Five Non-Statin Trials That Cardiologists Need to Know

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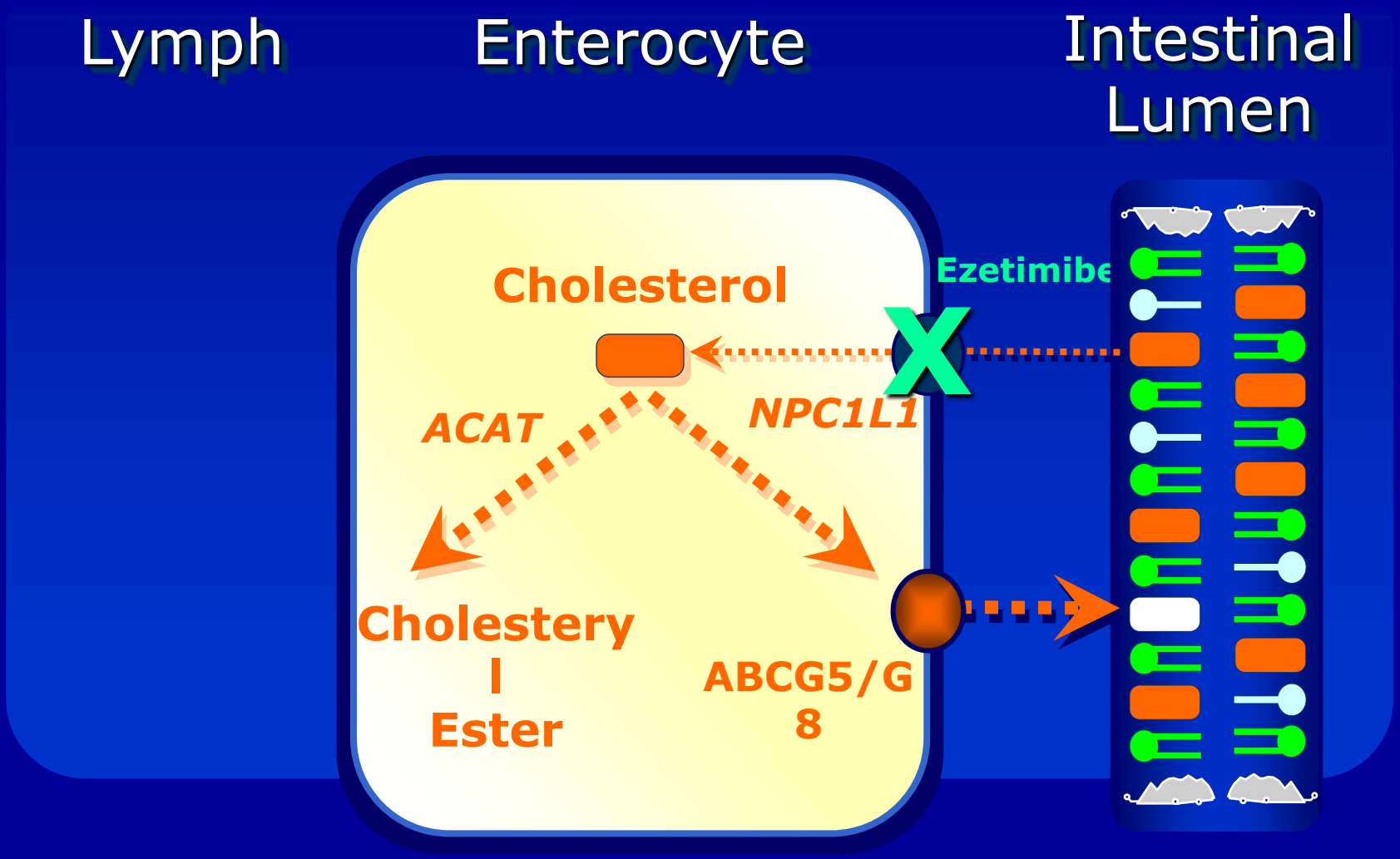
Disclosures

- Research support: Department of Veterans Affairs Health Services Research & Development, American Diabetes Association, American Heart Association, Baylor College of Medicine Global Initiatives, Department of Veterans Affairs Network 12
- Member, Steering Committee, Patient and Provider Assessment of Lipid Management (PALM) Registry at the Duke Clinical Research Institute (DCRI) [No financial remuneration].
- Associate Editor for Innovation, ACC.org

IMPROVE-IT

Ezetimibe: courtesy lipids online



Study Design (IMPROVE IT)

