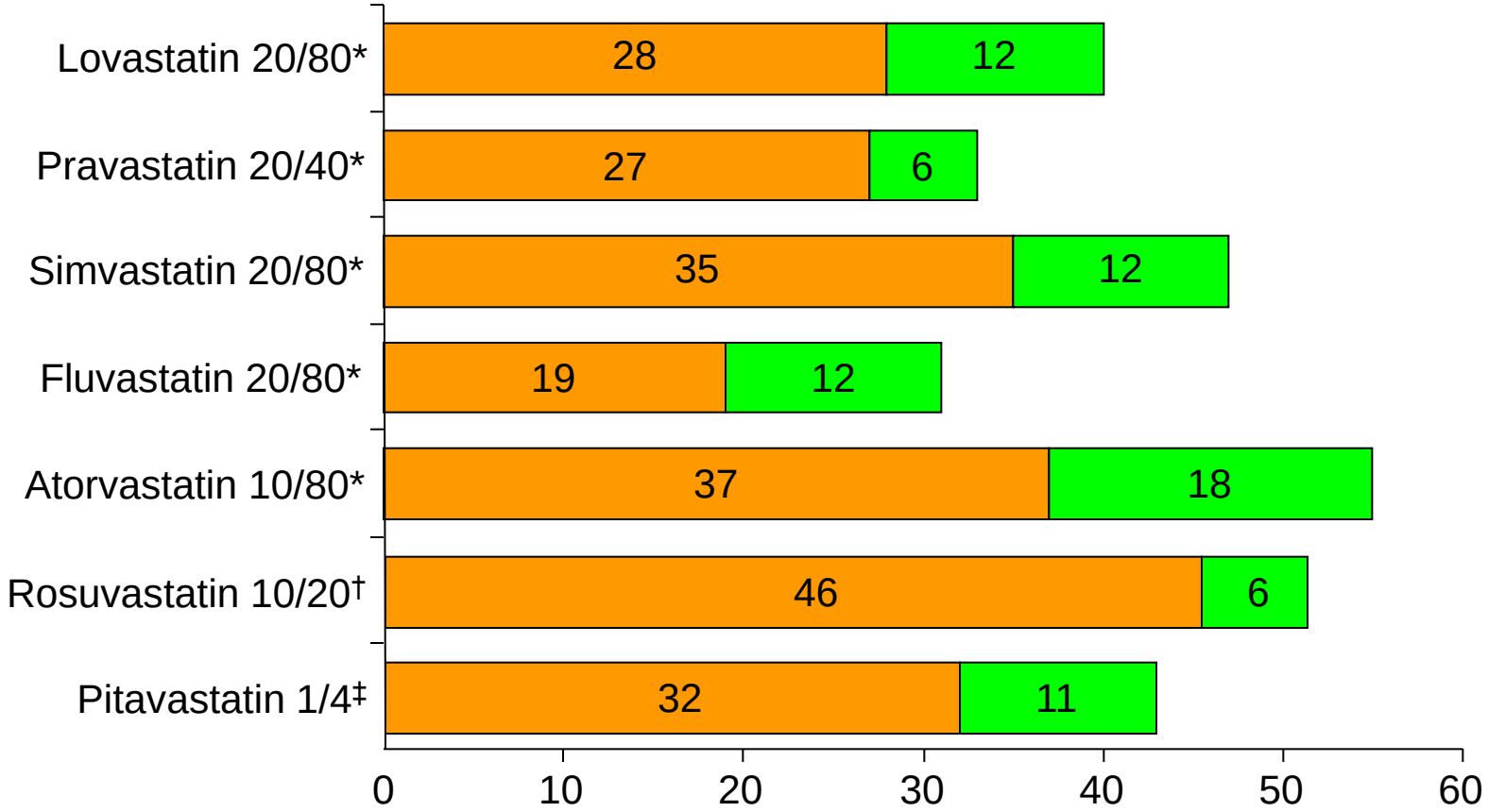
There is a proportionate reduction in CV events with greater LDL-cholesterol reduction

CV=Cardiovascular, LDL=Low density lipoprotein

Source: Cholesterol Treatment Trialists' Collaboration. Lancet 2010;376:1670-1681

HMG-CoA Reductase Inhibitor: Dose-Dependent Effect

The Rule of 6's



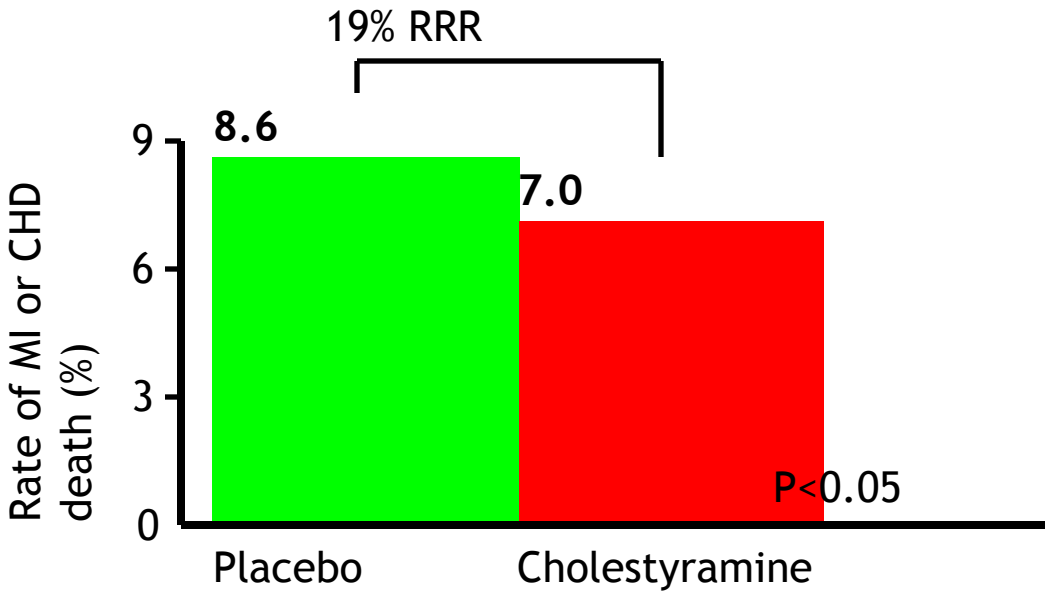
Each doubling of the statin dose produces an approximate 6% reduction in the LDL-C level

Sources:
*Illingworth DR. *Med Clin North Am* 2000;84-23-42
†Crestor Package Insert. http://www1.astrazeneca-us.com/pi/crestor.pdf
‡Livalo Package Insert. http://www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf

Bile Acid Sequestrant Evidence: Primary Prevention

Lipid Research Clinics-Coronary Primary Prevention Trial (LRC-CPPT)

3,806 men with primary hypercholesterolemia randomized to cholestyramine (24 grams) or placebo for 7.4 years



A bile acid sequestrant provides benefit in those with high cholesterol levels

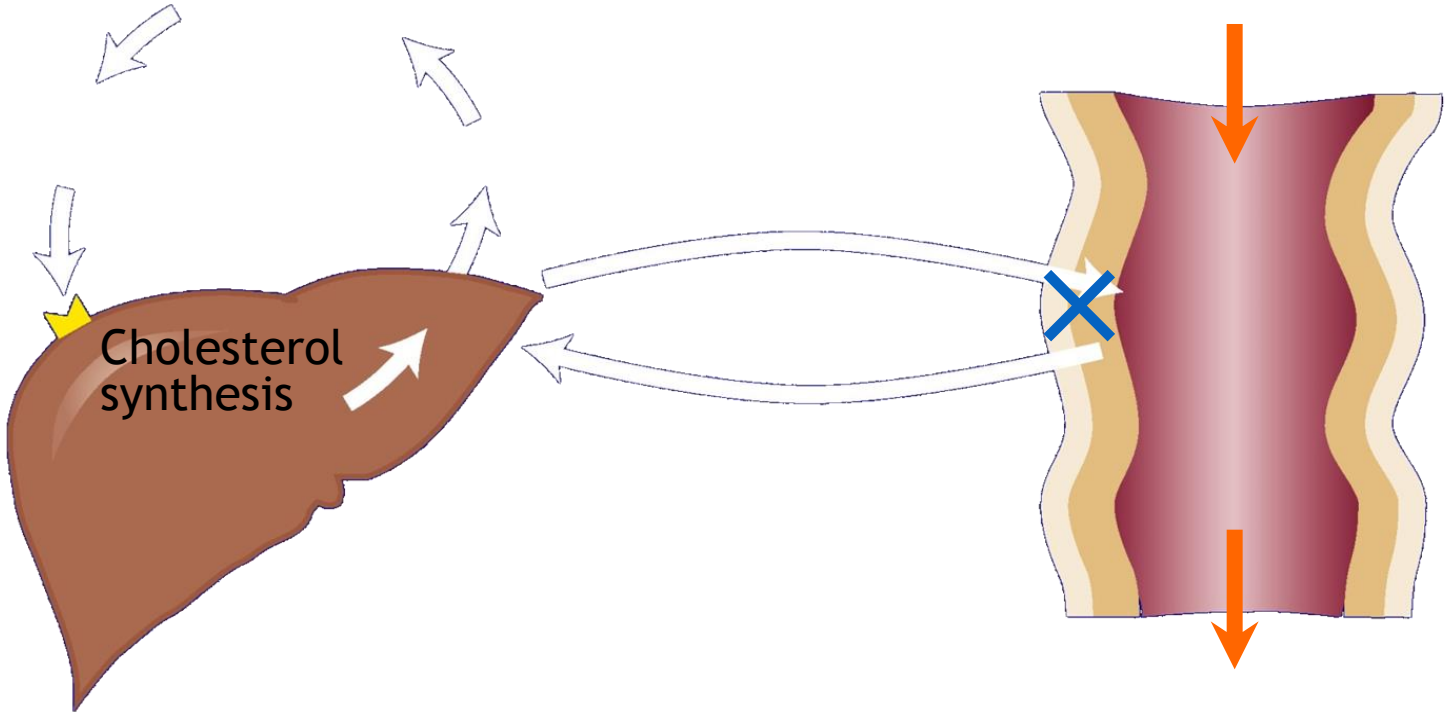
CHD=Coronary heart disease, MI=Myocardial infarction, RRR=Relative risk reduction

Source: The LRC-CPPT Investigators. *JAMA* 1984;251:351-364

Ezetimibe: Mechanism of Action

Production in liver

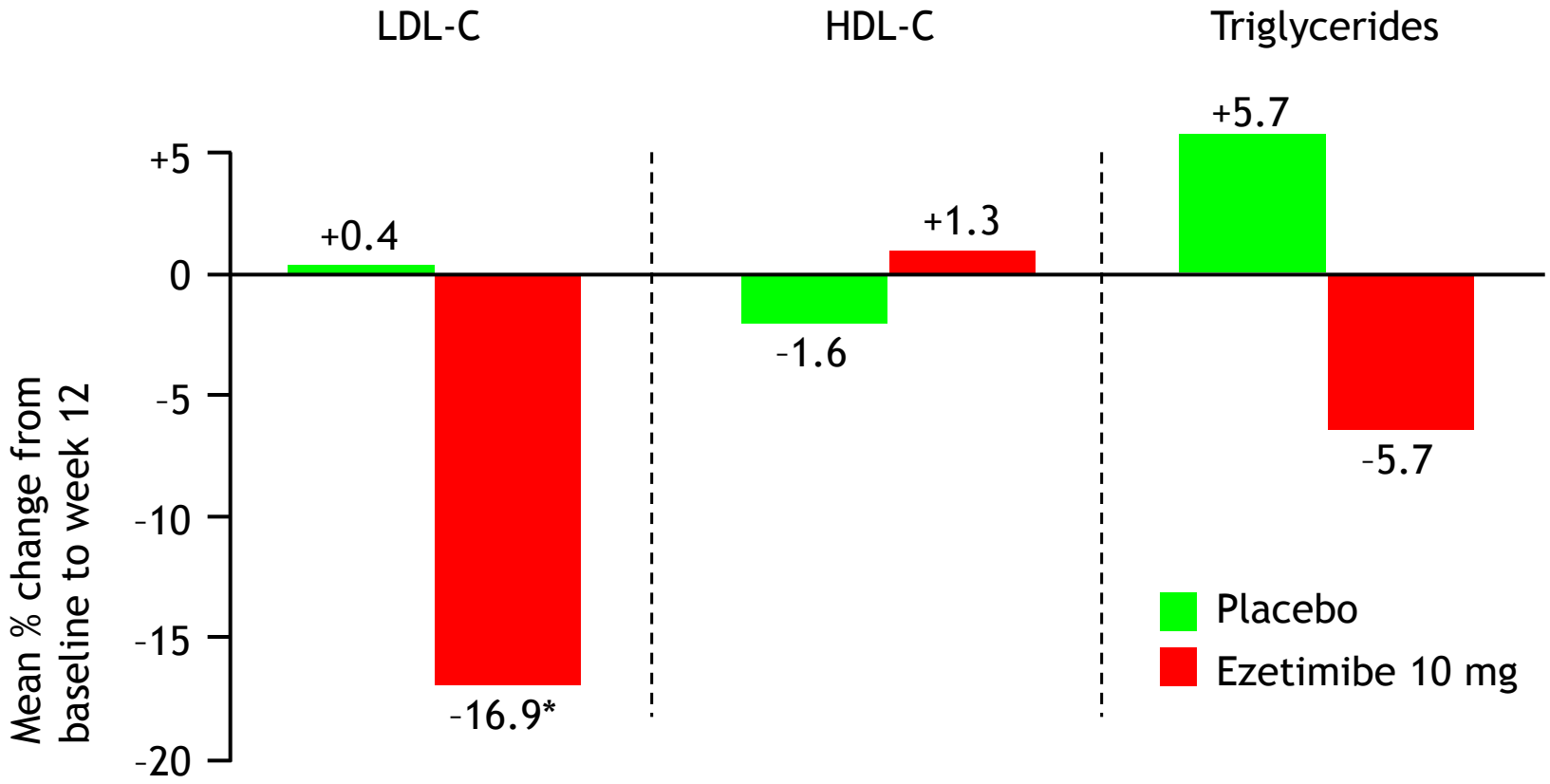
Absorption from intestine



Fecal sterols and neutral sterols

Ezetimibe Evidence: Efficacy at Reducing LDL-C

892 patients with primary hypercholesterolemia randomized to ezetimibe (10 mg) or placebo for 12 weeks



