Translating Evidence to Practice:
Improving Outcomes in Patients with ASCVD with PCSK9 Inhibitors

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TEACHING AFFILIATE

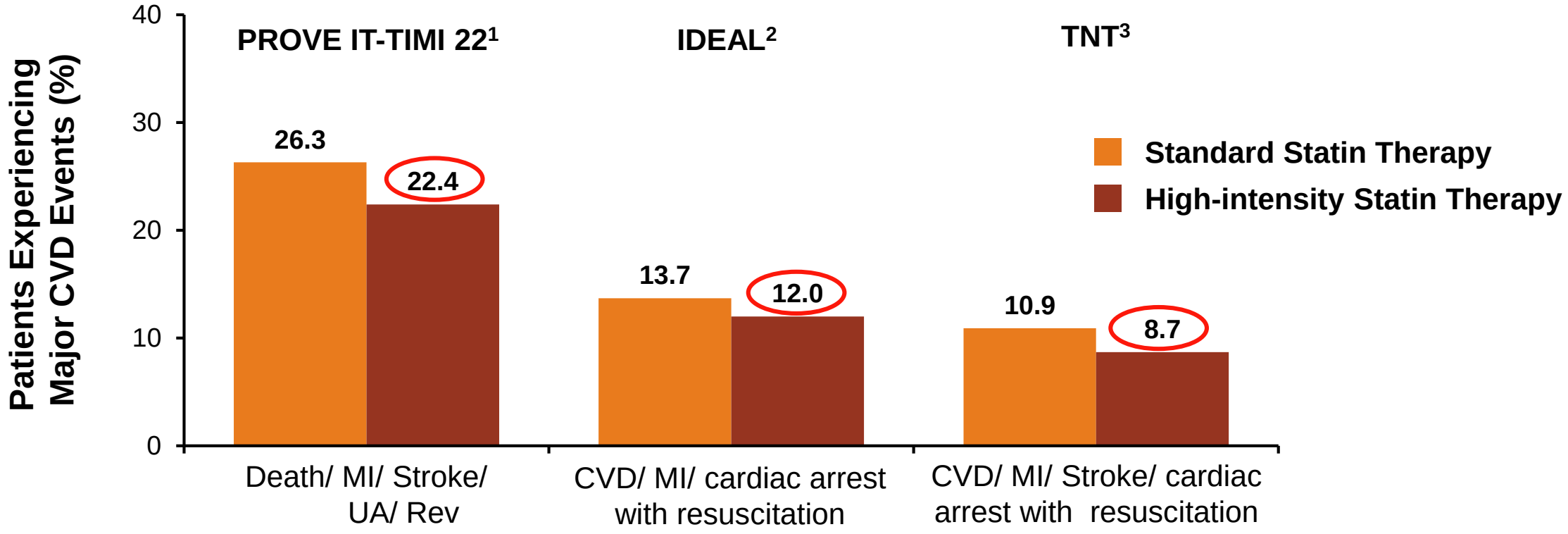
Relevant Disclosures

- Executive Committee Member:
  - IMPROVE-IT, LAPLACE-TIMI 57, FOURIER, EBBINGHAUS trials
- Research Grant to my institution:
  - Amgen, Merck
- Honoraria for CME programs:
  - ACC, Amgen, Daiichi Sankyo, Merck, Pfizer
- Consultant:
  - AKCEA, Amarin, Amgen, Bristol Myers Squibb, CVS Caremark, Daiichi Sankyo, GlaxoSmithKline, Merck, Pfizer, Sanofi

Learning Objectives

- Assess the safety and efficacy of PCSK9 inhibitors in reducing cardiovascular events in patients with acute coronary syndrome and hypercholesterolemia
- Appropriately integrate PCSK9 inhibitors in clinical practice to reduce the risk of cardiovascular events in high-risk patients
- Review current evidence and set optimal LDL-cholesterol targets for patients with documented ASCVD

Substantial Residual Risk Still Exists



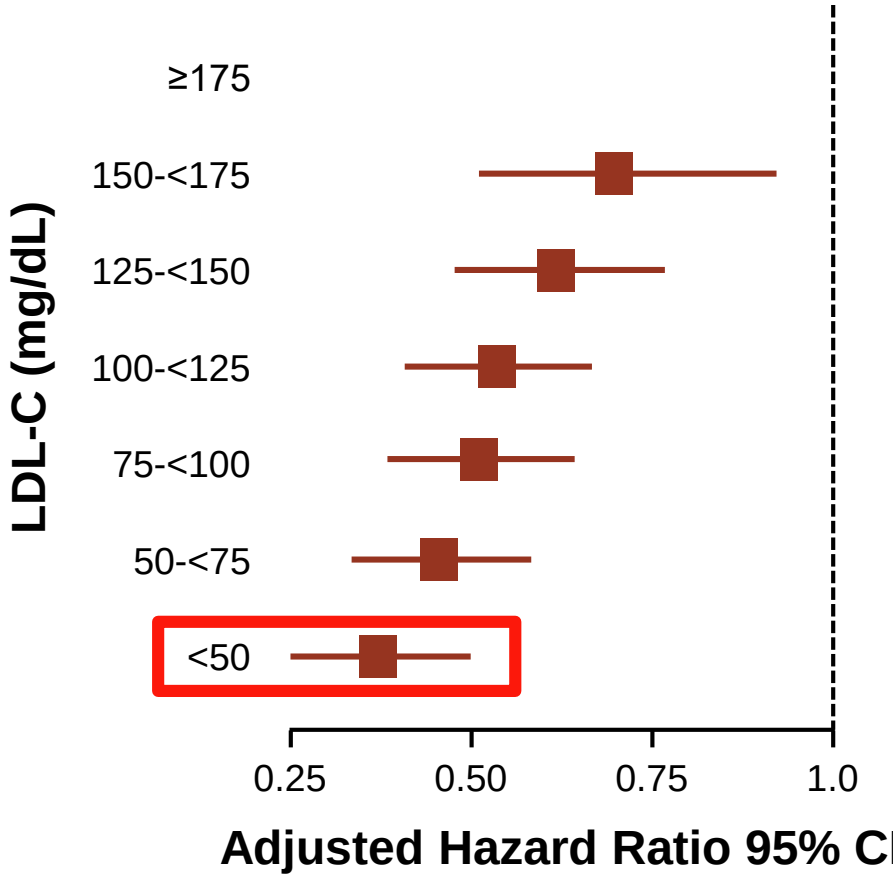
N	4162		8888		10,001	
LDL-C mg/dL	95	62	104	81	101	77

1. Cannon CP, et al. *N Engl J Med*. 2004;350(15):1495-1504. 2. Pedersen TR, et al. *JAMA*. 2005;294(19):2437-2445. 3. LaRosa JC, et al. *N Engl J Med*. 2005;352(14):1425-1435.