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

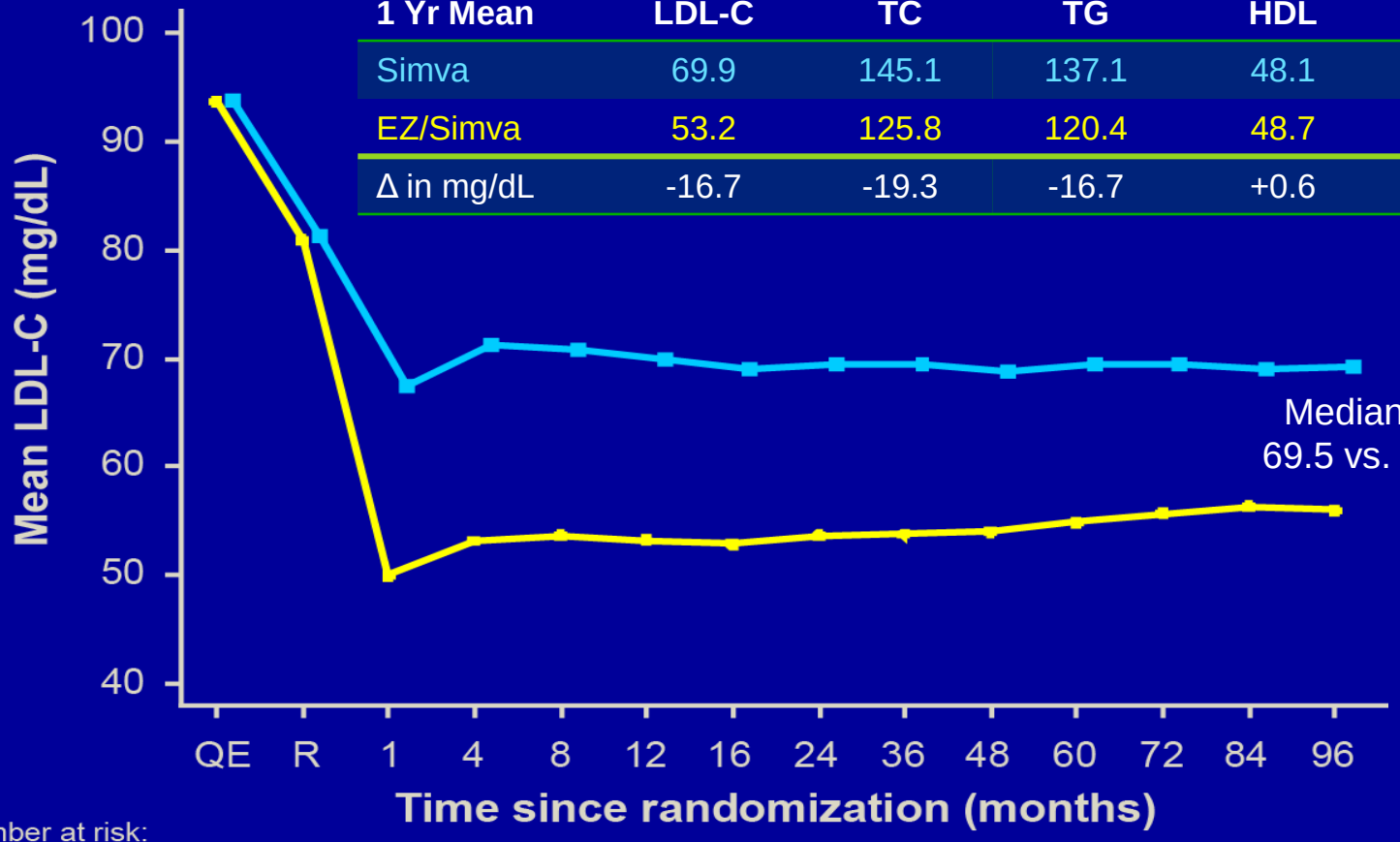
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

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

Cannon CP N Engl J Med. 2015 Jun 18;372(25):2387-97

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
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