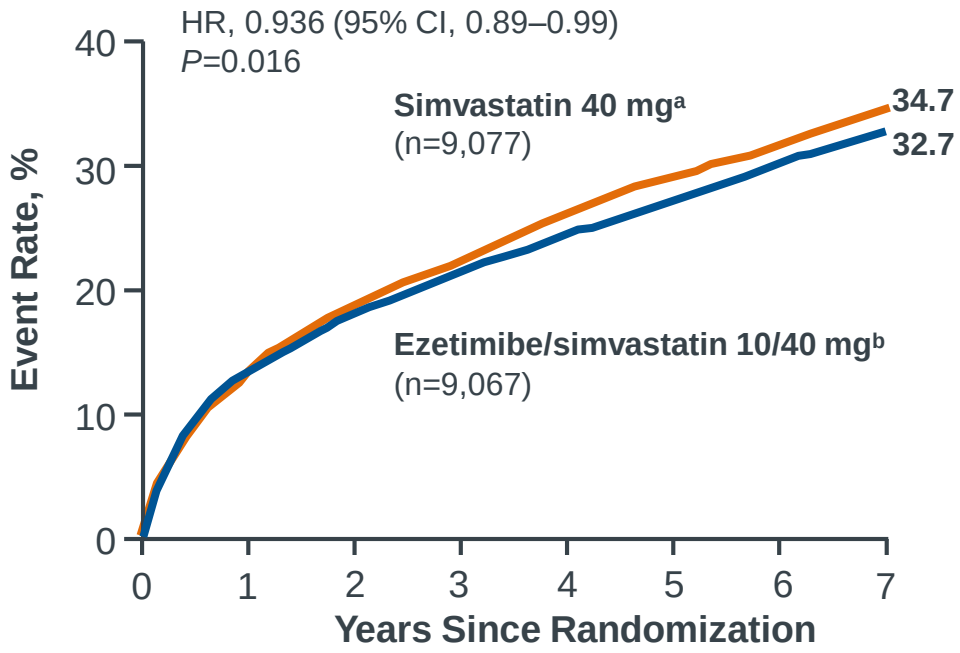
*p<0.01 compared to placebo

HDL-C=High density lipoprotein cholesterol,
LDL-C=Low density lipoprotein cholesterol

Dujovne CA et al. *Am J Cardiol* 2002;90:1092-1097

IMPROVE-IT: Ezetimibe + Statin Improved CV Outcomes Beyond a Statin Alone[1]

Ezetimibe/simvastatin significantly reduced CV events more than simvastatin alone



Primary End Point

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

Used with permission from Cannon CP et al.[1]

[a]27% were uptitrated to simvastatin 80 mg.

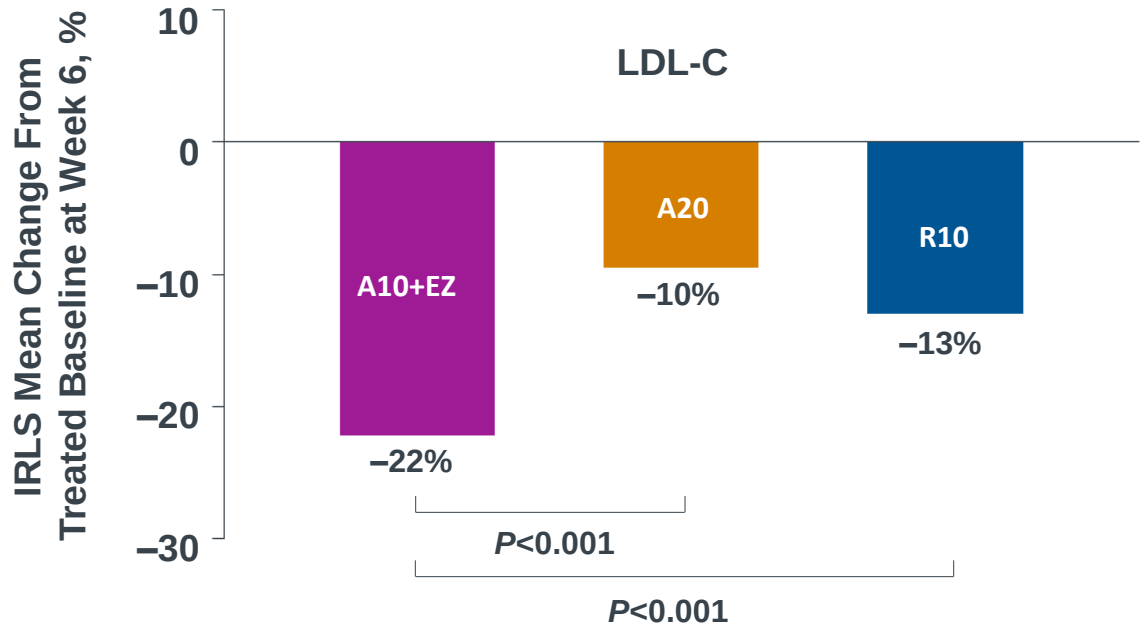
[b]6% were uptitrated to ezetimibe/simvastatin 10/80 mg.

CV = cardiovascular; HR = hazard ratio; CI = confidence interval; RRR = relative risk reduction; MI = myocardial infarction; UA = unstable angina.

Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397.

PACE Phase I: Adding Ezetimibe to Atorvastatin 10 mg Provided Greater Additional LDL-C Reduction vs Doubling Atorvastatin to 20 mg or Switching to Rosuvastatin 10 mg

Ezetimibe as an adjunct to diet when diet and exercise alone are not enough



Adding ezetimibe to atorvastatin 10 mg
(n=120)
Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)

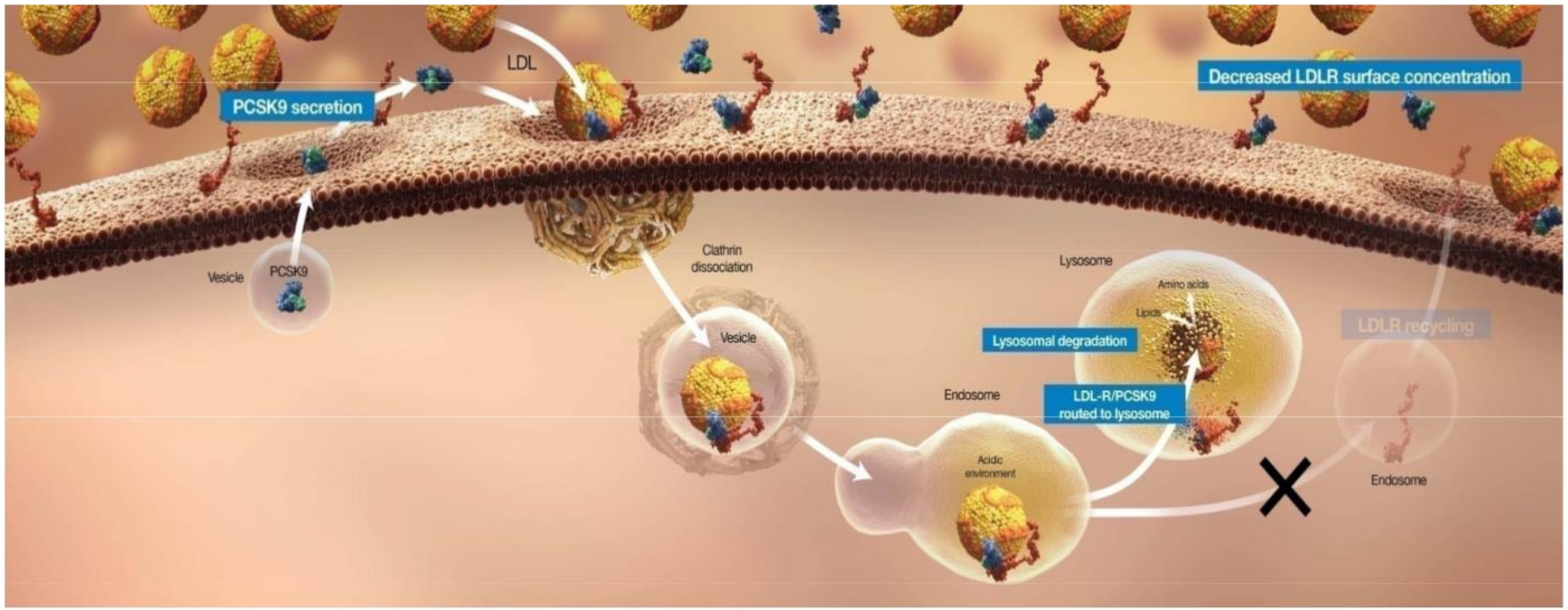
Doubling atorvastatin to 20 mg
(n=480)
Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)

Switching to rosuvastatin 10 mg
(n=939)
Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)

IRLS = iteratively reweighted least squares.

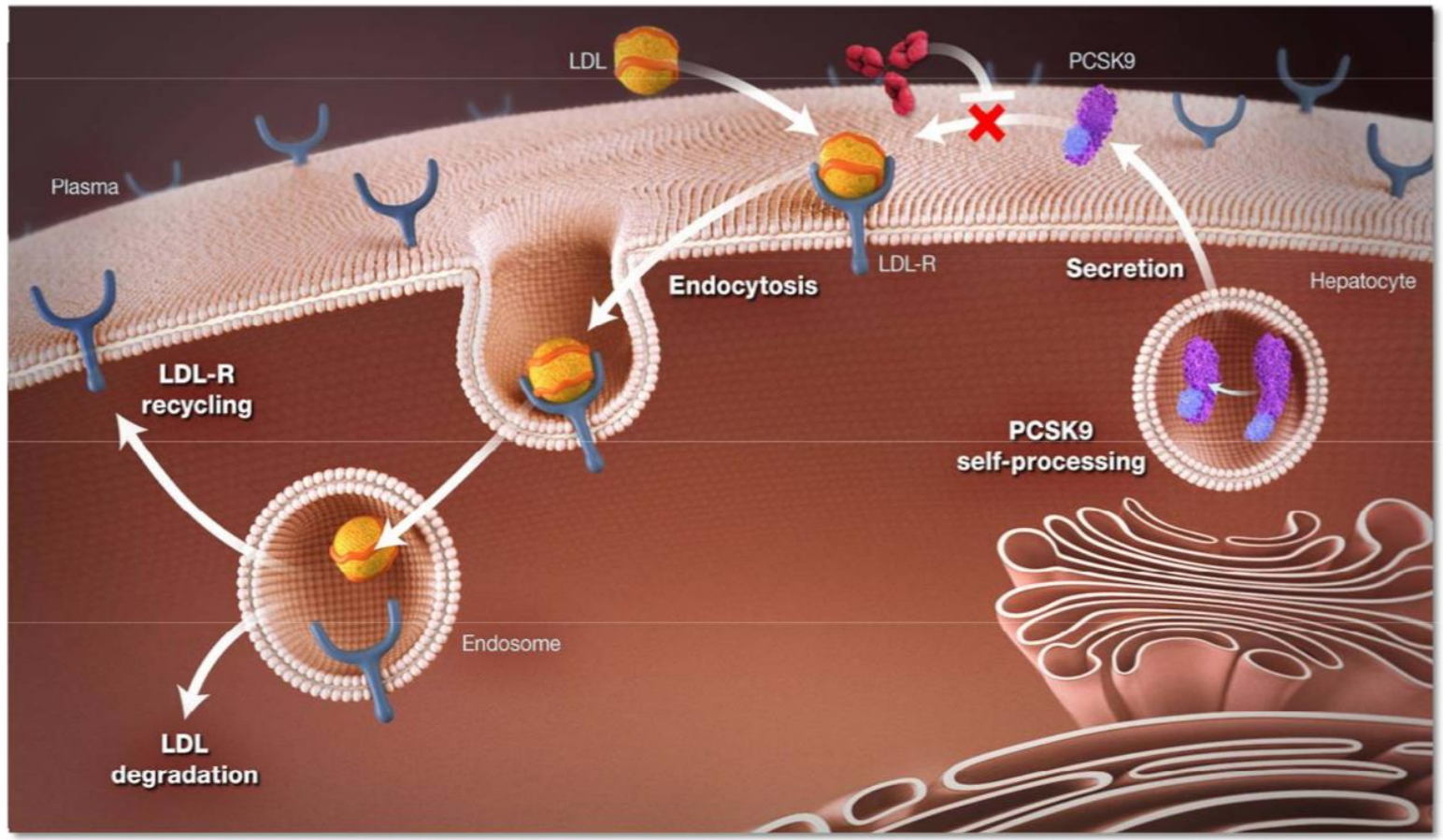
Bays HE et al. *Am J Cardiol*. **2013**;112:1885–1895.

PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting Them for Lysosomal Degradation



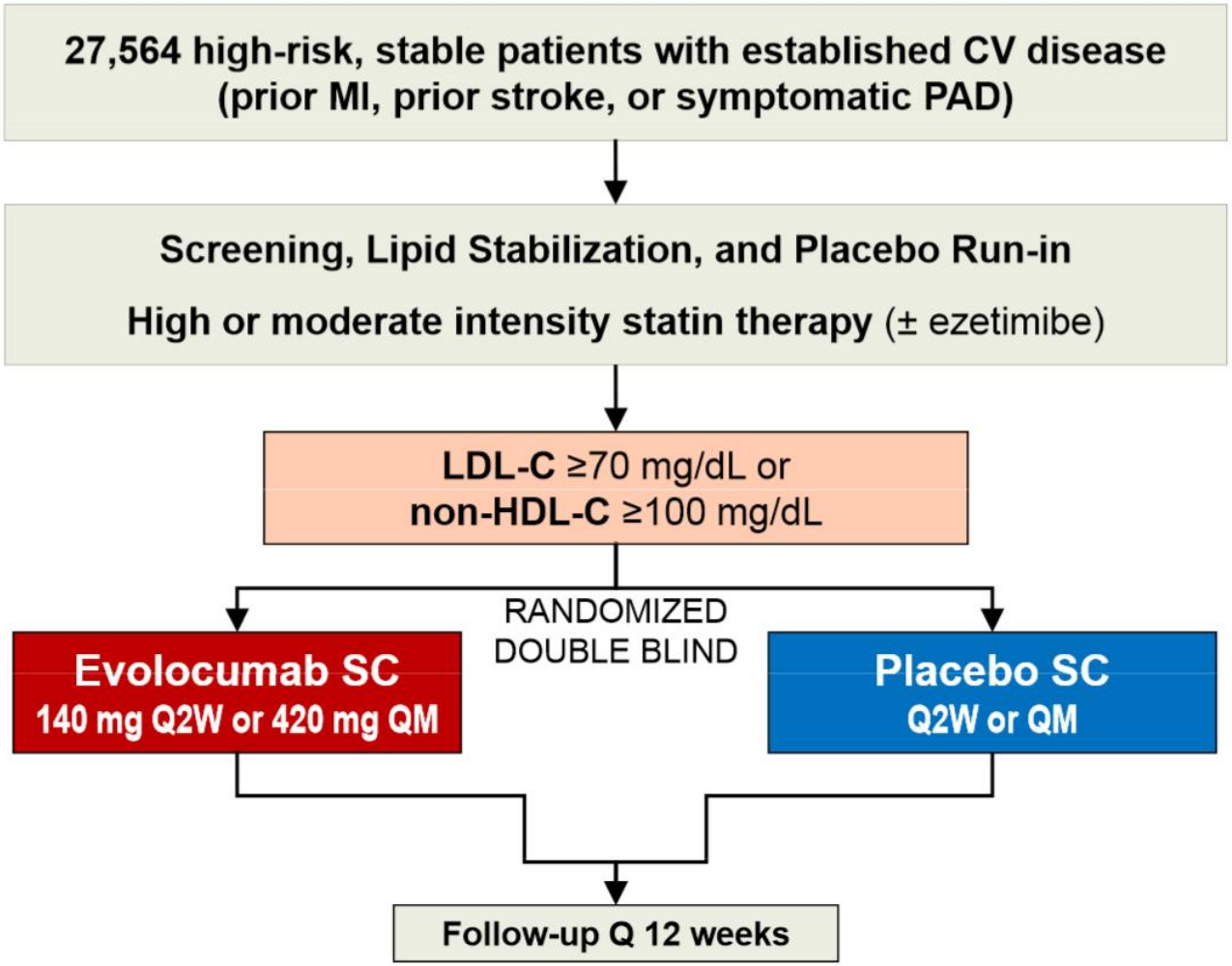
Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
Zhang DW, et al. *J Biol Chem*. 2007;282:18602-18612.

PCSK9 Inhibition with a Monoclonal Antibody



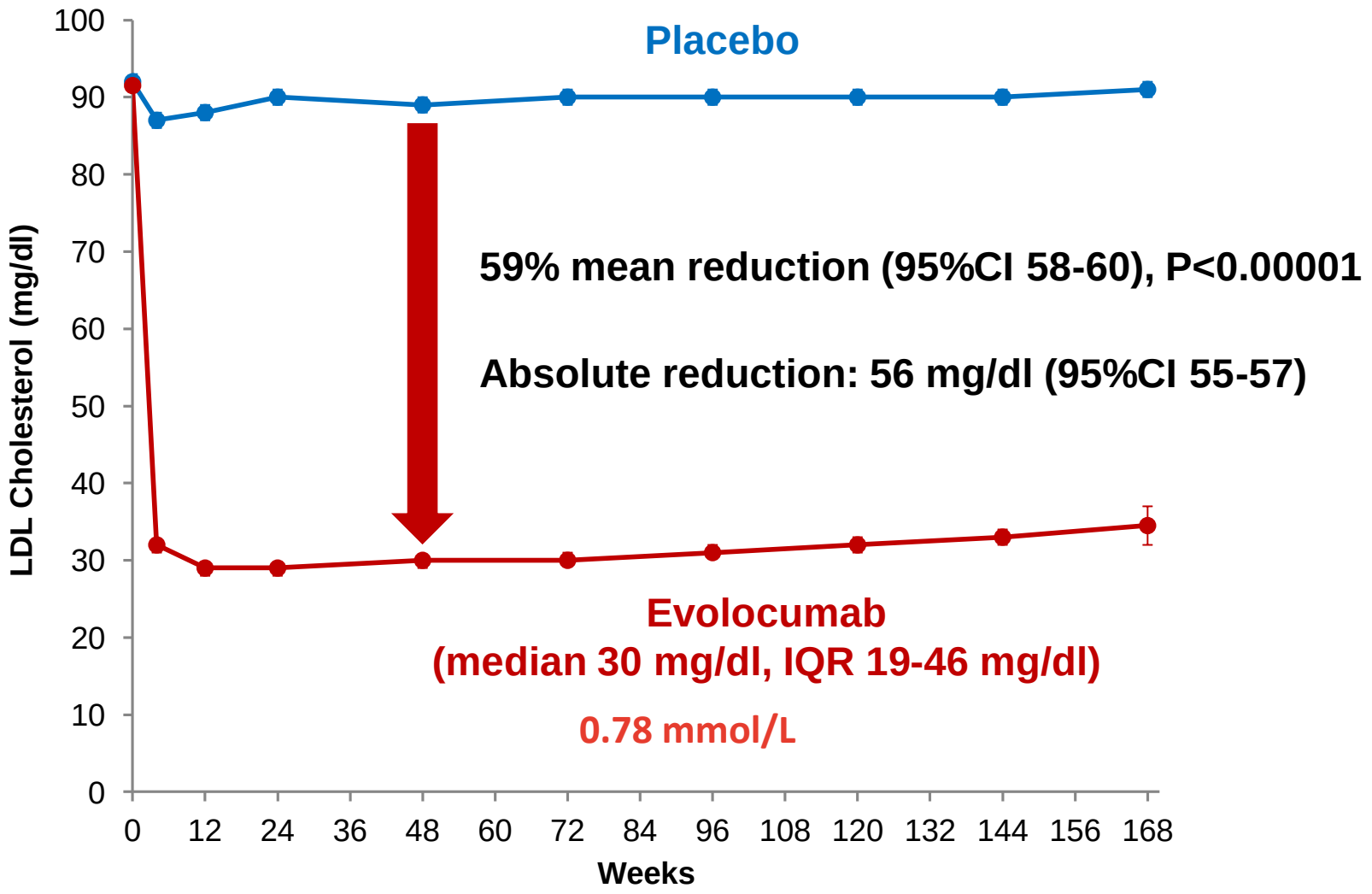
Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res*. 2007;48:1488-1498
Horton JD, Cohen JC, Hobbs HH. *J Lipid Res*. 2009;50(suppl):S172-S177
Rashid S et al. *PNAS* 2005;102:5374-5379
Chan JC, Piper DE, Cao Q, et al. *Proc Natl Acad Sci U S A*. 2009;106:9820-9825