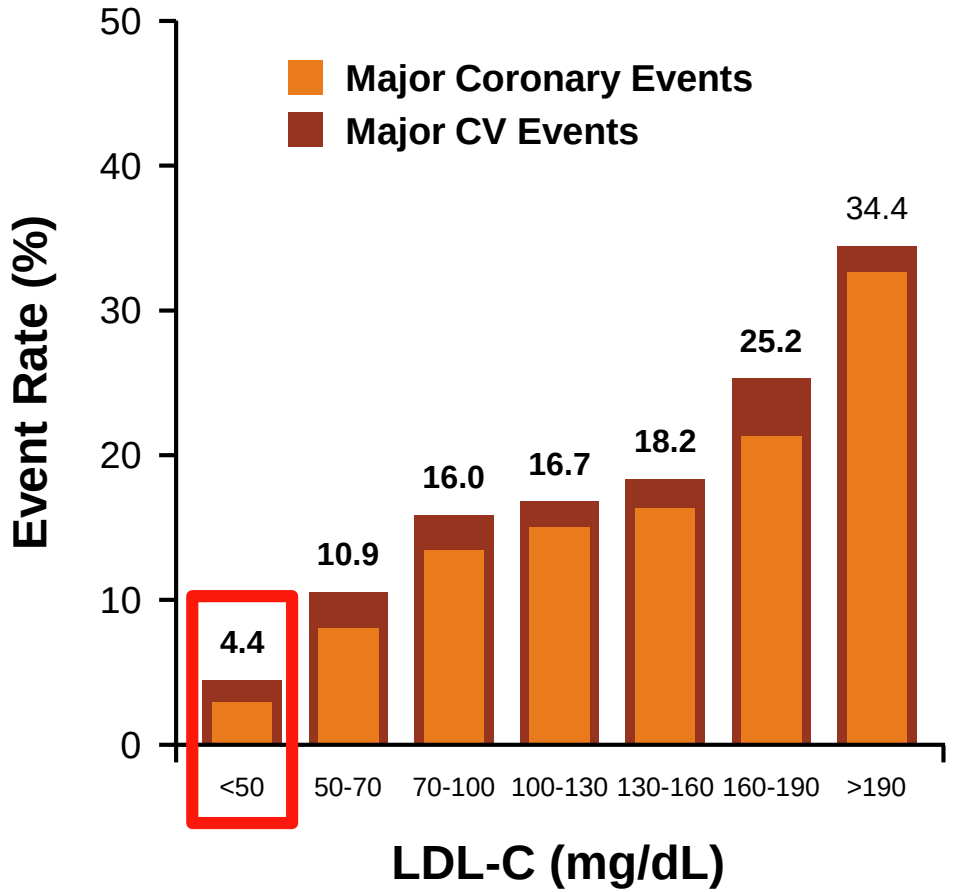
Rationale for Pushing LDL-C Levels Even Lower

Meta-analysis of 38,153 patients from eight randomized statin trials

LDL-C Levels and Risk of CV Events



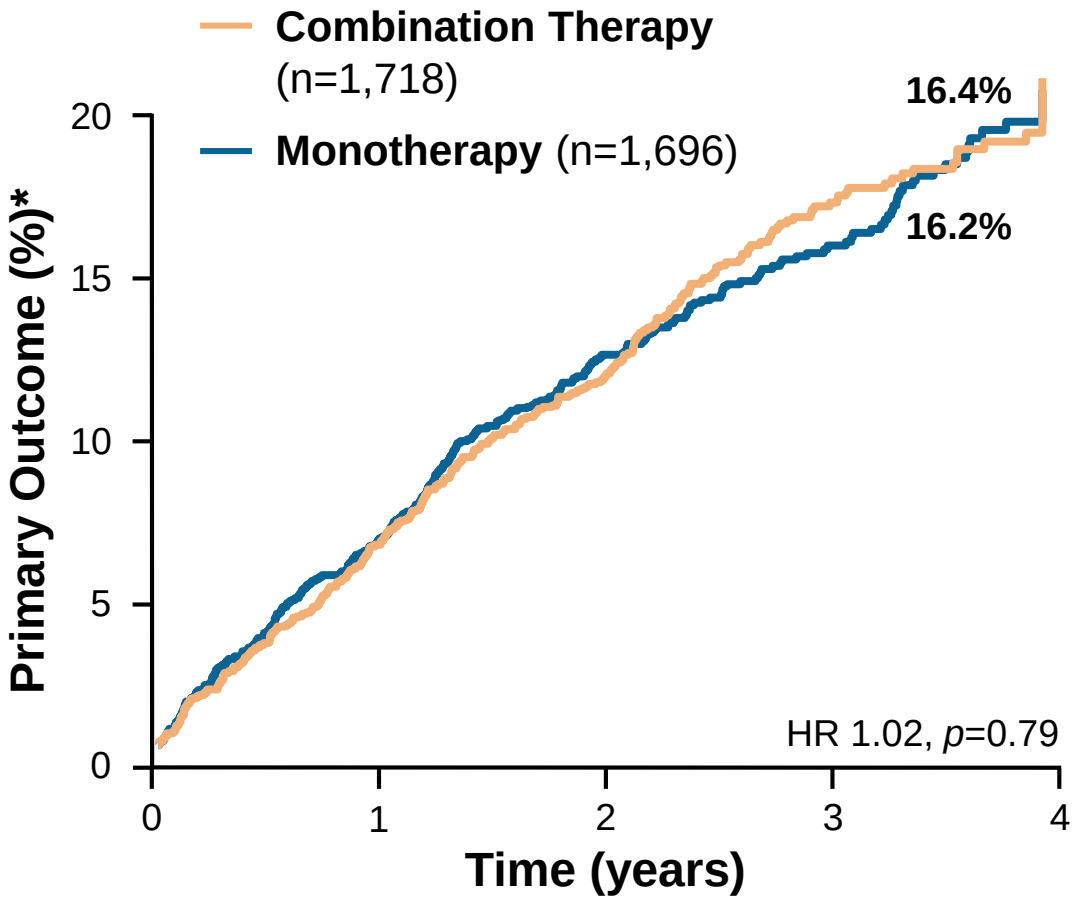
Major CV and Coronary Event Rates vs Various LDL-C Levels



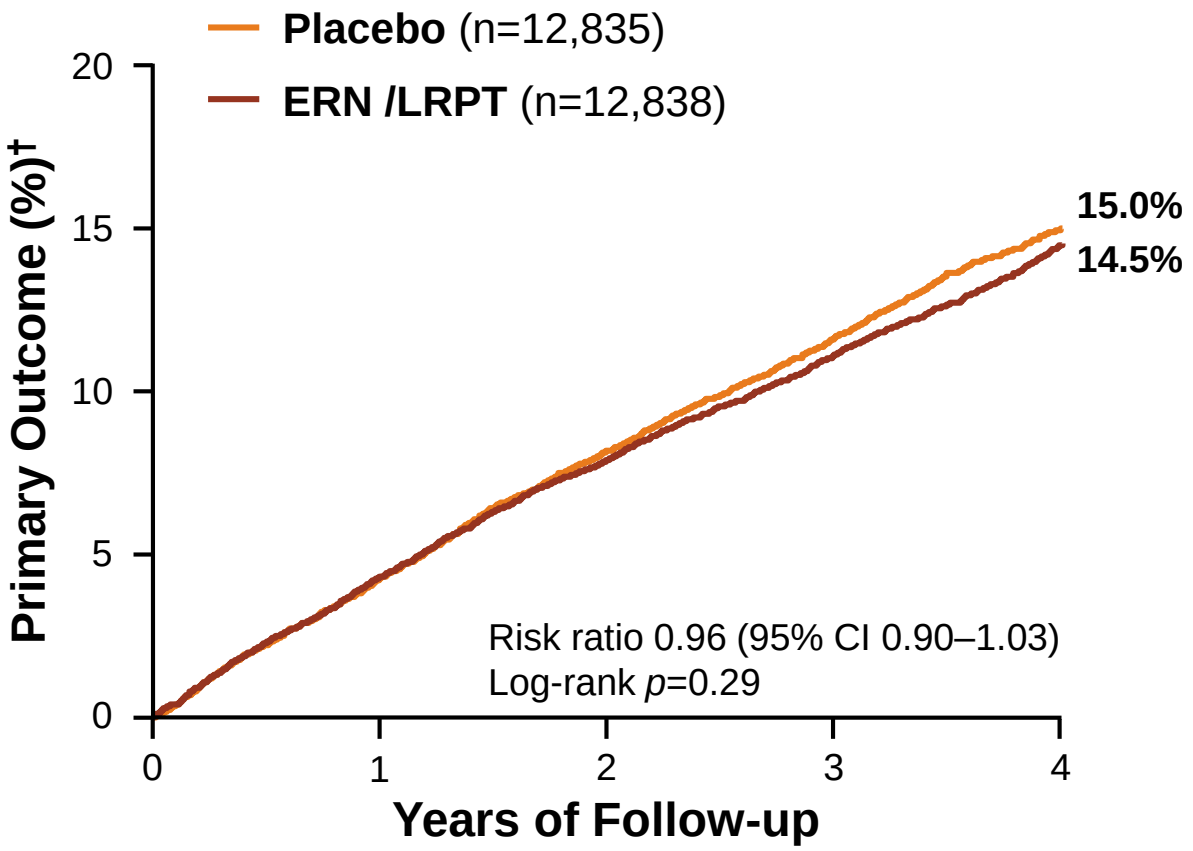
Boekholdt SM, et al. *JACC*. 2014;64(5):485-494.