Median Time avg
69.5 vs. 53.7 mg/dL

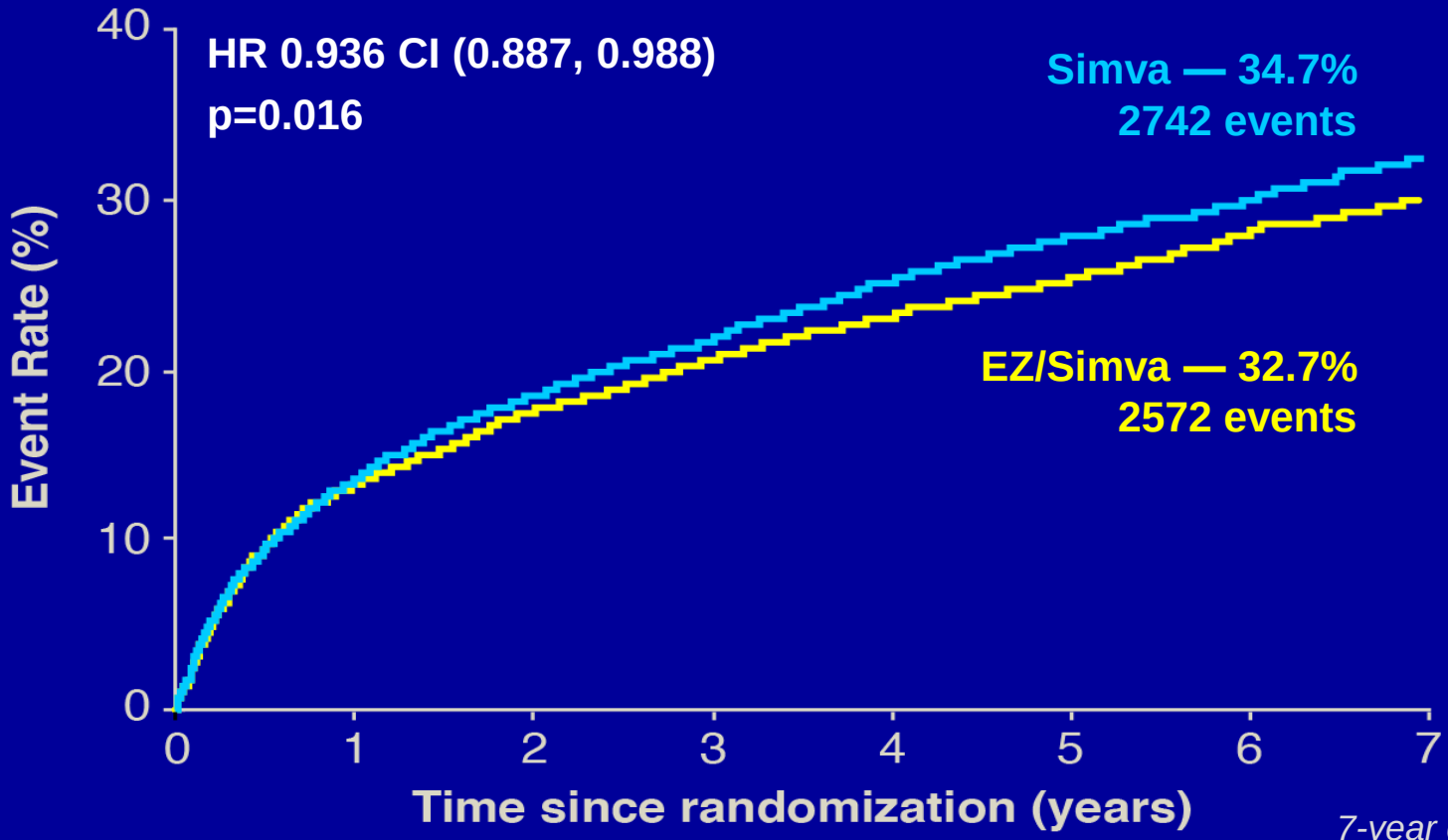
Number at risk:

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

Cannon CP N Engl J Med. 2015 Jun 18;372(25):2387-97

Primary Endpoint — ITT

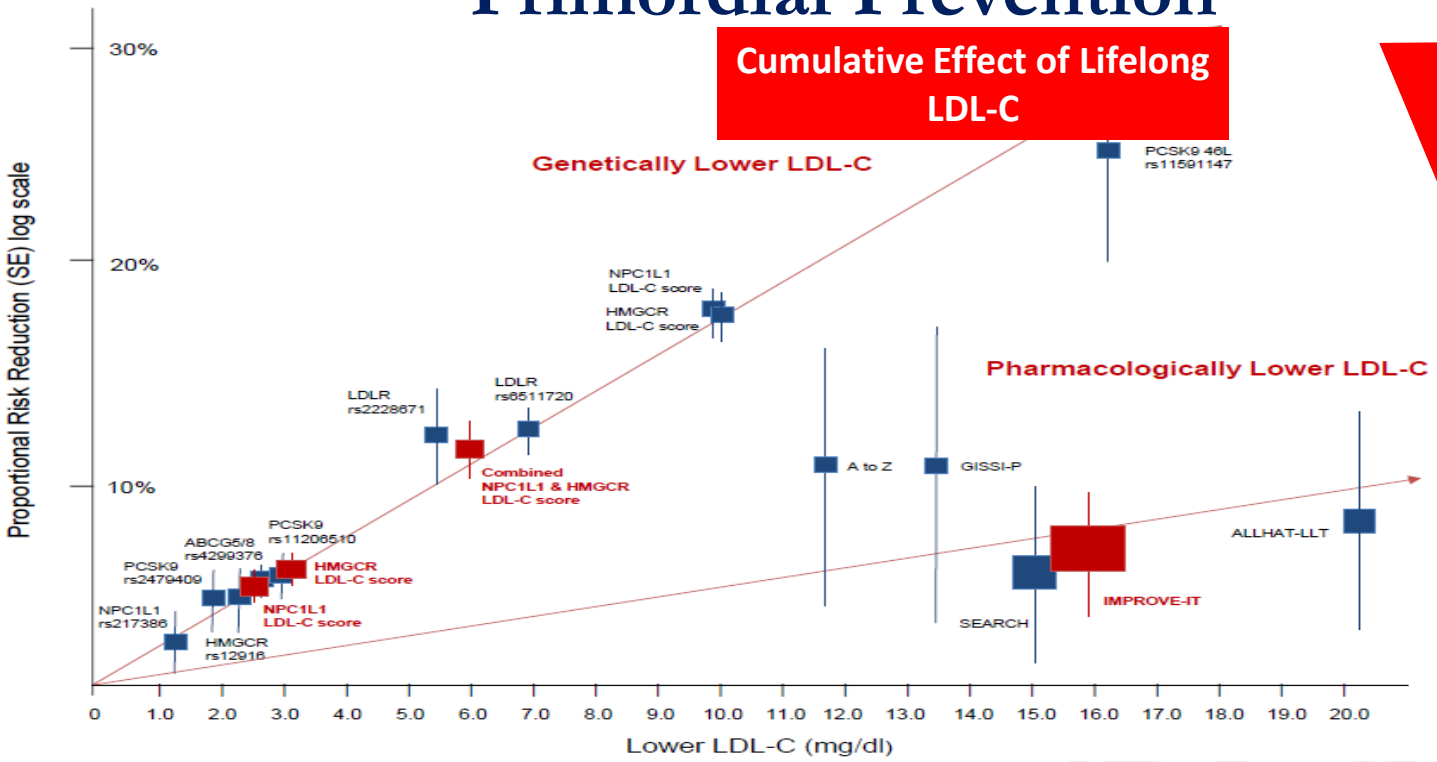
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