Trial Design

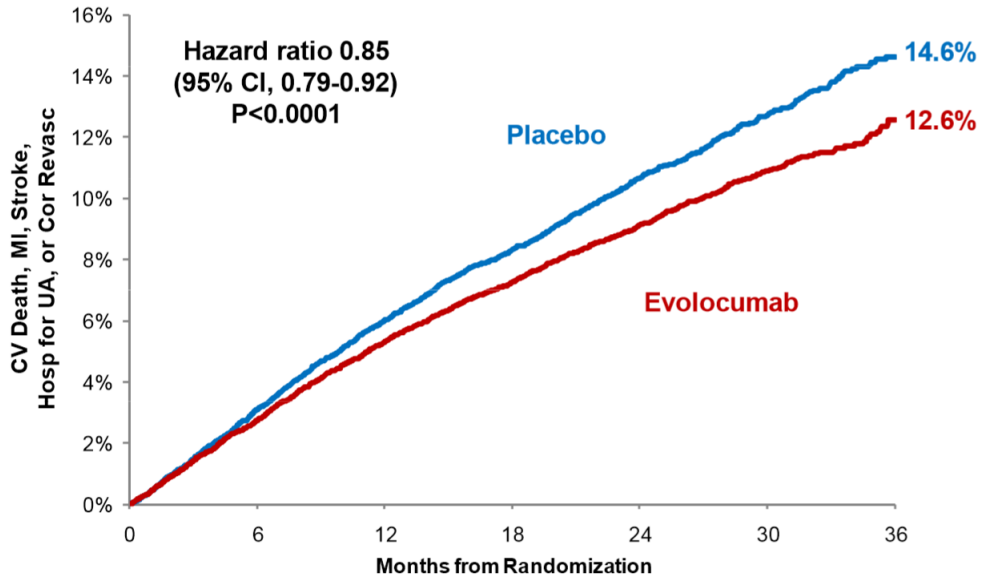


Sabatine MS et al. *Am Heart J* 2016;173:94-101

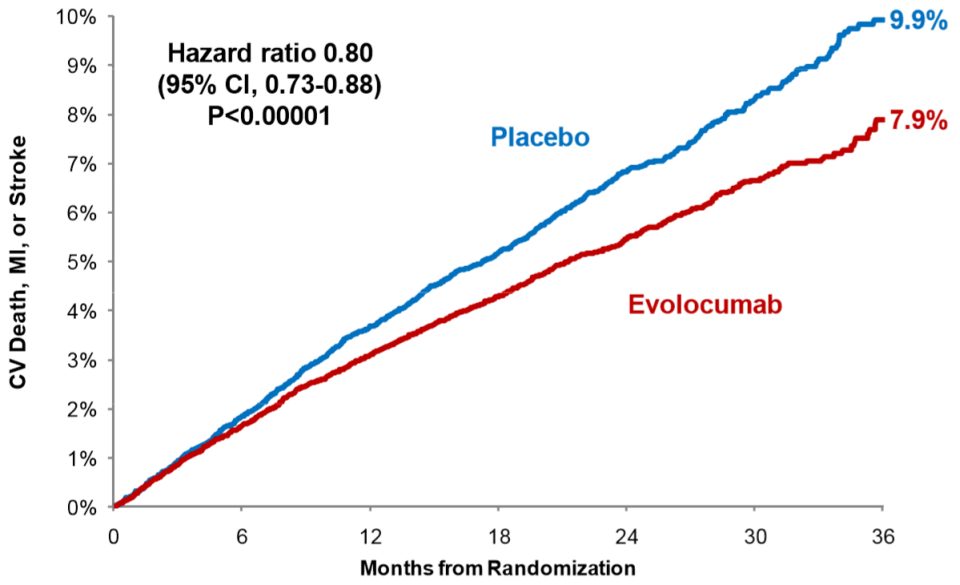
LDL Cholesterol



Primary endpoint



Secondary endpoint

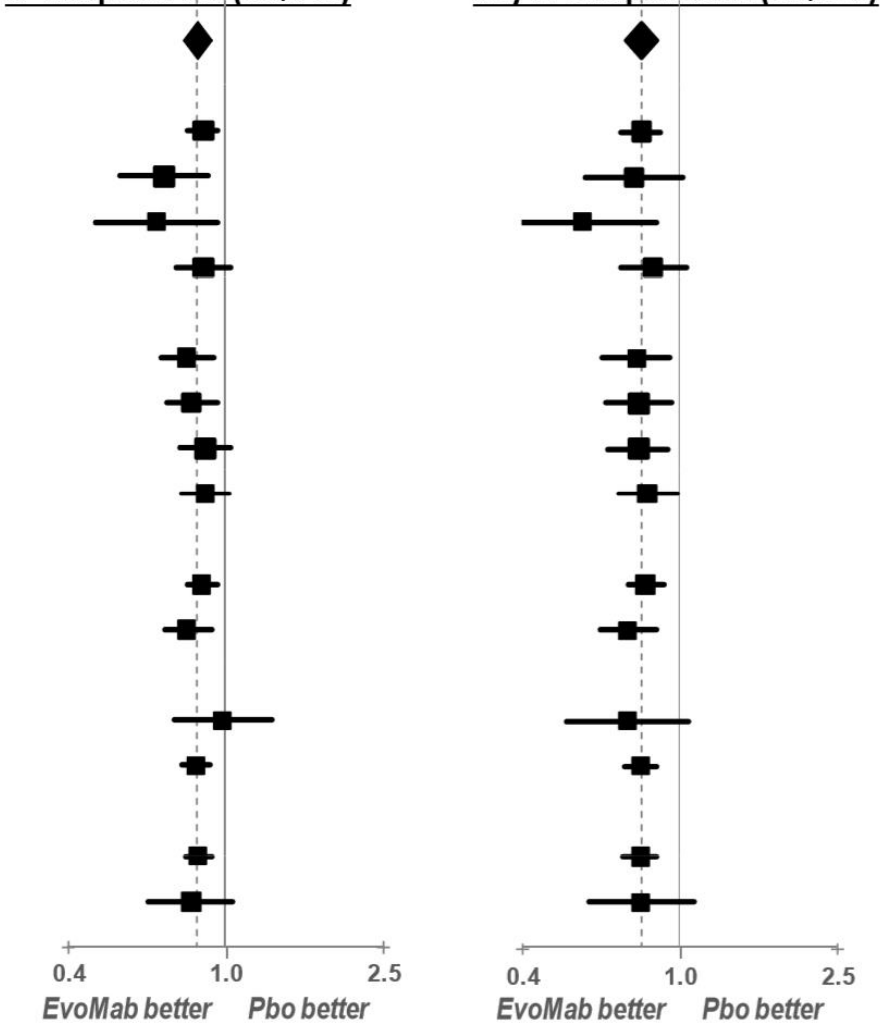


Types of CV Outcomes

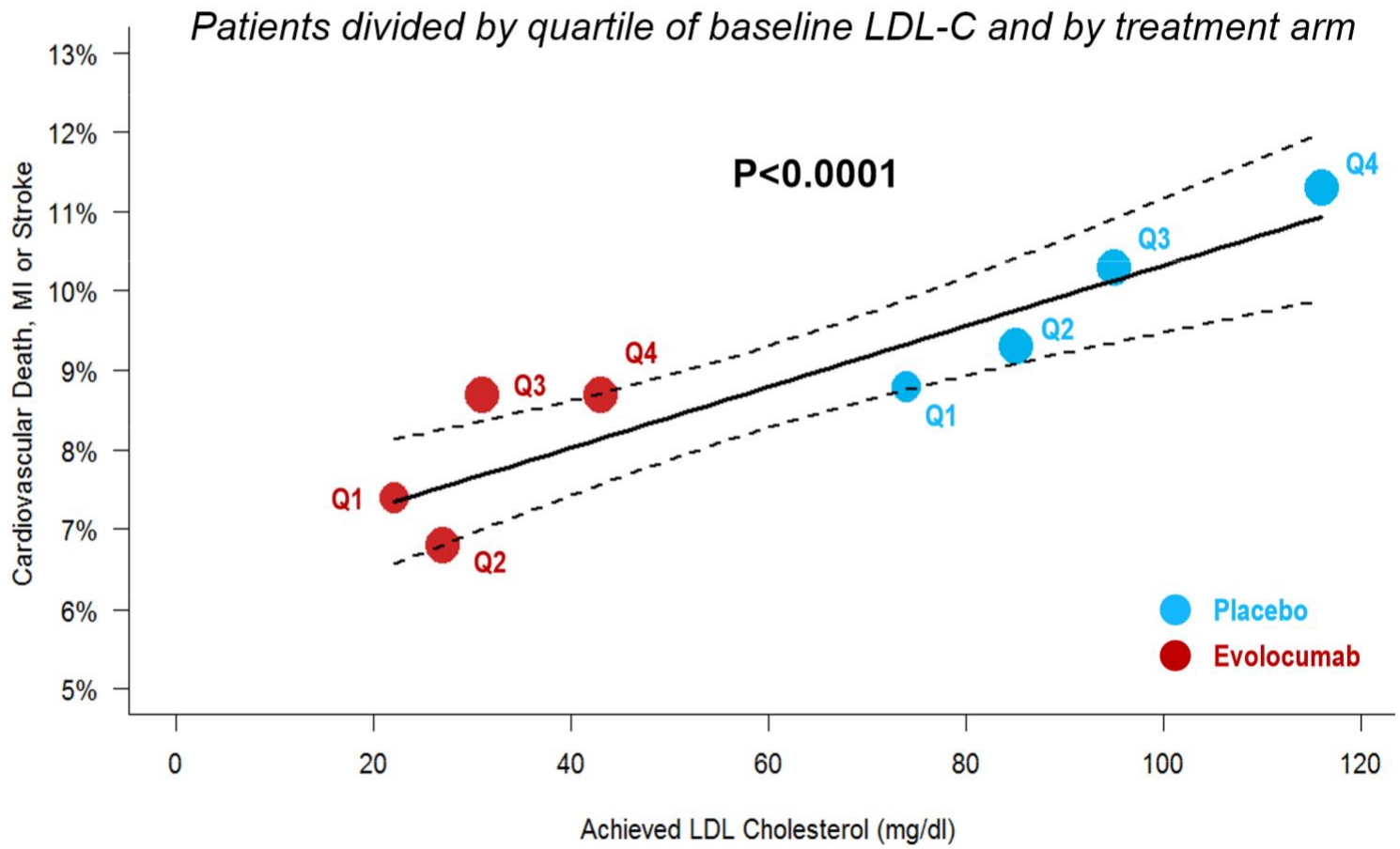
Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
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)**

Key Subgroups

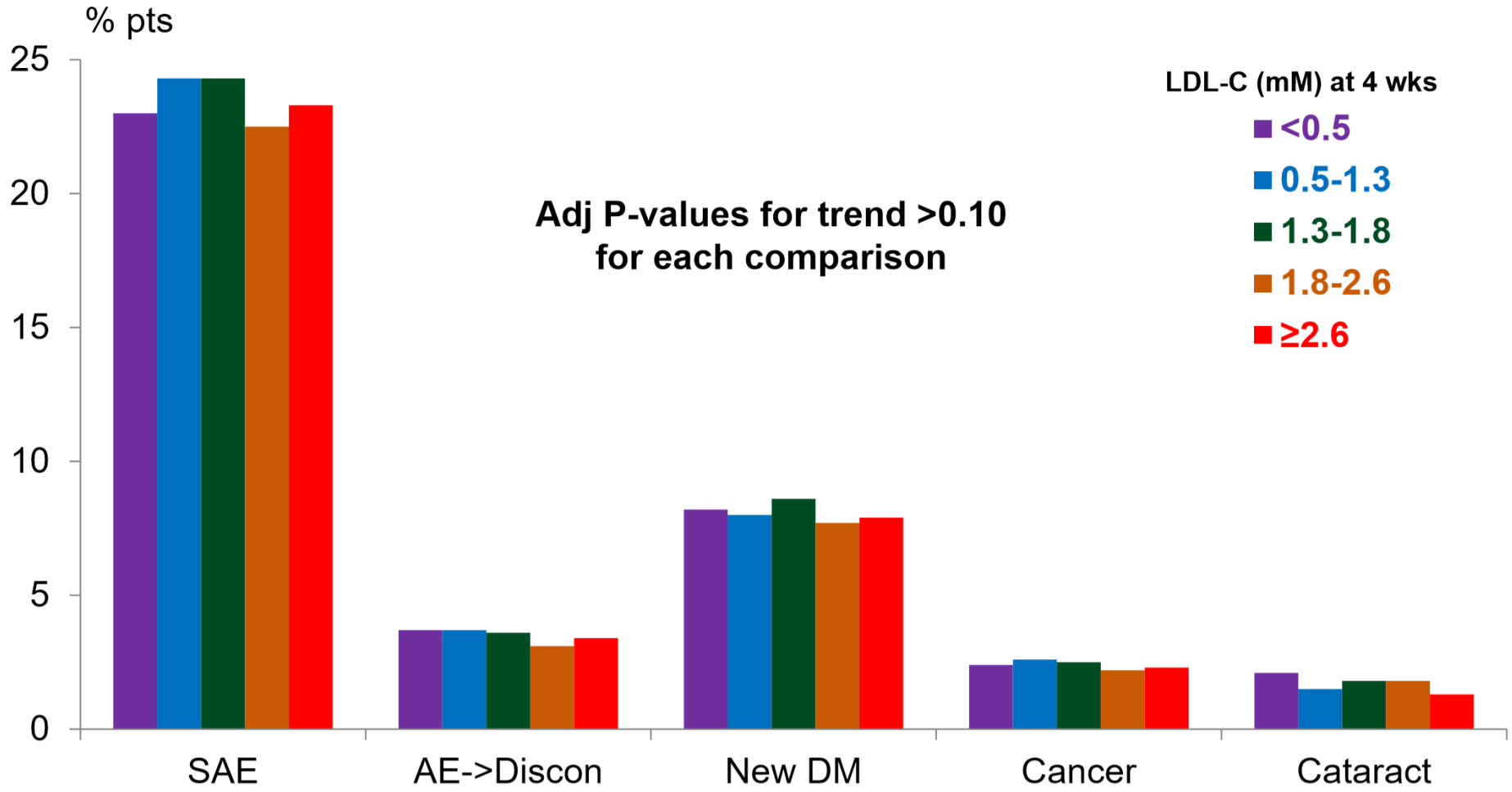
Subgroup	Patients
Overall	*27564*
Type of disease	
MI alone	19113
Stroke alone	3366
PAD alone	1505
Polyvascular disease	3563
Baseline LDL-C	
Q1 (<80 mg/dl)	6961
Q2 (80-<92 mg/dl)	6886
Q3 (92-109 mg/dl)	6887
Q4 (>109 mg/dl)	6829
Baseline statin intensity	
High	19103
Not high	8461
Ezetimibe	
Yes	1440
No	26124
Initial Dosing Regimen	
Every 2 weeks	24774
Monthly	2790