Impact of Nicotinic Acid in ASCVD

AIM-HIGH Trial



HPS2-THRIVE Trial



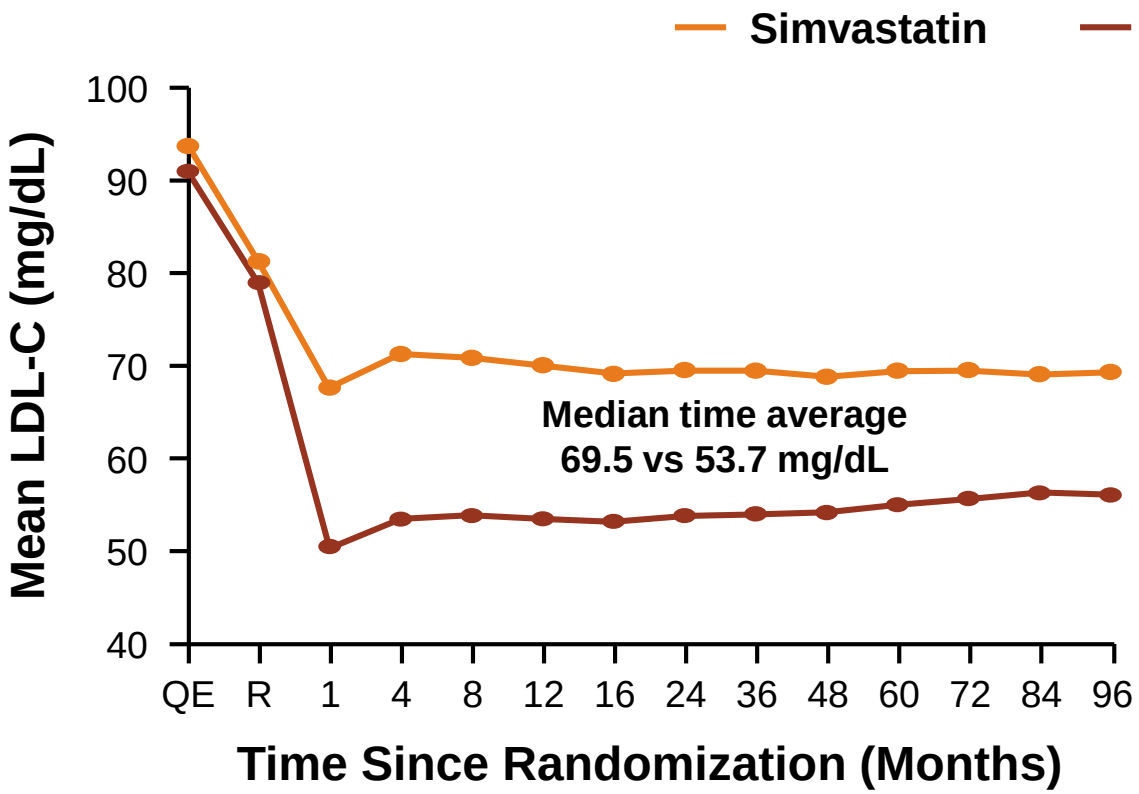
***CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary/cerebral revascularization; †Patients with CV death, MI, stroke, or revascularization; ERN/LRPT = extended-release niacin/laropiprant.**

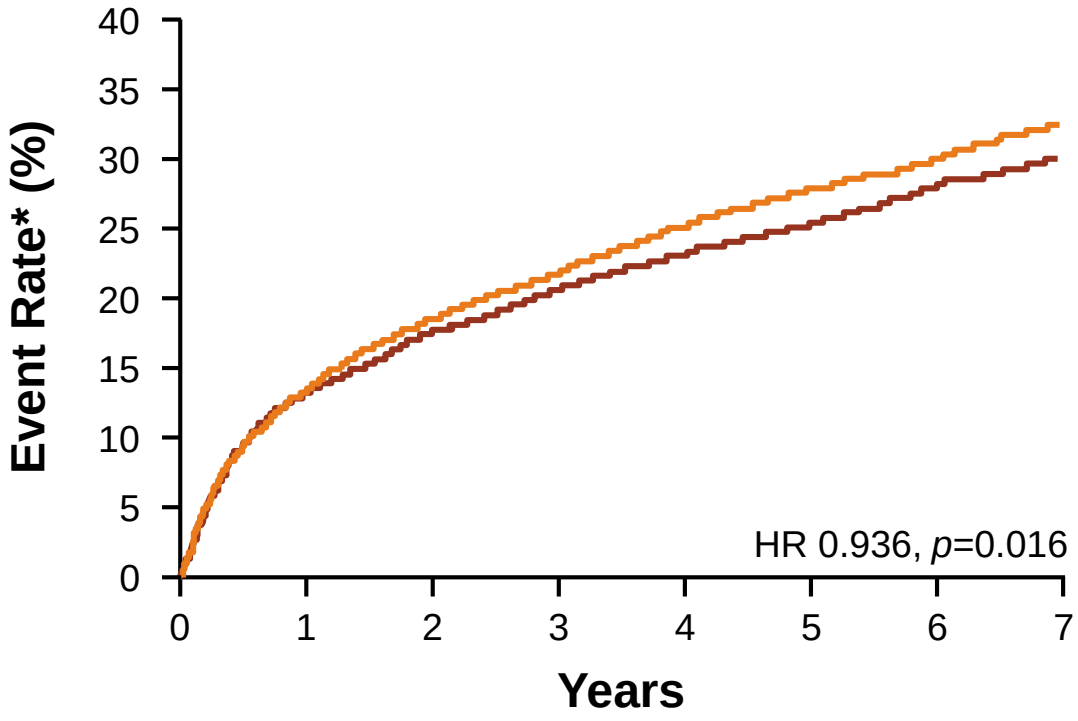
AIM-HIGH Investigators. *N Engl J Med*. 2011;365(24):2255-2267. HPS2-THRIVE Collaborative Group, Landray MJ, et al. *N Engl J Med.* 2014;371(3):203-12.

Impact of Ezetimibe in ASCVD

IMPROVE-IT Study

18,144 ACS patients randomized to simvastatin (40 mg QHS) or simvastatin/ezetimibe (40 mg/10 mg QHS) for seven years