Cannon CP N Engl J Med. 2015 Jun 18;372(25):2387-97

Effect of Lower LDL-C on CHD: Importance of Primordial Prevention



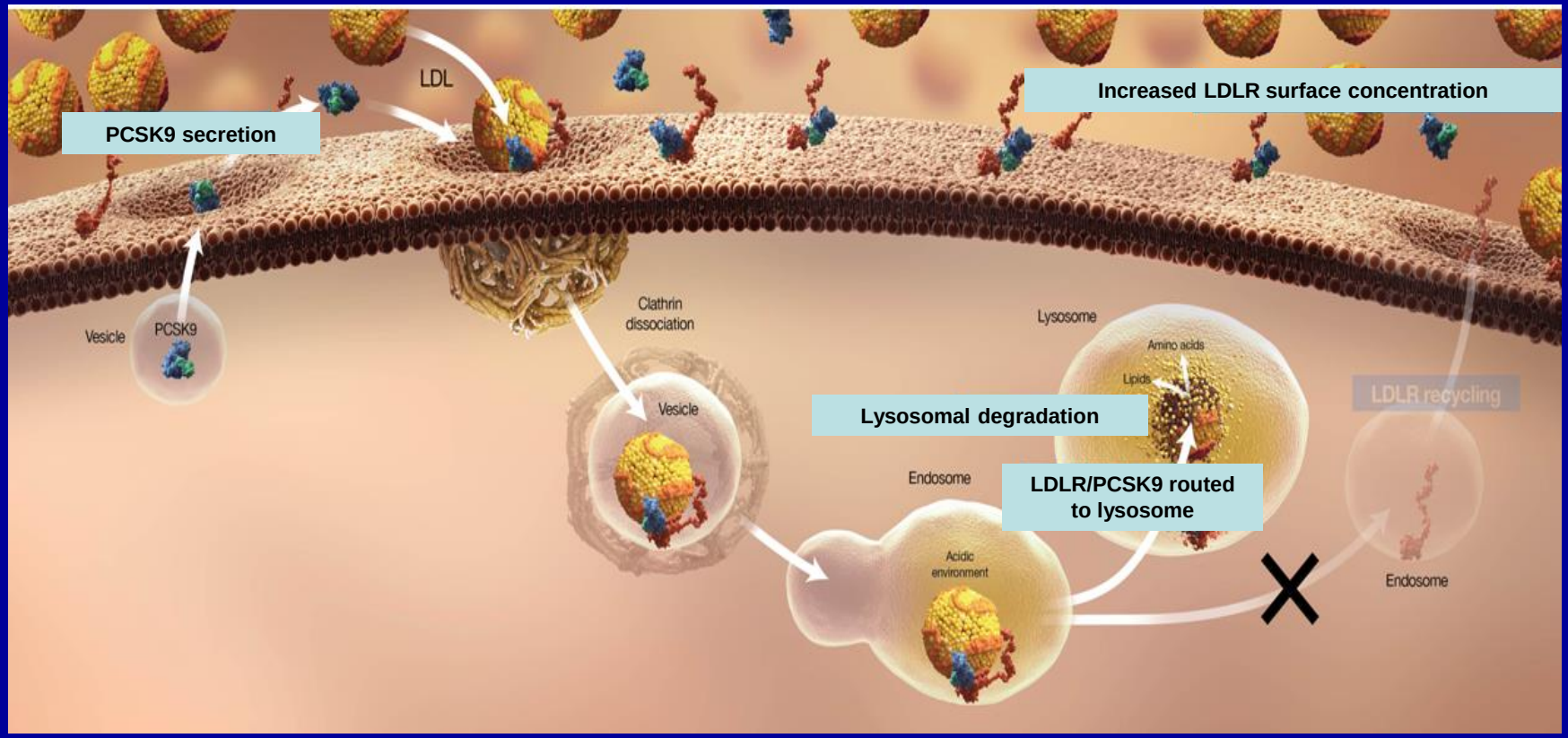
Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

Cannon CP, et al. AHA, November, 17 2014.

AMERICAN COLLEGE of CARDIOLOGY

FOURIER

PCSK9 Is a Key Regulator of LDLR Recycling by Targeting the Receptor for Degradation[1-3]



1. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177. **2.** Qian YW, et al. *J Lipid Res.* 2007;48:1488-1498. **3.** Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

FOURIER

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

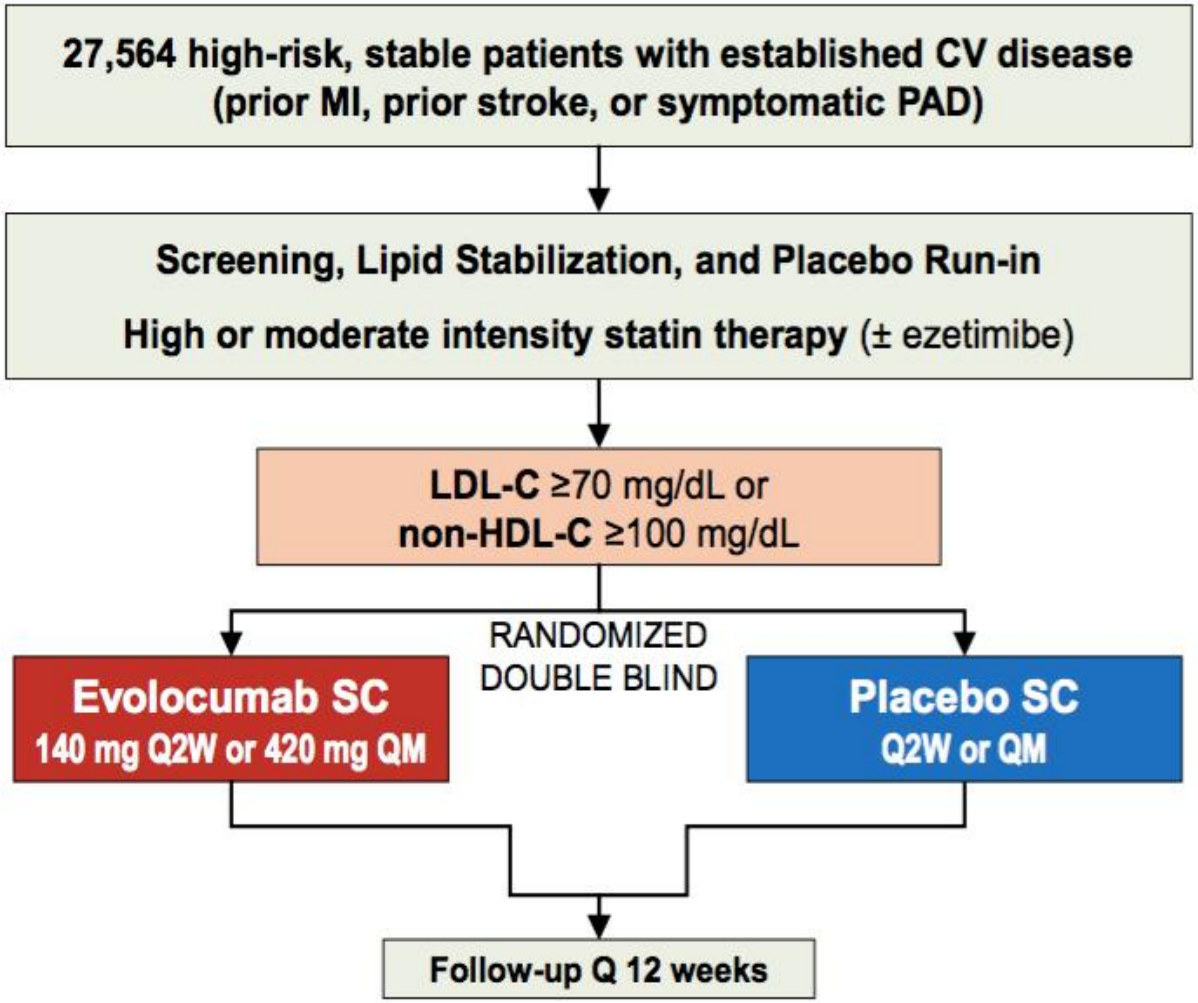
MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