Lower LDL-C Is Better

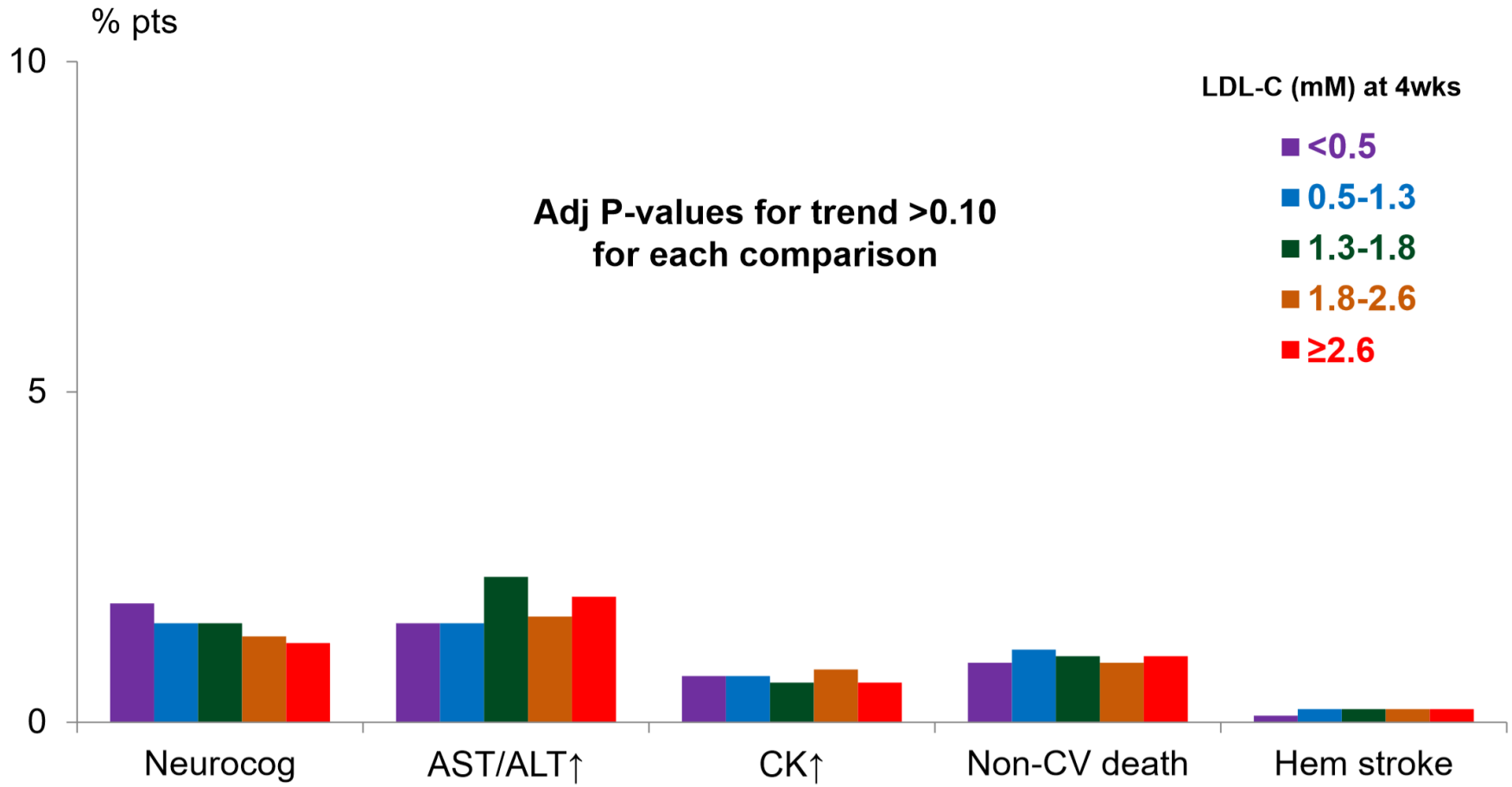


Safety Events - 1



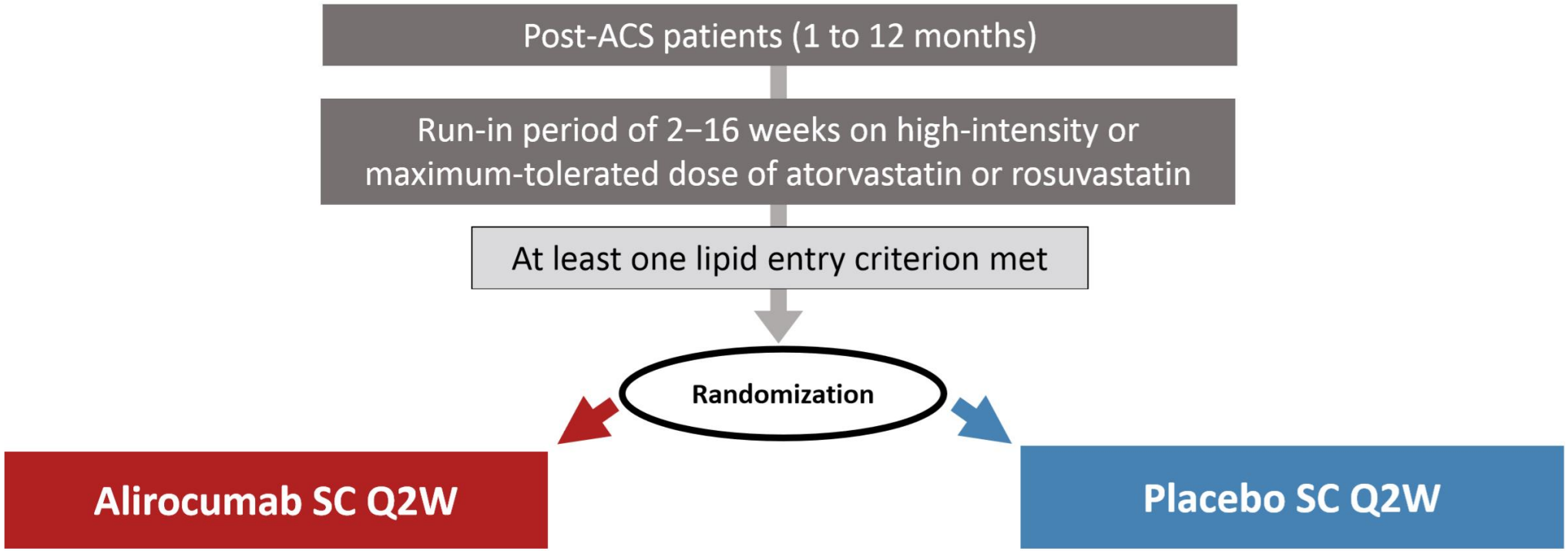
Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Safety Events - 2



Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Treatment Assignment

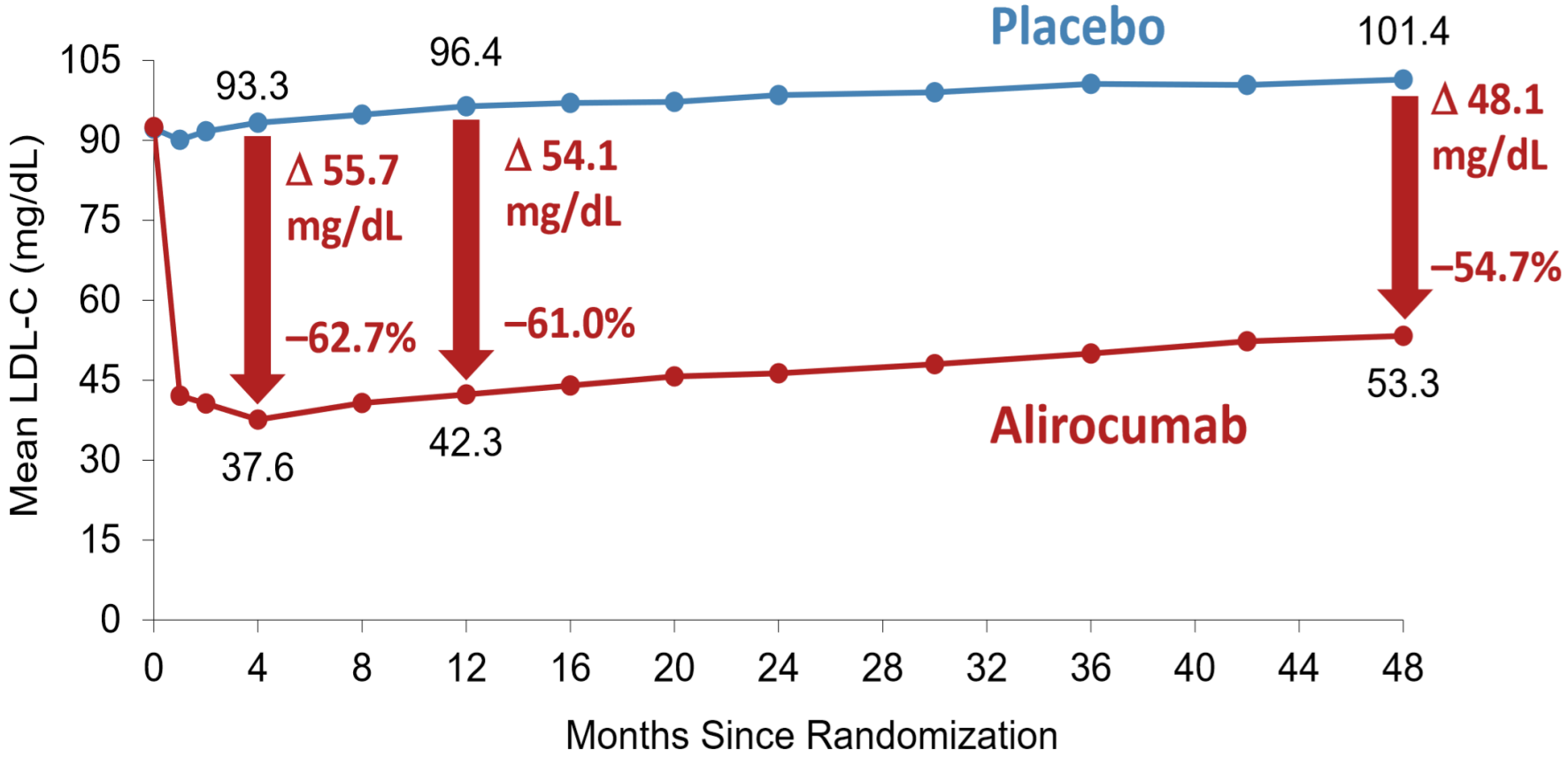


Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

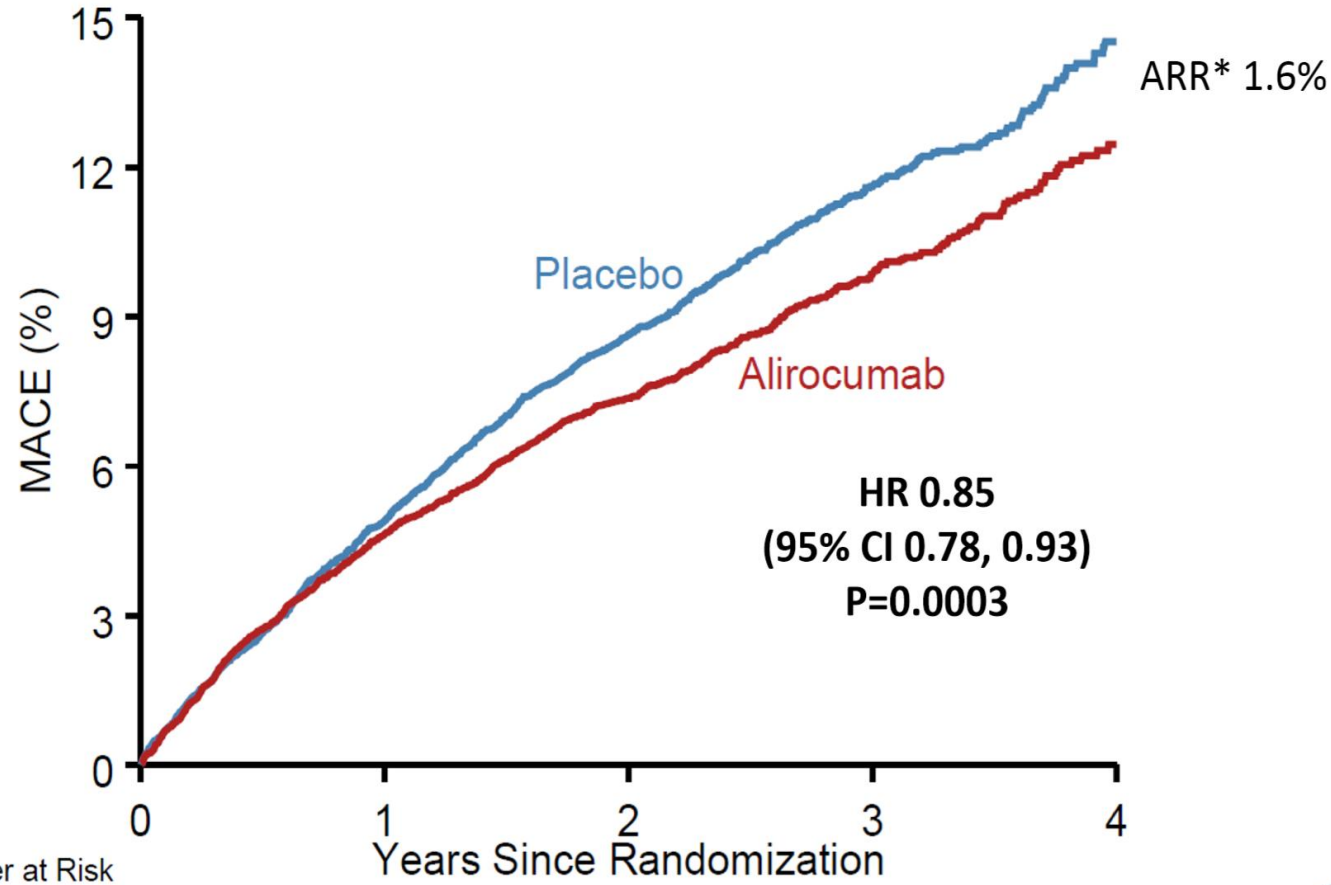
LDL-C: On-Treatment Analysis



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

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE



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

*Based on cumulative incidence

ODYSSEY OUTCOMES

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

ODYSSEY OUTCOMES

Main Secondary Efficacy Endpoints:
Hierarchical Testing

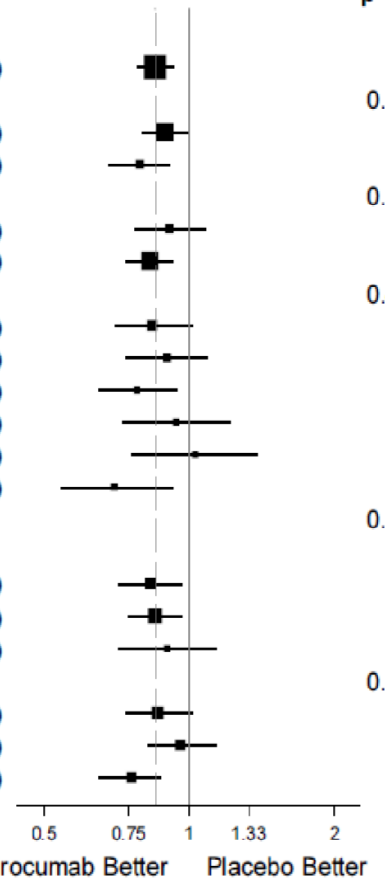
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
CV death	**240 (2.5)**	**271 (2.9)**	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

*Nominal P-value

ODYSSEY OUTCOMES

Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
Overall	18924	9.5	11.1	0.85 (0.78, 0.93)	
Age					0.19
< 65 Yr	13840	8.5	9.5	0.89 (0.80, 0.99)	
≥ 65 Yr	5084	12.4	15.5	0.79 (0.68, 0.91)	
Sex					0.35
Female	4762	10.7	11.8	0.91 (0.77, 1.08)	
Male	14162	9.2	10.9	0.83 (0.74, 0.92)	
Region					0.40
Eastern Europe	5437	7.9	9.3	0.84 (0.70, 1.01)	
Western Europe	4175	9.1	10.0	0.90 (0.74, 1.09)	
North America	2871	13.7	17.1	0.78 (0.65, 0.94)	
South America	2588	9.1	9.7	0.94 (0.73, 1.21)	
Asia	2293	7.7	7.6	1.03 (0.76, 1.38)	
Rest of World	1560	12.2	16.7	0.70 (0.54, 0.92)	
Time from Index Event to Randomization					0.85
<2 Months	6178	10.3	12.3	0.83 (0.71, 0.96)	
2 - <6 Months	9518	9.6	11.1	0.85 (0.75, 0.96)	
≥6 Months	3228	8.0	8.7	0.90 (0.71, 1.14)	
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	

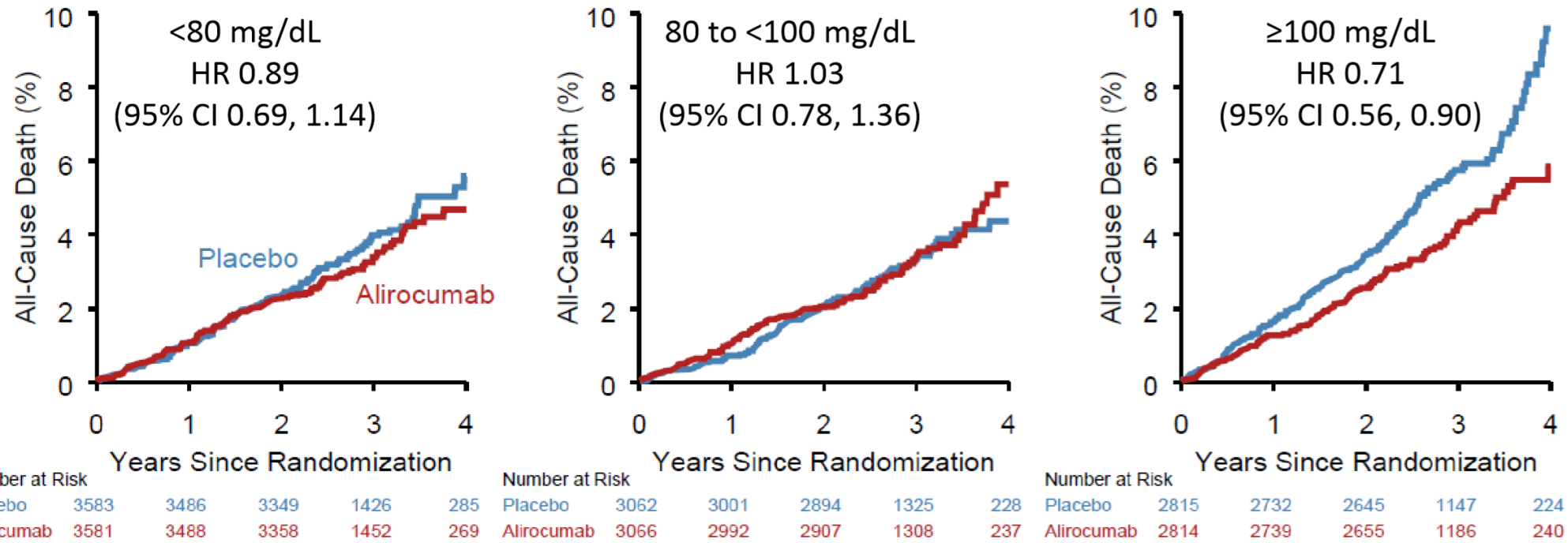


*P-values for interaction

ODYSSEY OUTCOMES

Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR* 1.7% $P_{interaction}$=0.12



*Based on cumulative incidence

ODYSSEY OUTCOMES

Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

ODYSSEY OUTCOMES

Safety (1)

Treatment-emergent adverse events, n (%)	Alirocumab (N=9451)	Placebo (N=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

ODYSSEY OUTCOMES

Safety (2)

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

ODYSSEY OUTCOMES

Cognition and Statins

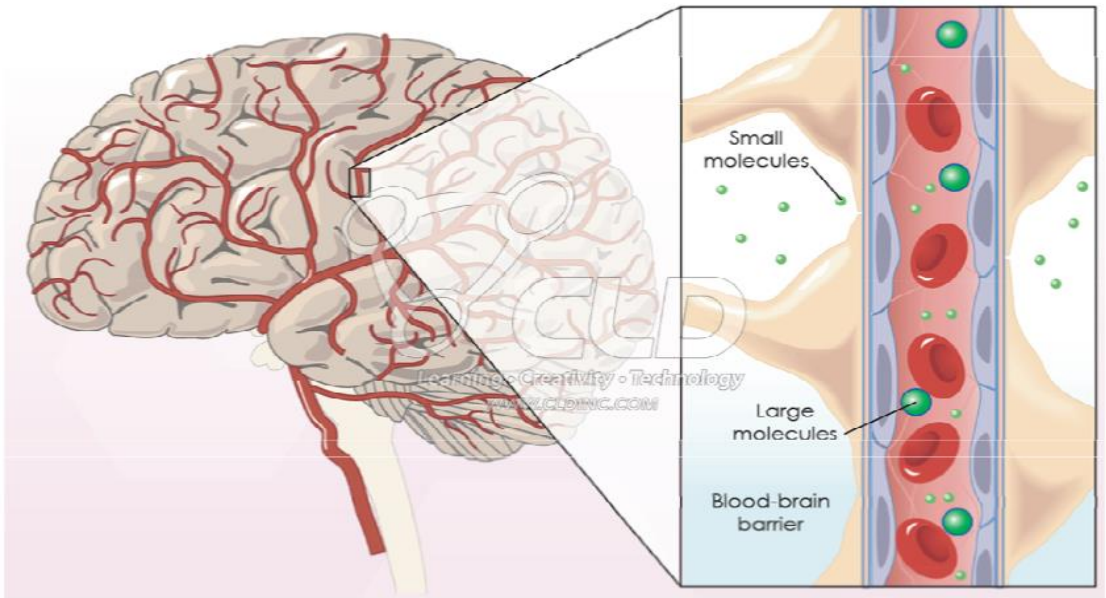
- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits
- In 2012 FDA added risk of adverse cognitive effects to label of all statins
- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association

Rojas-Fernandez CH, et al. *J Clin.Lipidol.* 2014;8(3 Suppl):S5-16.

Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



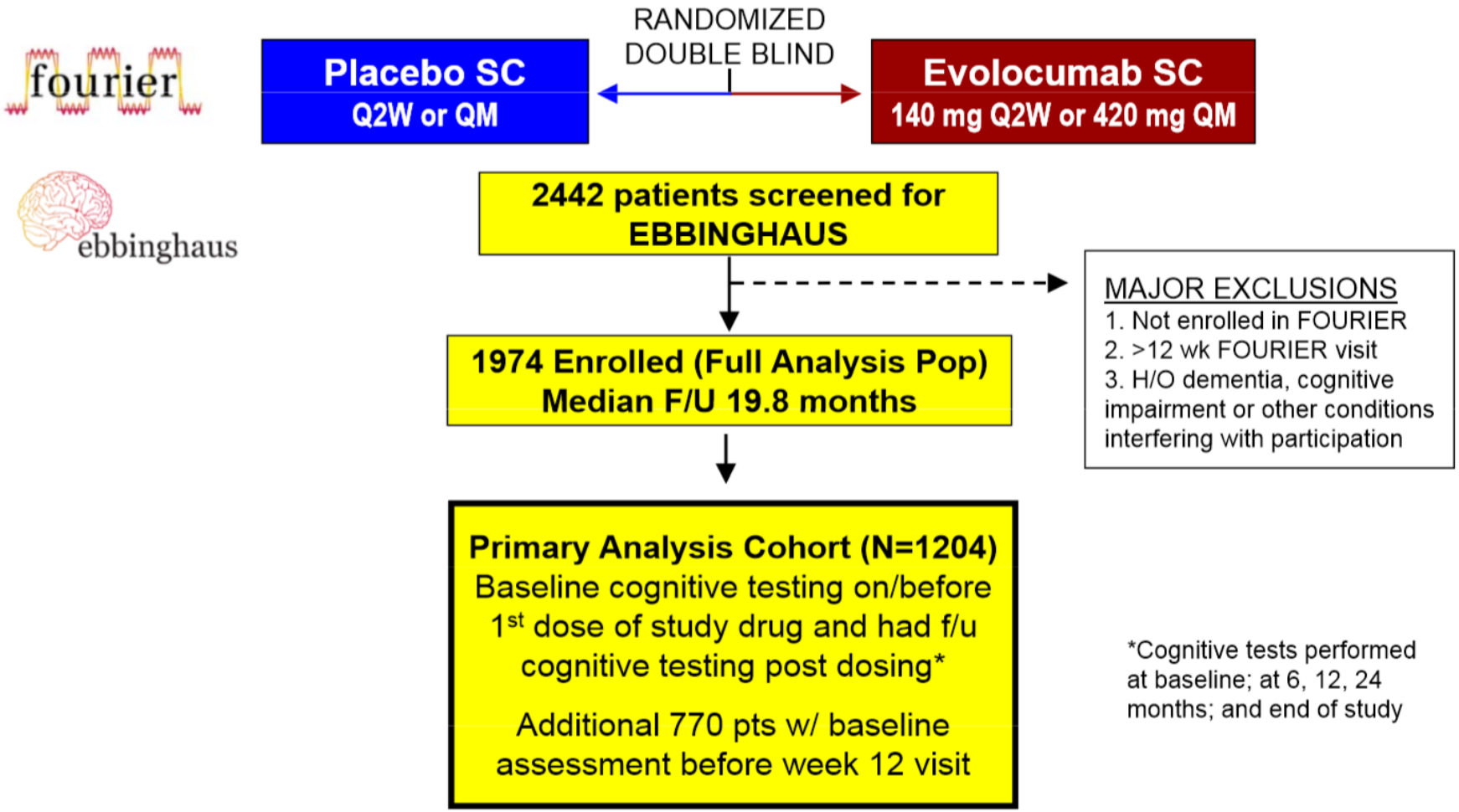
mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

*Lipinski MJ, et al. *Eur Heart J.* 2016;37(6):536-545.