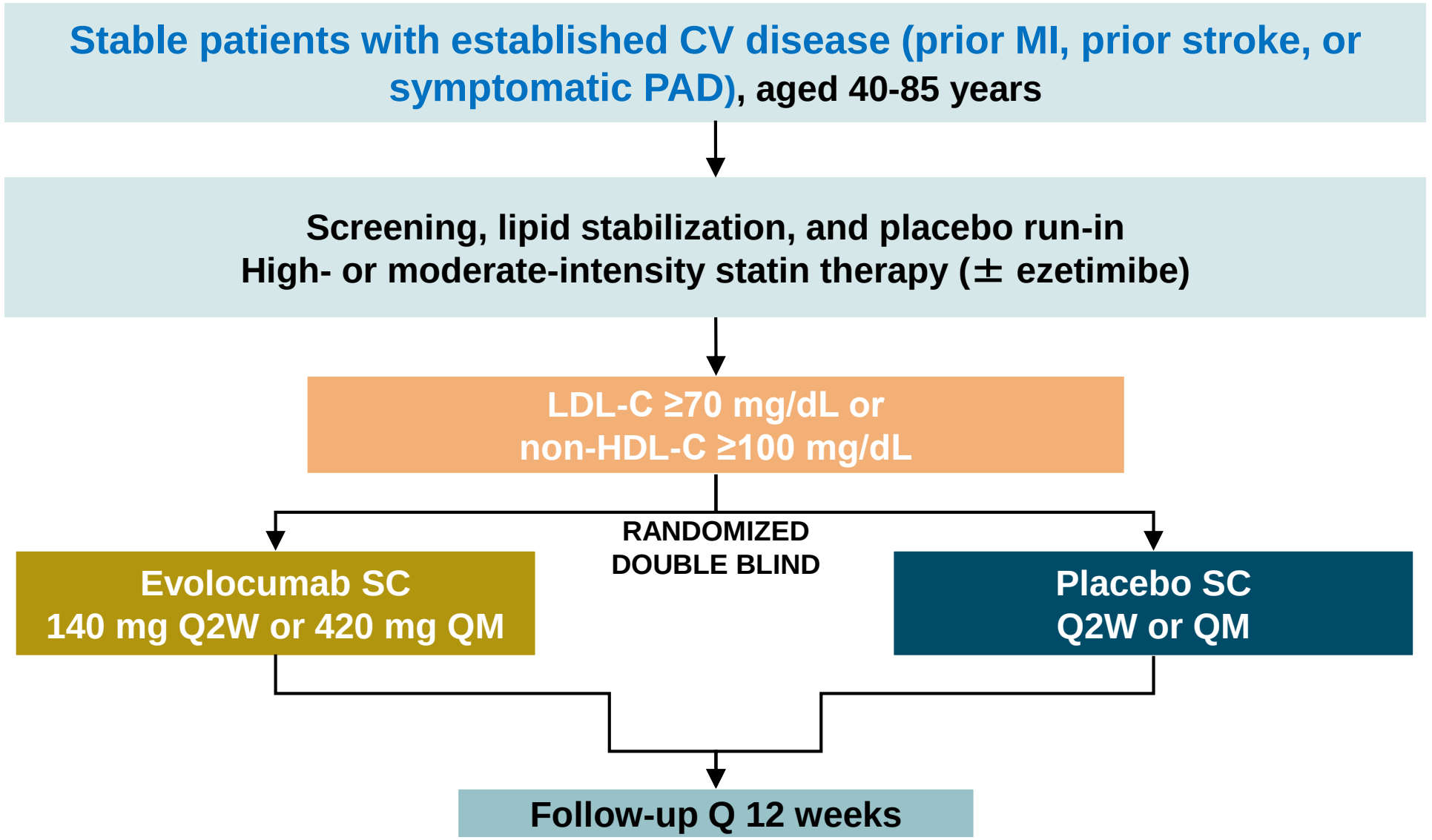




***Composite of CV death, MI, unstable angina, coronary revascularization, or stroke.**
ACS = acute coronary syndrome; HR = hazard ratio.

Cannon CP, et al. *New Engl J Med* . 2015;372(25):2387-2397.

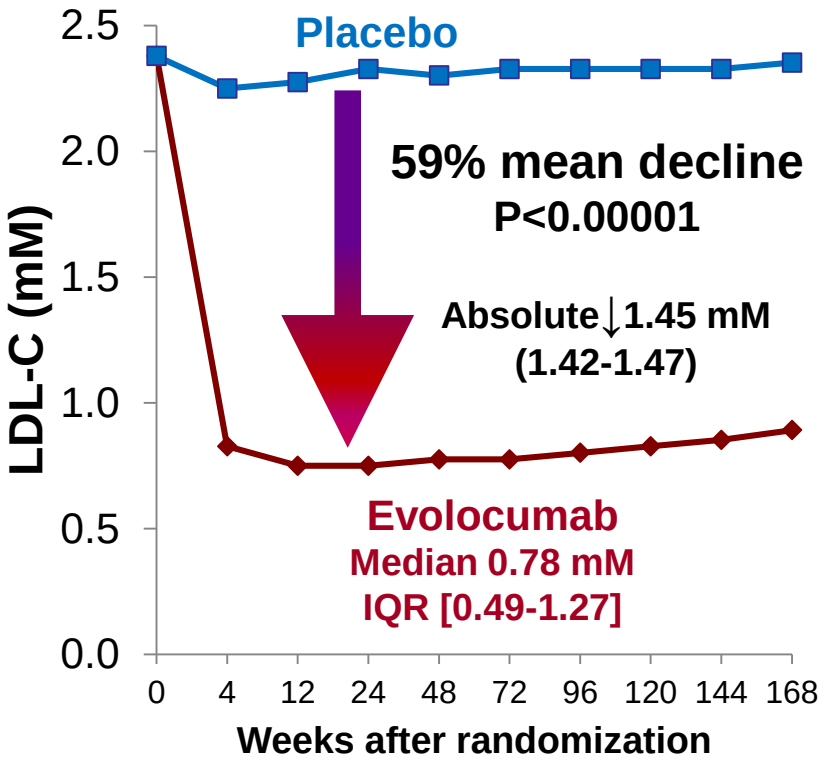
FOURIER Trial: Design

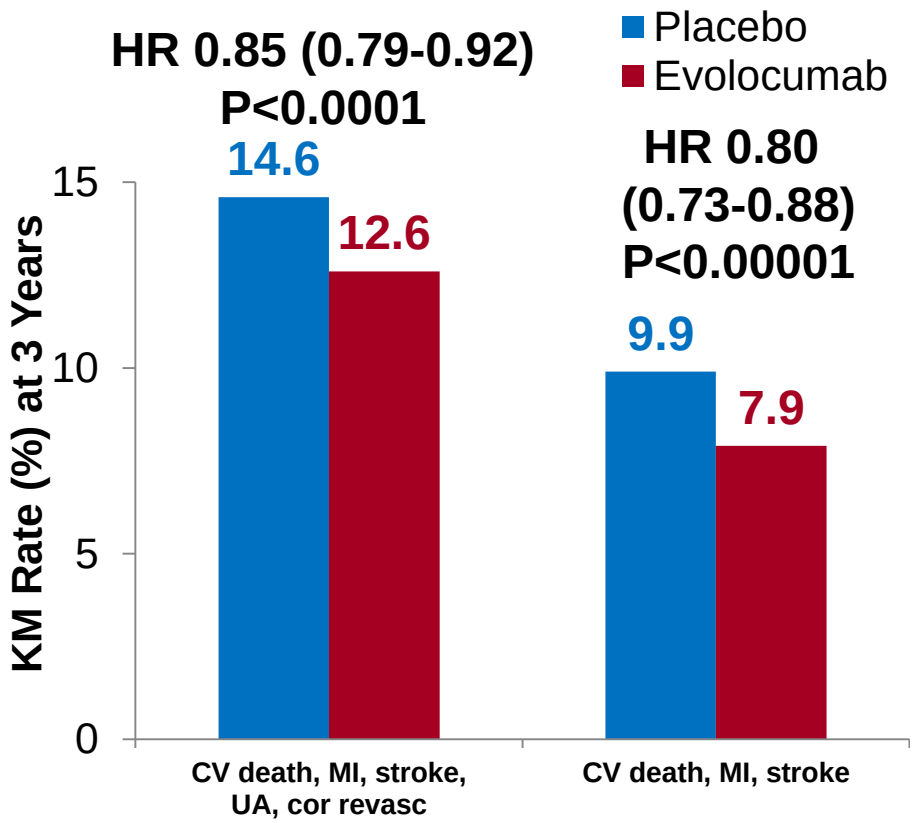


Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.