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

Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

Trial Design



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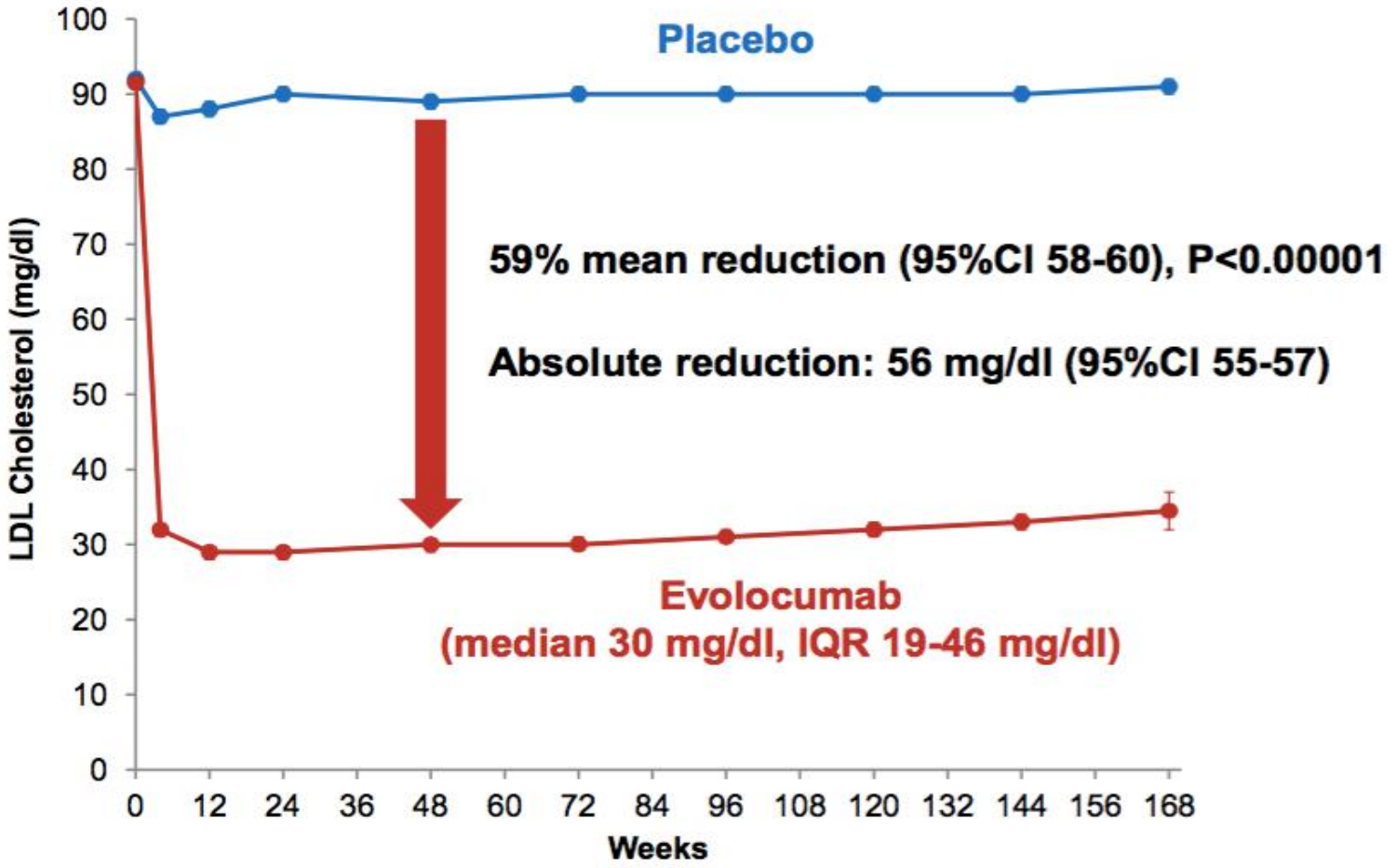
Sabatine MS et al. *Am Heart J* 2016;173:94-101

Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

LDL Cholesterol



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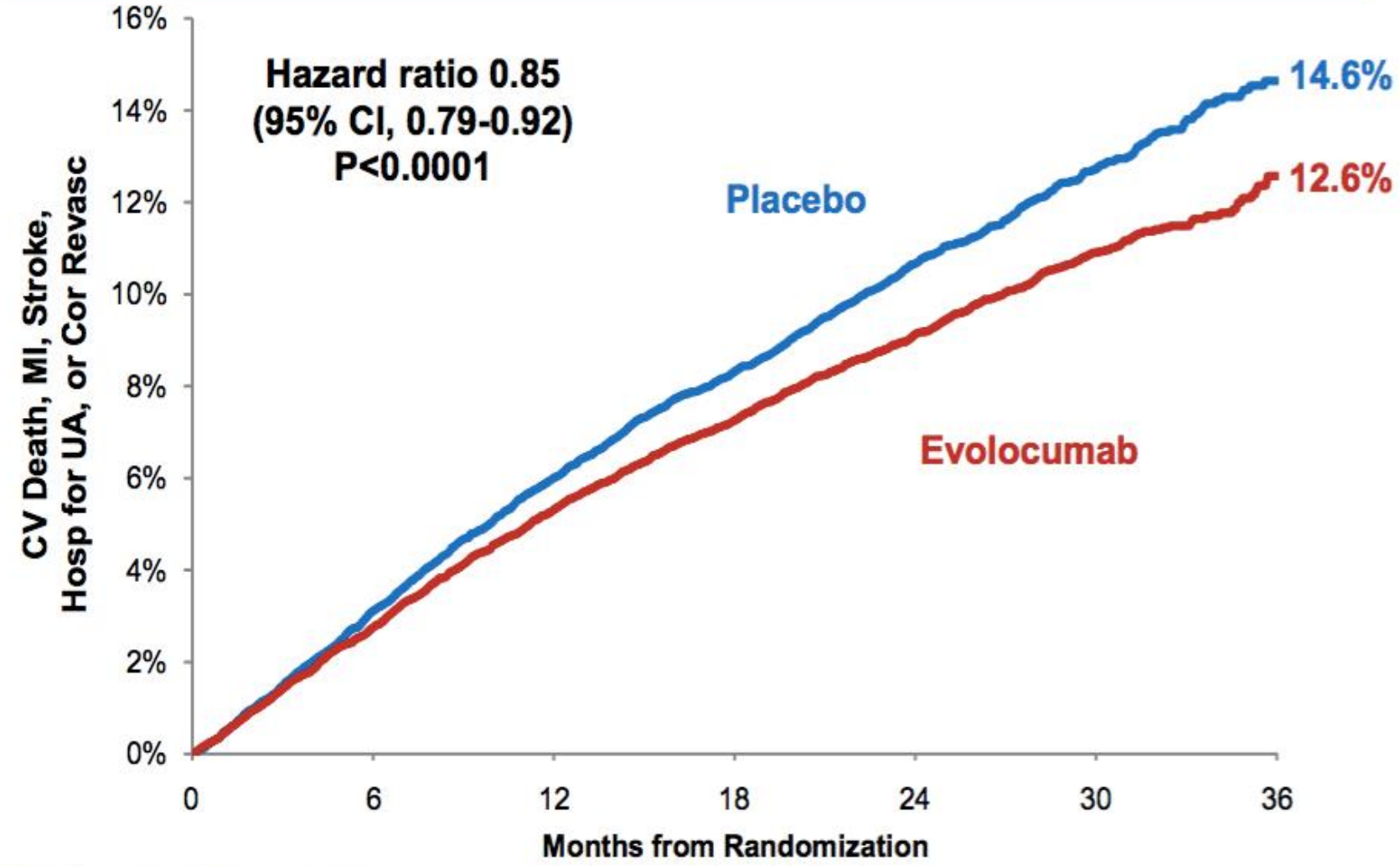
Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