EBBINGHAUS Trial Design

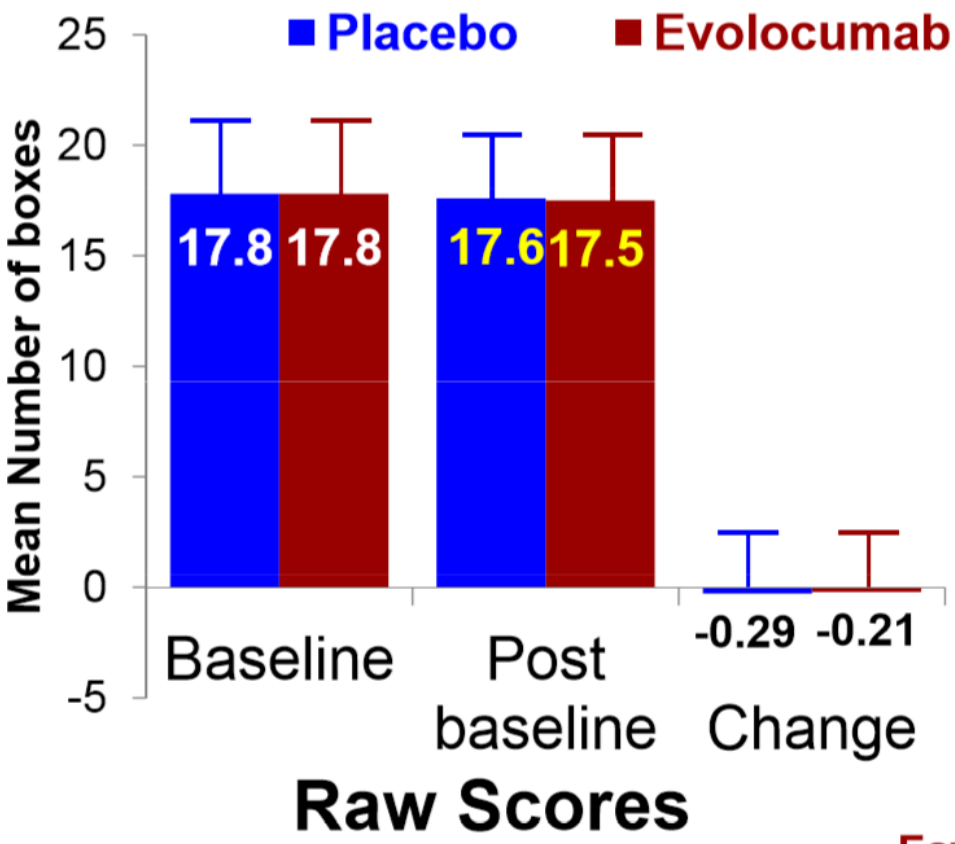


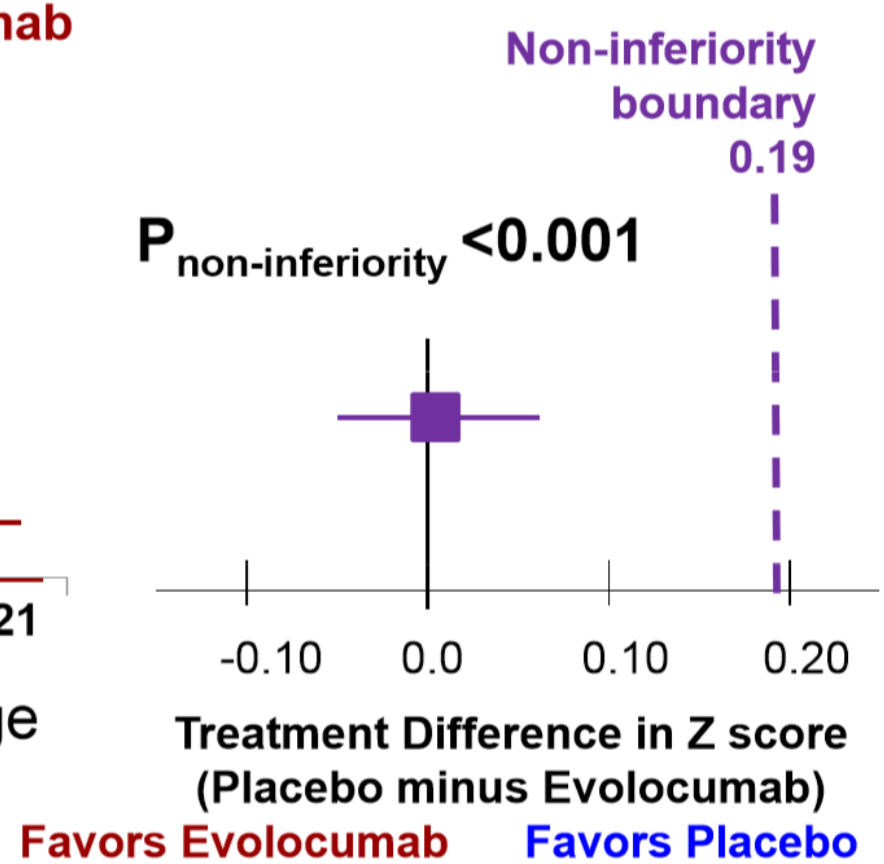
Giugliano RP et al. *Clin Card* 2017;40:59–65

Primary Endpoint

Spatial Working Memory Strategy Index

ebbinghaus





Secondary Endpoint Results

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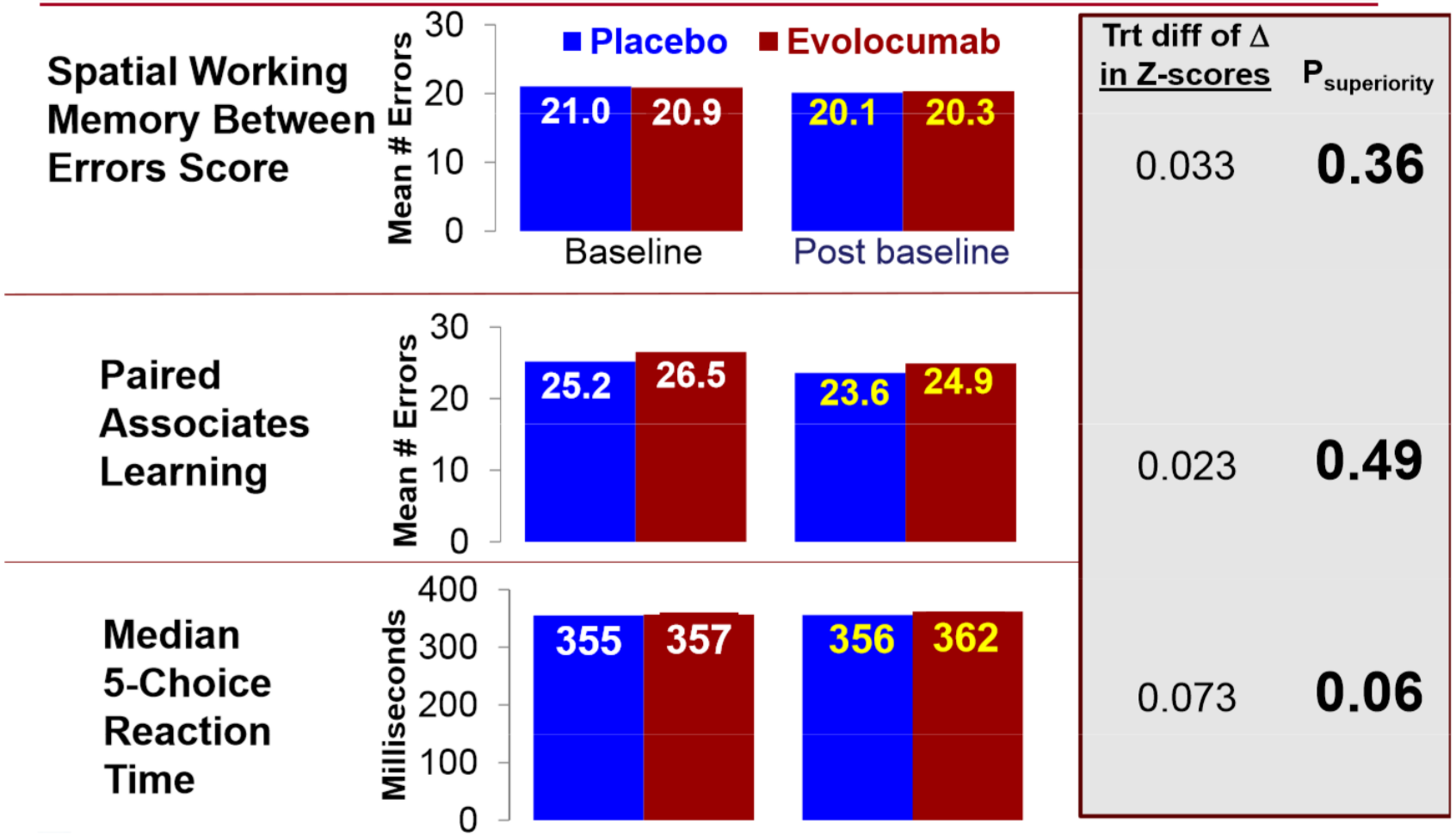


Neurocognitive Summary

ebbinghaus

In patients with known cardiovascular disease on background statin followed for 20 months

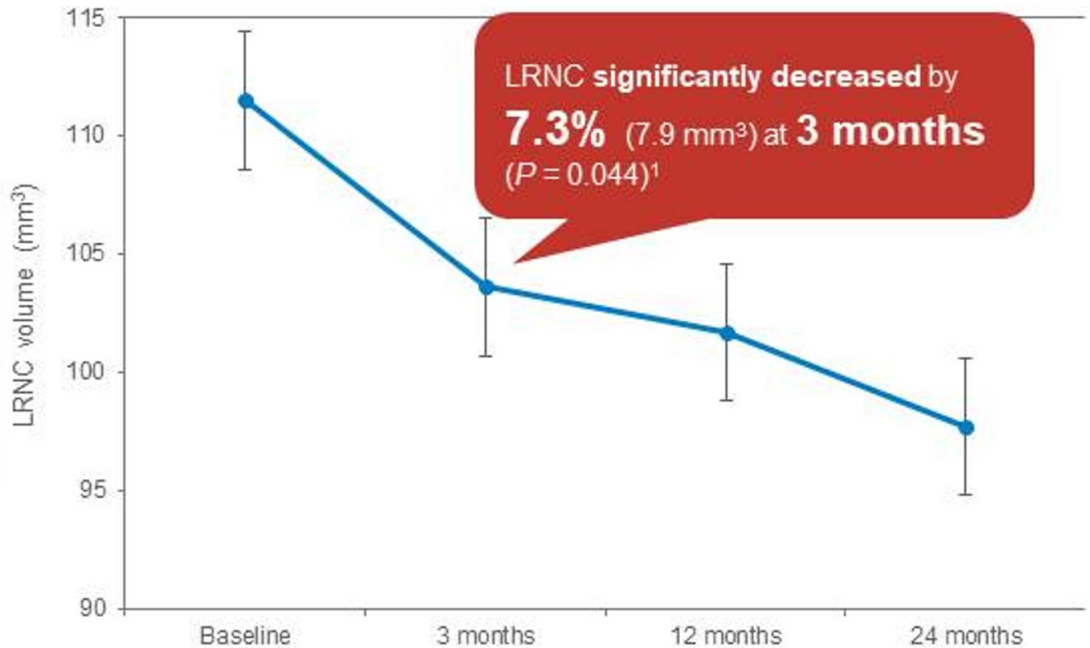
1. **No differences btw evolocumab vs placebo**
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL**

Rosuvastatin Induces a Rapid Decrease in Carotid Plaque Lipid Content Among Chinese Patients

Evaluation of the Onset of Plaque Regression With Rosuvastatin Treatment (5–20 mg/Day) in 32 LLT-Naïve Patients With Carotid Atherosclerosis[1]

At 3 months:
LDL-C levels were **significantly reduced** by **47%**
(125.2 ± 24.4 mg/dL vs 66.7 ± 17.3 mg/dL; $P < 0.001$)[1]



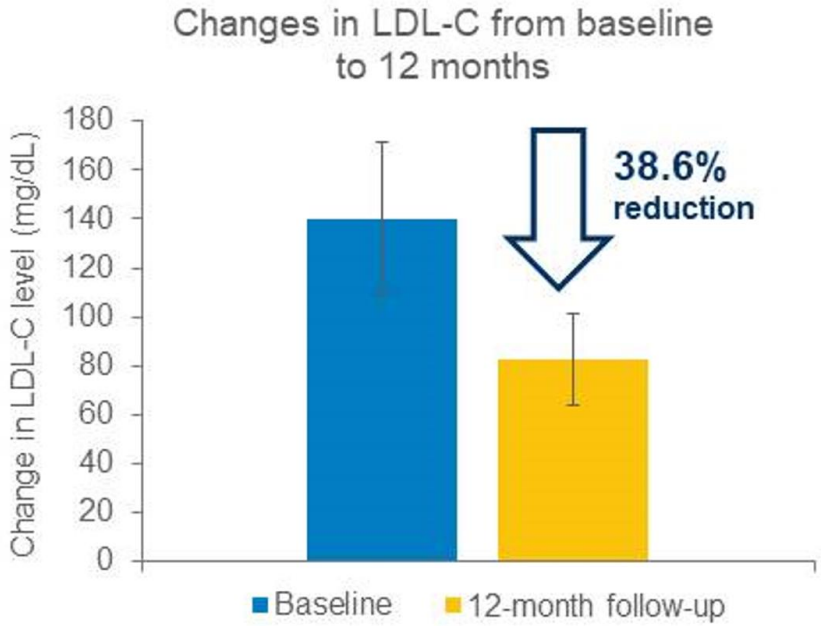
These findings suggest that **early onset of plaque stabilization** can be achieved within the **first 3 months of statin therapy**[1]

LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; LRNC, lipid-rich necrotic core.