Summary of FOURIER

- ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated

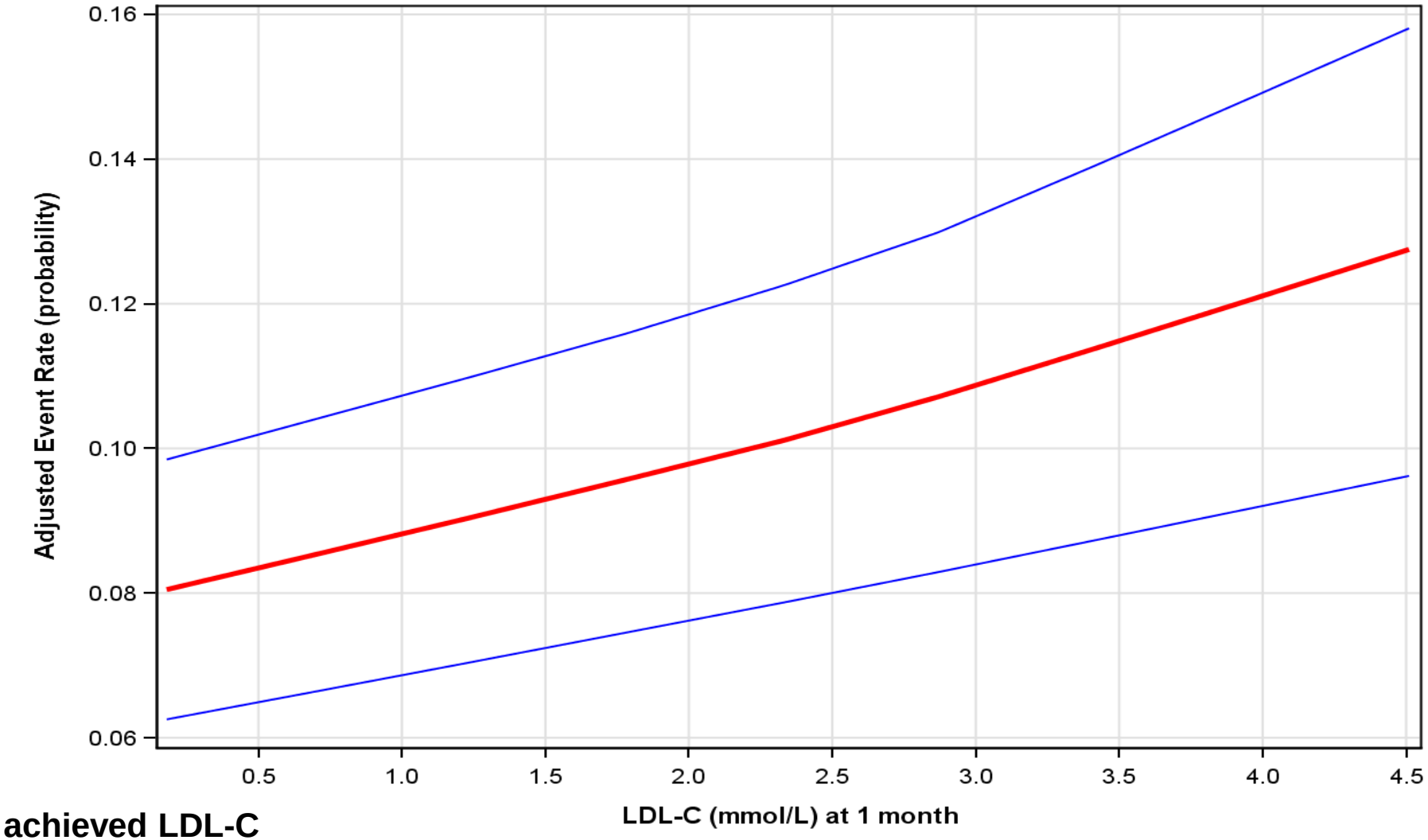




Sabatine MS et al. *New Engl J Med* 2017;376:1713-22

FOURIER – Lower CV Event Rates with Lower LDL-C Levels*

There were no safety concerns with very low LDL-cholesterol concentrations over a median of 2.2 years.



***Relationship between the achieved LDL-C at 4 weeks and the risk of CVD, MI, or stroke.**

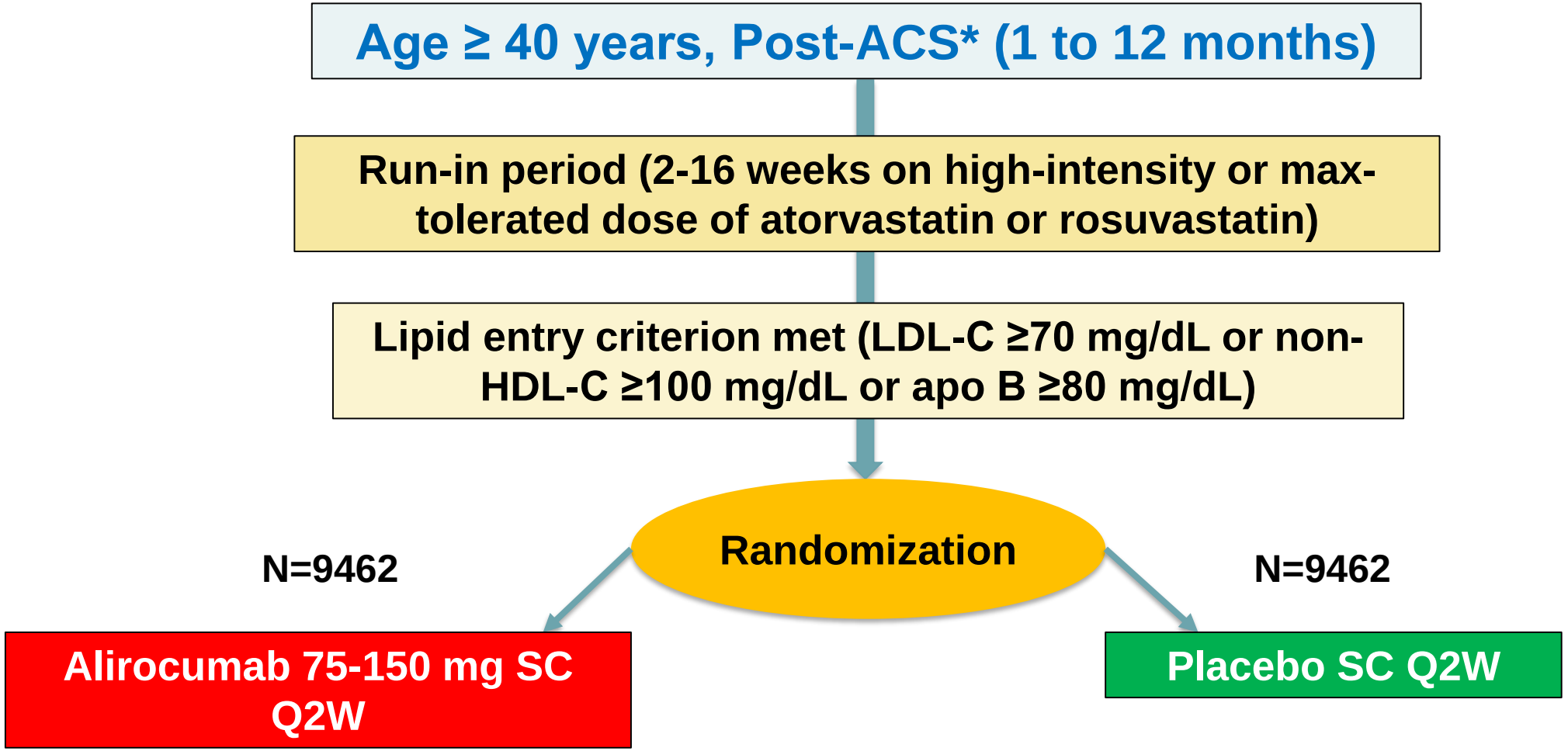
. Giugliano RP, Lancet. 2017;390(10106):1962-71

Safety Outcomes

	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
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a
Muscle-related	5.0	4.8
Rhabdomyolysis	0.1	0.1
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Aminotransferase >3× ULN	1.8	1.8
Creatine kinase >5× ULN	0.7	0.7

Sabatine MS et al. *New Engl J Med* 2017;376:1713-22

ODYSSEY OUTCOMES Trial: Design



Primary endpoint: CHD, MI, fatal or not-fatal stroke, or UA requiring hospitalization