1. Du R, et al. *BMC Cardiovasc Disord.* 2014;14:83.

Rosuvastatin Decreases Coronary Atheroma Volume in Patients with CAD

76-Week Study (COSMOS) to Assess the Effect of Rosuvastatin (2.5–20 mg OD) on Coronary Artery Atheroma Volume in 126 Japanese Patients With CAD[1]



- **Plaque volume was significantly reduced by 5.1%** (SD 14.1%, $P < 0.0001$) at 12 months
- Plaque volume was significantly reduced **regardless of prior LLT** ($P < 0.02$)
- Safety and tolerability of rosuvastatin was acceptable, even though 72% of patients were treated with the highest approved dosage

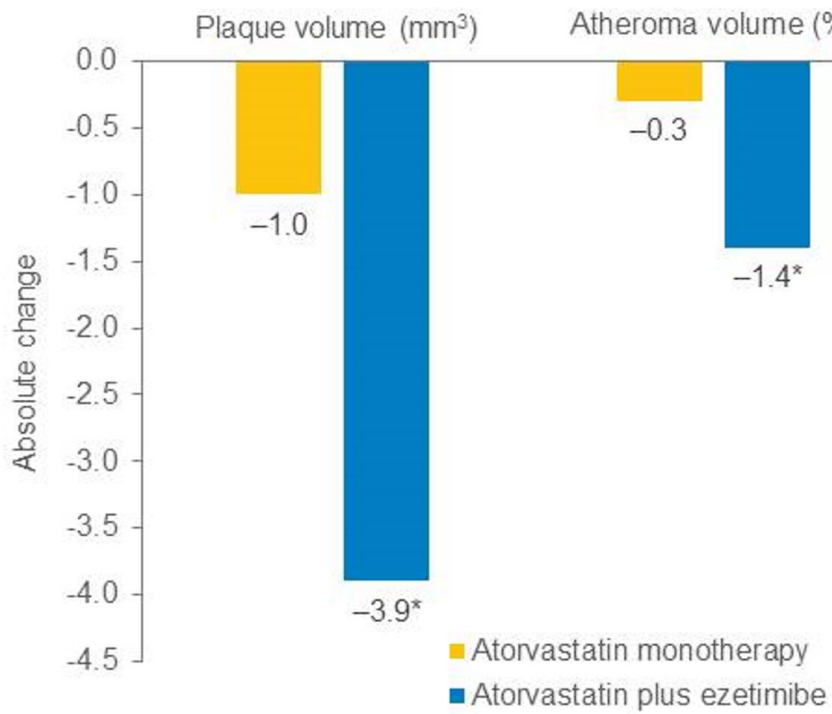
Rosuvastatin exerted **significant regression of coronary plaque** volume in Japanese patients and exhibited an **acceptable safety profile**, even at high doses !

CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; OD, once daily; SD, standard deviation.

1. Takayama T, et al. *Circ J*. 2009;73:2110-2117.

Additional LDL-C Lowering Achieved When Adding Ezetimibe to Statin Leads to Greater Plaque Regression

Plaque Regression After 9–12 Months of Treatment With Atorvastatin Alone or in Combination With Ezetimibe in Patients Who Underwent PCI From 17 Centers in Japan (N = 202; PRECISE-IVUS RCT)[1]



- Ezetimibe in combination with atorvastatin demonstrated **superior reduction of percentage atheroma volume** over atorvastatin monotherapy[1]
- Significantly more patients who received ezetimibe plus atorvastatin showed coronary plaque regression than with atorvastatin monotherapy (78% vs 58%; *P* = 0.004)

*$P = 0.001$ versus atorvastatin monotherapy.
LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.
1. Tsujita K, et al. *J Am Coll Cardiol*. 2015;66:495-507.

GLAGOV

968 high risk patients with symptomatic CAD and 20-50% stenosis by invasive coronary angiography 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 at baseline

Statin Monotherapy (n=484)

18 months treatment

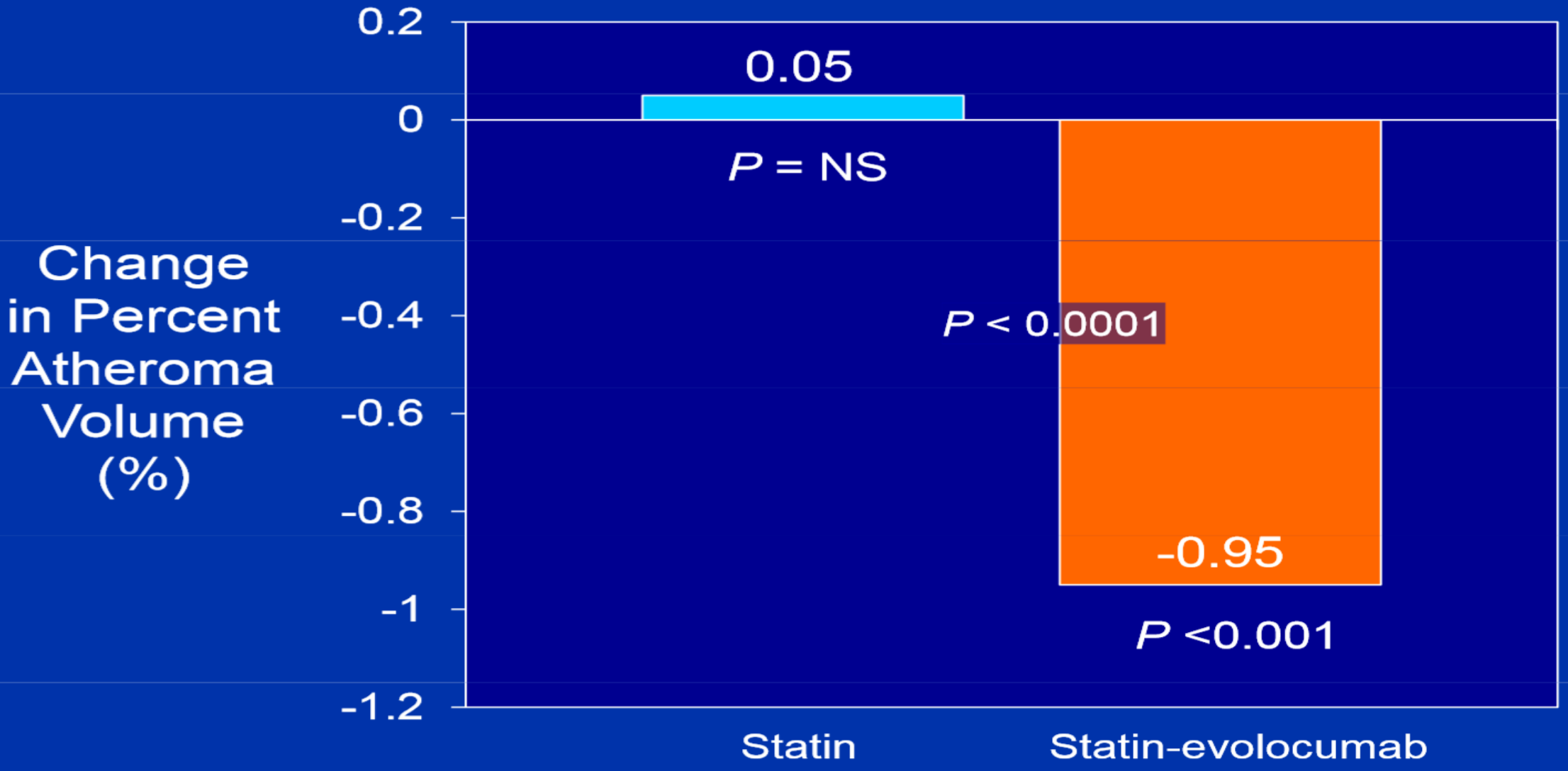
Statin plus evolocumab 420 mg QM (n=484)

423 statin completers

423 evolocumab completers

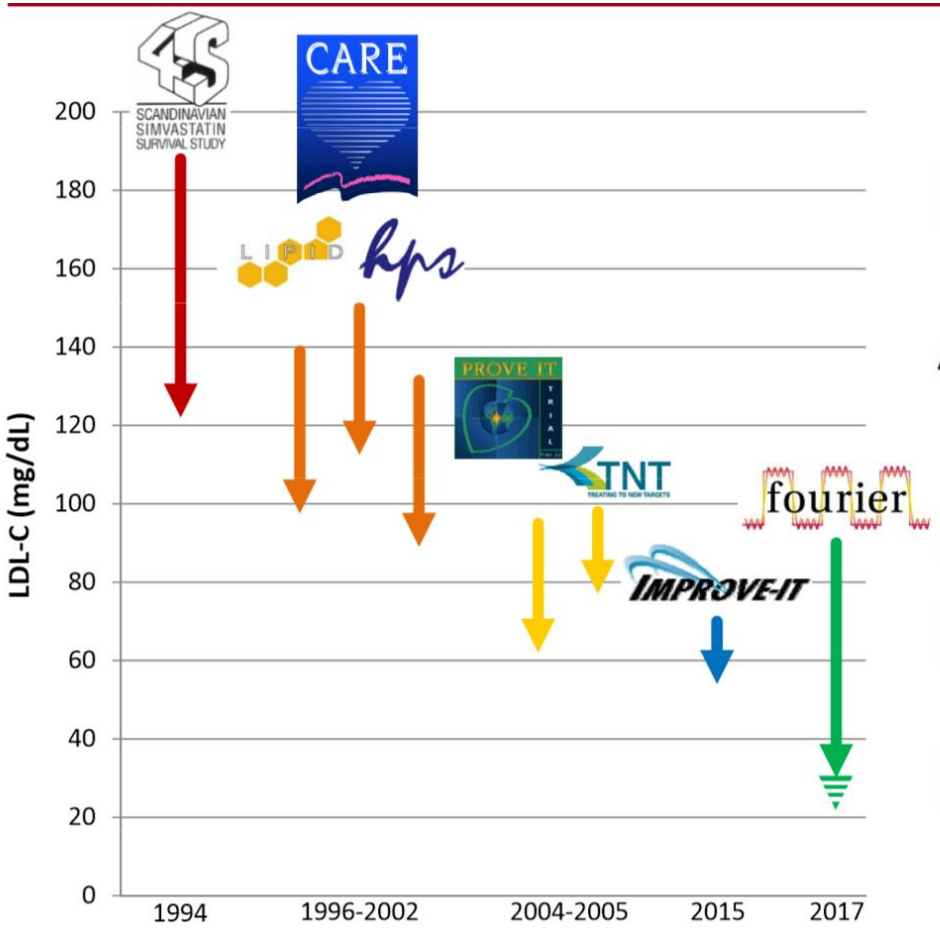
Follow-up IVUS of originally imaged "target" vessel (n=846)

Primary Endpoint: Percent Atheroma Volume



JAMA 2016;316:2373-84

Battle towards lowest LDL-C



High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

Conclusion

- Consistent evidence showing lower LDL-C is associated with lower CV event
- Rapid evolving medication in achieving ever possible lowest target of LDL
- Risk stratified your patient, personalized medicine