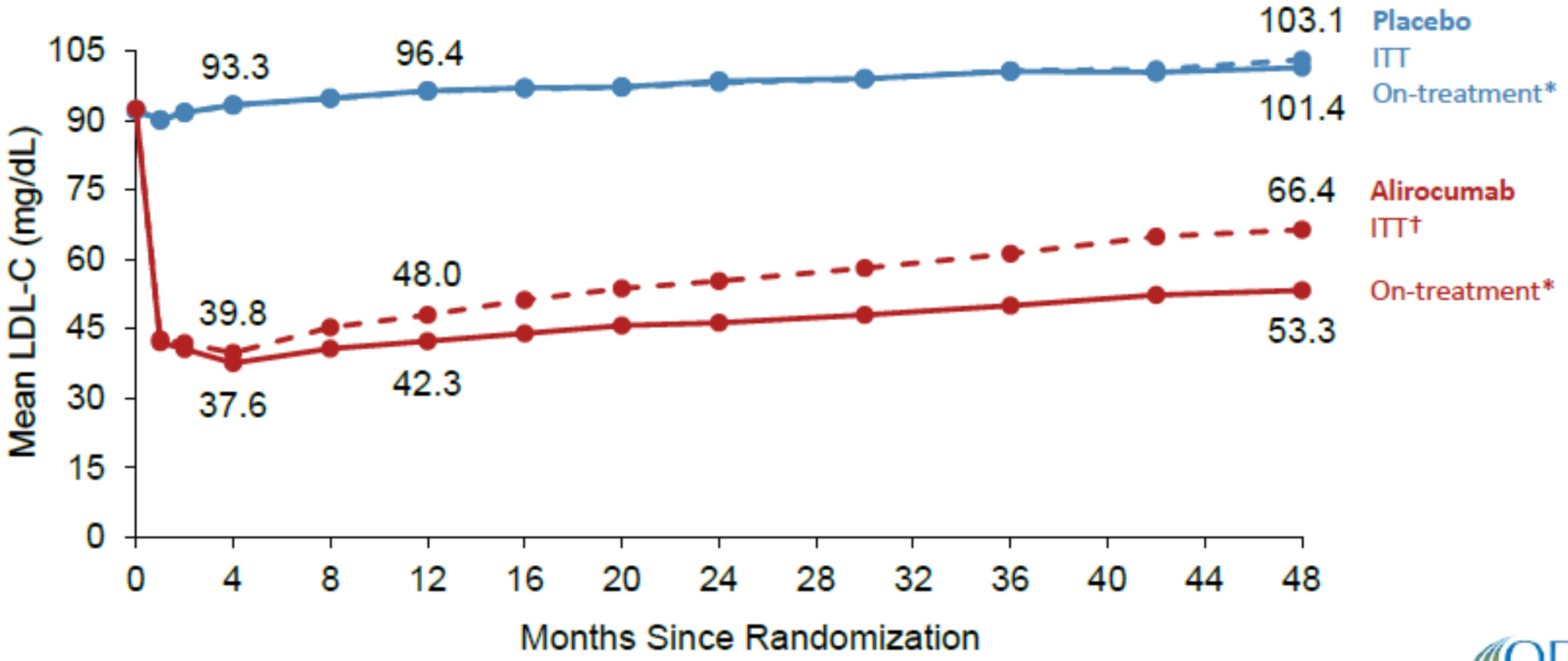
ACS is defined as acute MI or unstable angina (UA); CHD = Coronary heart disease death

Schwartz GG, et al. Am Heart J. 2014;168(5):682-9.

ODYSSEY OUTCOMES

ODYSSEY Outcomes Trial: LDL-C Reduction with Alirocumab in ACS

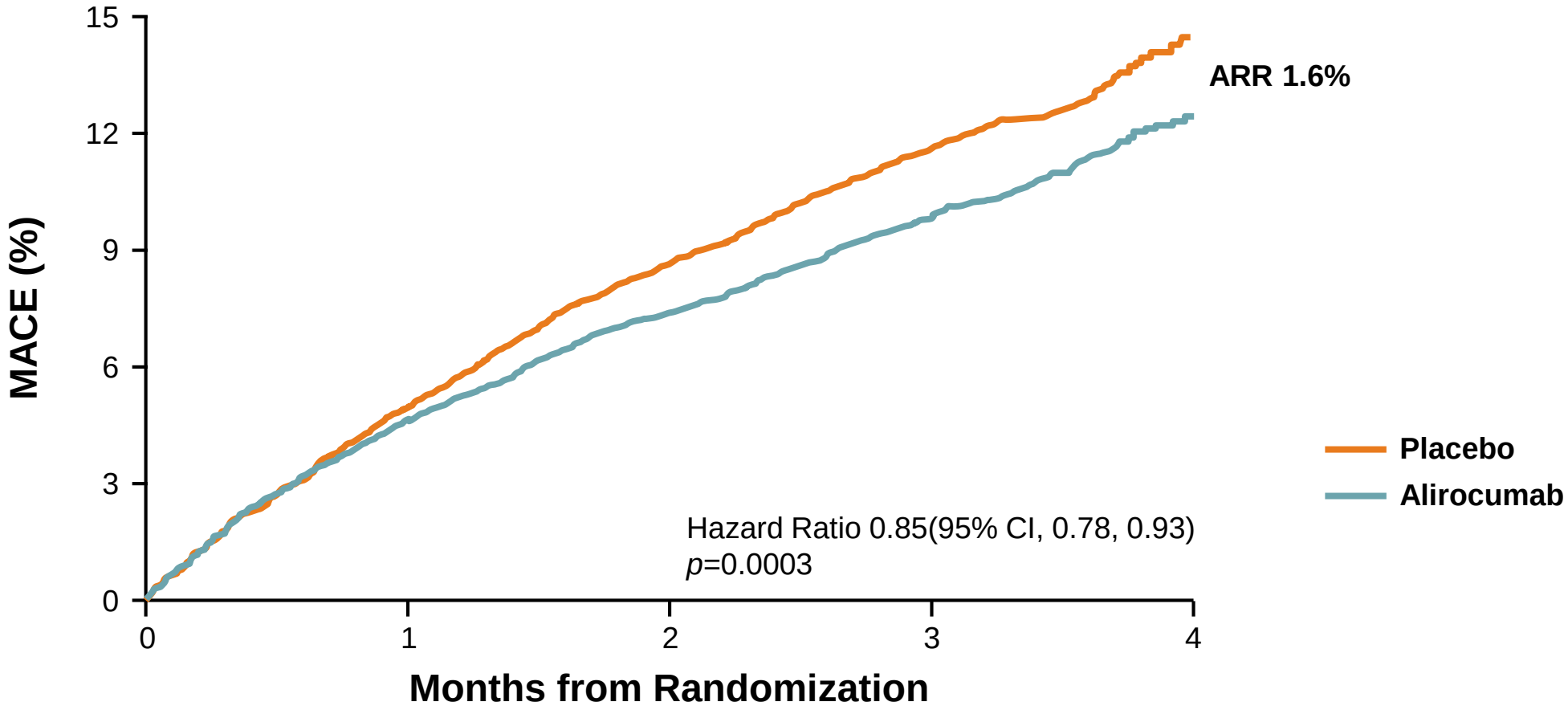
18,924 high-risk patients with an ACS within the preceding 1-12 months and an LDL-C ≥70 mg/dL on background high-intensity statin therapy randomized to alirocumab or placebo for a median of 2.8 years



Schwartz GG, NEJM 2018;379:2097-107

ODYSSEY OUTCOMES

ODYSSEY Outcomes Trial: Primary Endpoint Results



ARR = absolute risk reduction.

Schwartz GG, NEJM 2018;379:2097-107

ODYSSEY OUTCOMES

ODYSSEY Outcomes Trial: Primary and Secondary Outcomes

Endpoint	Alirocumab	Placebo	HR (95% CI)	*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
Nonfatal 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
Death, MI, ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86 (0.79-0.93)	0.0003
Coronary heart disease death	205 (2.2%)	222 (2.3%)	0.92 (0.76-1.11)	0.38
Cardiovascular death	240 (2.5%)	271 (2.9%)	0.88 (0.71-1.05)	0.15
All-cause death	334 (3.5%)	392 (4.1%)	0.85 (0.73-0.98)	0.026*

***Nominal *p* value.**
CHD = coronary heart disease; MACE = major adverse cardiac events.

Schwartz GG, NEJM 2018;379:2097-107

ODYSSEY OUTCOMES

Safety in ODYSSEY OUTCOMES

Variable	Alirocumab (N=9451)	Placebo (N=9443)
Adverse events — no. (%)		
Any adverse event	7165 (75.8)	7282 (77.1)
Serious adverse event	2202 (23.3)	2350 (24.9)
Adverse event that led to death	181 (1.9)	222 (2.4)
Adverse event that led to discontinuation of the trial regimen	343 (3.6)	324 (3.4)
Local injection-site reaction	360 (3.8)	203 (2.1)
General allergic reaction	748 (7.9)	736 (7.8)
Diabetes worsening or diabetic complication among patients with diabetes at baseline — no./total no. (%)	506/2688 (18.8)	583/2747 (21.2)
New-onset diabetes among patients without diabetes at baseline — no./total no. (%)*	648/6763 (9.6)	676/6696 (10.1)
Neurocognitive disorder	143 (1.5)	167 (1.8)
Hepatic disorder	500 (5.3)	534 (5.7)
Cataracts	120 (1.3)	134 (1.4)
Hemorrhagic stroke, adjudicated	9 (<0.1)	16 (0.2)
Laboratory abnormalities at any time — no./total no. (%)		
Alanine aminotransferase >3 times upper limit of normal range	212/9369 (2.3)	228/9341 (2.4)
Aspartate aminotransferase >3 times upper limit of normal range	160/9367 (1.7)	166/9338 (1.8)
Total bilirubin >2 times upper limit of normal range	61/9368 (0.7)	78/9341 (0.8)
Creatine kinase >10 times upper limit of normal range	46/9369 (0.5)	48/9338 (0.5)
Antidrug antibodies†	67/9091 (0.7)	32/9097 (0.4)
Neutralizing antidrug antibodies	43/9091 (0.5)	6/9097 (<0.1)

Schwartz GG, NEJM 2018;379:2097-107

ODYSSEY OUTCOMES

FOURIER vs ODYSSEY OUTCOMES

	Alirocumab (*N* = 9,462)[1]	Evolocumab (*N* = 13,784)[2]
Patient type	ACS patients (within 1–12 months of event)	ASCVD patients with history of MI, stroke, or symptomatic PAD
Time from index event to randomization	2.6 months	~3.3 years (MI or stroke)
High-intensity statin	88.6%	69.5%
Baseline LDL-C	87 mg/dL	92 mg/dL
Median follow up	2.8 years	2.2 years
Outcomes		
Primary endpoint[a,b]	0.85 HR *P* = 0.0003	0.85 HR *P* <0.001
Nonfatal MI	0.86 HR *P* = 0.006	0.73 HR *P* <0.001
Stroke	0.73 HR *P* = 0.01	0.79 HR *P* = 0.01
CVD	0.92 HR *P* = 0.38	1.05 HR *P* = 0.62
All-causes death	0.85 HR *P* = 0.026	1.04 HR *P* = 0.54

[a] Alirocumab = CVD, non-fatal MI, ischemic stroke, or UA requiring hospitalization; [b] Evolocumab = CVD, MI, stroke, hospitalization for UA, or coronary revascularization.

1. Schwartz GG, *New Engl J Med* 2018;379;2097-107 . 2. Sabatine MS, *New Engl J Med.* 2017;376:1713–1722.

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

(Anderson TJ, Canadian J of Cardiology 32 (2016) 1263e1282)

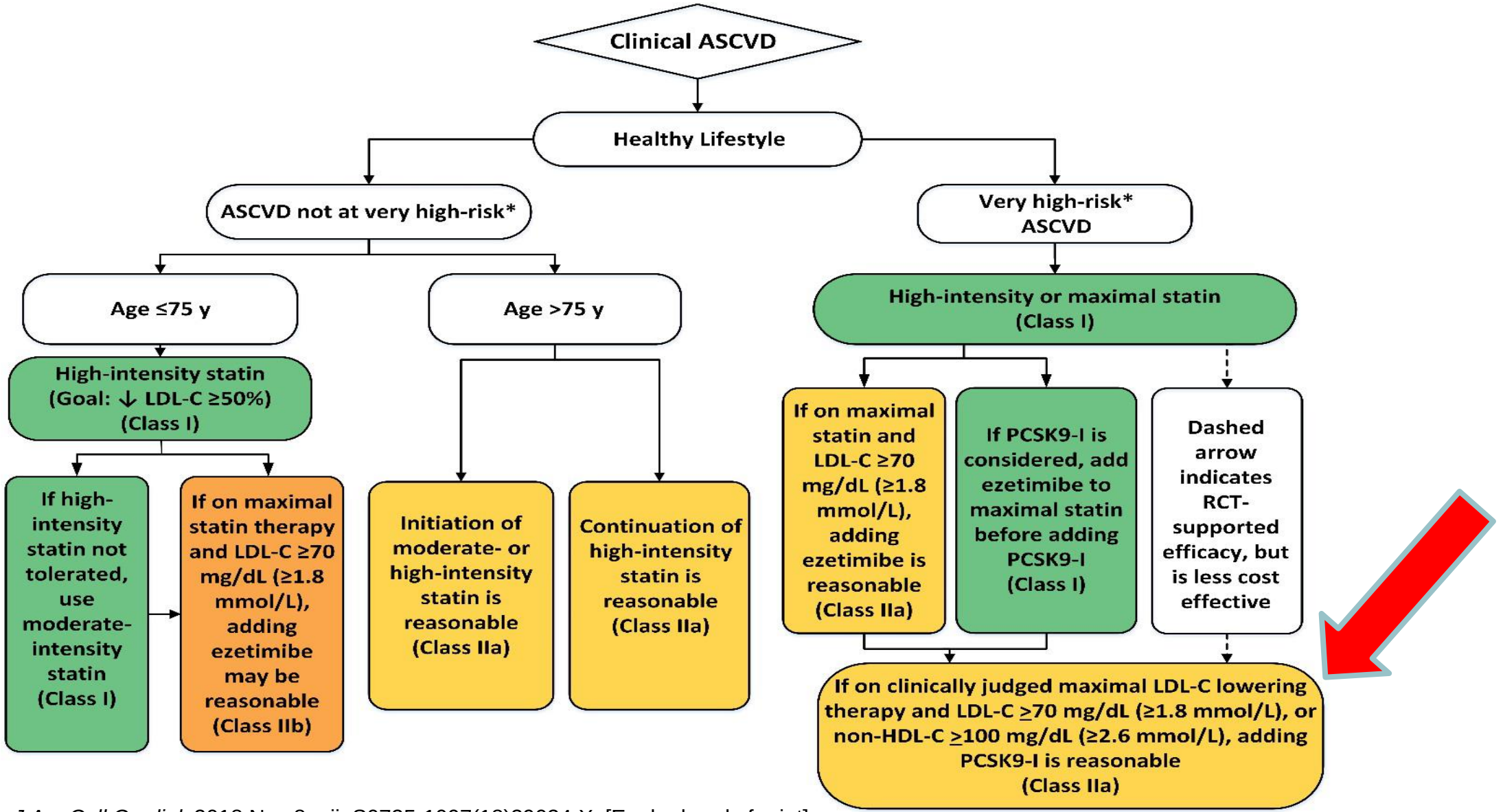
This Guideline preceded results from FOURIER and ODYSSEY OUTCOMES

"We suggest that PCSK9 inhibitors be considered to lower LDL-C level for patients with atherosclerotic CVD in those not at LDL-C goal despite maximally tolerated statin doses with or without ezetimibe therapy"
(Conditional Recommendation; Moderate-Quality Evidence).

GRADE and Evidence Review

"For patients whose LDL-C is <15-20% away from target, the addition of ezetimibe is likely to achieve target. However, for patients whose LDL-C is >20% away from target, no drug other than a PCSK9 inhibitor is likely to get the LDL-C to target"

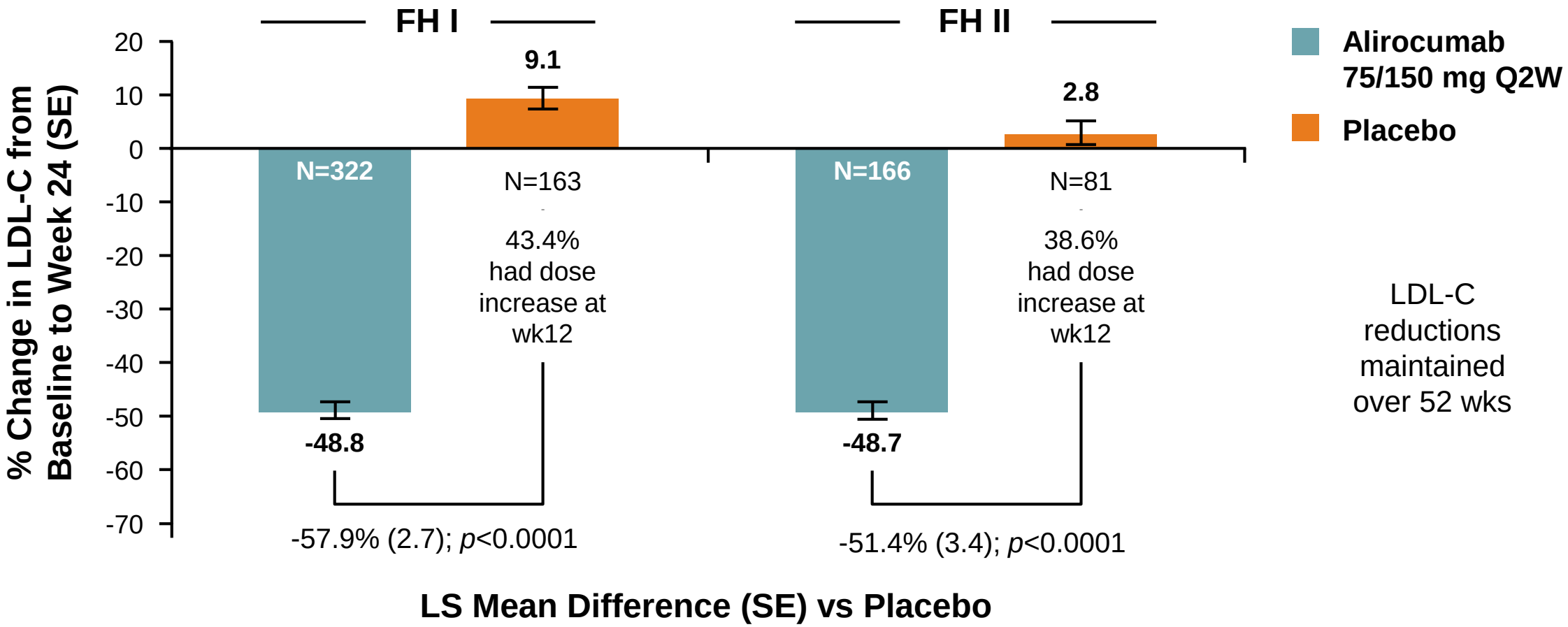
2018 US Cholesterol Guidelines
Secondary ASCVD Prevention



Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X. [Epub ahead of print]

ODYSSEY FH I and FH II: Alirocumab in Patients with FH

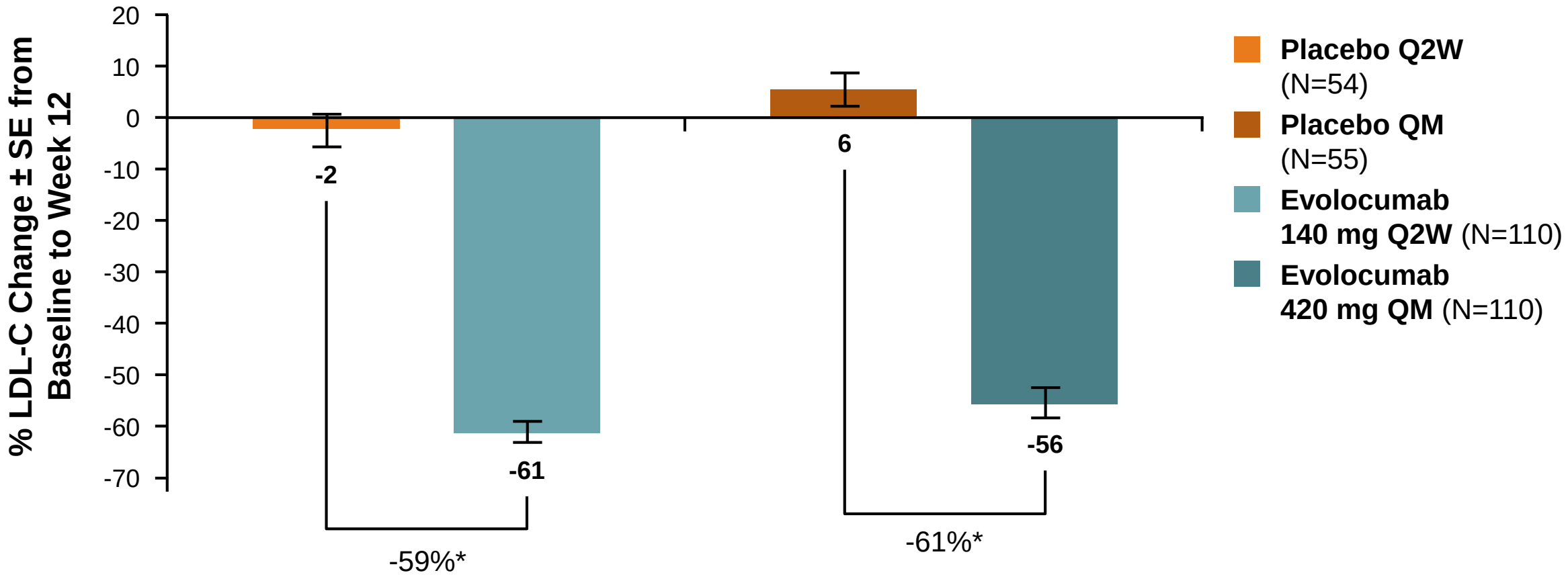
All patients on background maximally-tolerated statin ± another LLT



Kastelein JJ, et al. *Eur Heart J*. 2015;36(43):2996-3003.

RUTHERFORD-2: Evolocumab in Patients with FH

All patients on background maximally-tolerated statin ± another LLT



***p<0.001; SE = standard error.**

Raal FJ, et al. *Lancet*. 2015;385(9965):331-40.

Canadian Journal of Cardiology 34 (2018) 1553–1563

Society Position Statement

Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018

Primary Panel: Liam R. Brunham, MD, PhD,[a,b] Isabelle Ruel, PhD,[c] Sumayah Aljenedil, MD,[c]

- **Est 10% of FH patients in Canada have been diagnosed**
- **STRONG RECOMMENDATIONS**
  - FH should be defined using established criteria*
  - Perform cascade screening on all 1st degree relatives
  - Offer genetic testing, when available
  - Treat with statins (primary); ezetimibe, PCSK9i (secondary)
  - Don’t use statins during pregnancy
  - Refer HoFH patients to specialized clinics

*Dutch Lipid Clinic Network, Simon Broome Registry, or FH Canada

MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA

Familial Hypercholesterolemia

LDL-C >5 mmol/L*

Presence of tendon xanthomas in patients

Or

*First-degree relative with LDL-C >5 mmol/L**

Or

Premature ASCVD in proband or first-degree relative (<65 yr in women; <55 yr in men)

→

- *Implement a healthy lifestyle (healthy eating, no smoking, appropriate body weight, stress management)*
- *Treat conventional cardiovascular risk factors (hypertension, diabetes, obesity, etc)*

→

- *Implement therapy to reduce LDL-C by 50% AND LDL-C <2.5 mmol/L OR <2 mmol/L if ASCVD*[9]
  - *1-Statin*
  - *2-Ezetimibe*
  - *3-PCSK9 inhibitors combined with maximally tolerated statins ± ezetimibe*

Genetic Diagnosis

Presence of a mutation known to cause FH

→

- *Implement cascade screening of family members*

* LDL-C ≥ 4.0 mM if <18 yrs; LDL ≥ 4.5 mM if age 18-40

Brunham LR, Canadian J Card 2018;54:1553-63

Key Takeaways

- While statins remain the standard for treatment of patients with ASCVD and hypercholesterolemia, non-statin therapies such as ezetimibe, alirocumab, and evolocumab offer additional options for reducing the risk of adverse CV events.
- ODYSSEY OUTCOMES and FOURIER have shown PCSK9 inhibitors alirocumab and evolocumab to be effective in lowering LDL-C and CV events in patients with ACS and stable ASCVD, respectively
- Achieving lower LDL levels (< 50 mg/dL) has been shown to be safe and significantly reduces the risk of cardiovascular events