Primary Endpoint



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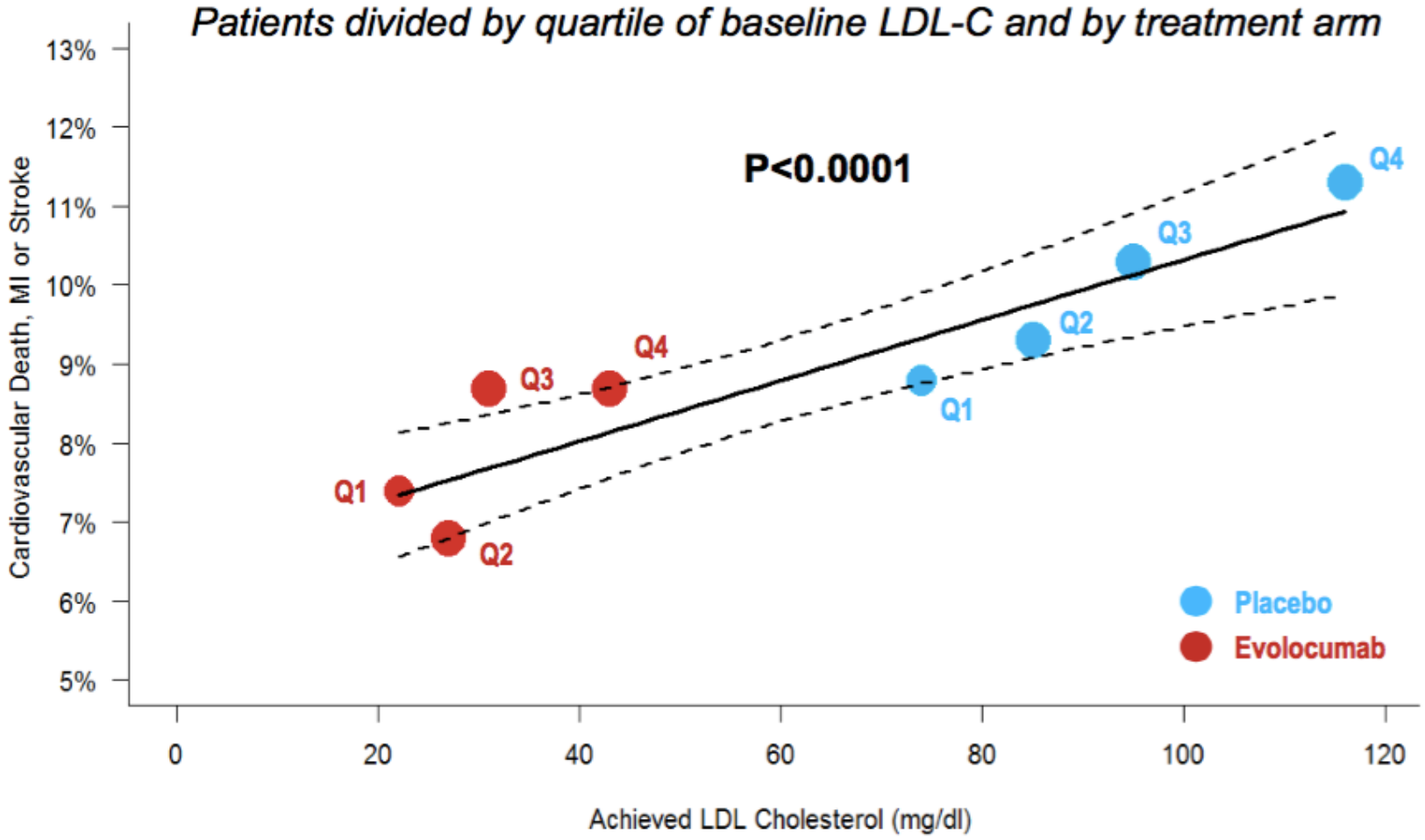
Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

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)**

Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

Lower LDL-C Is Better



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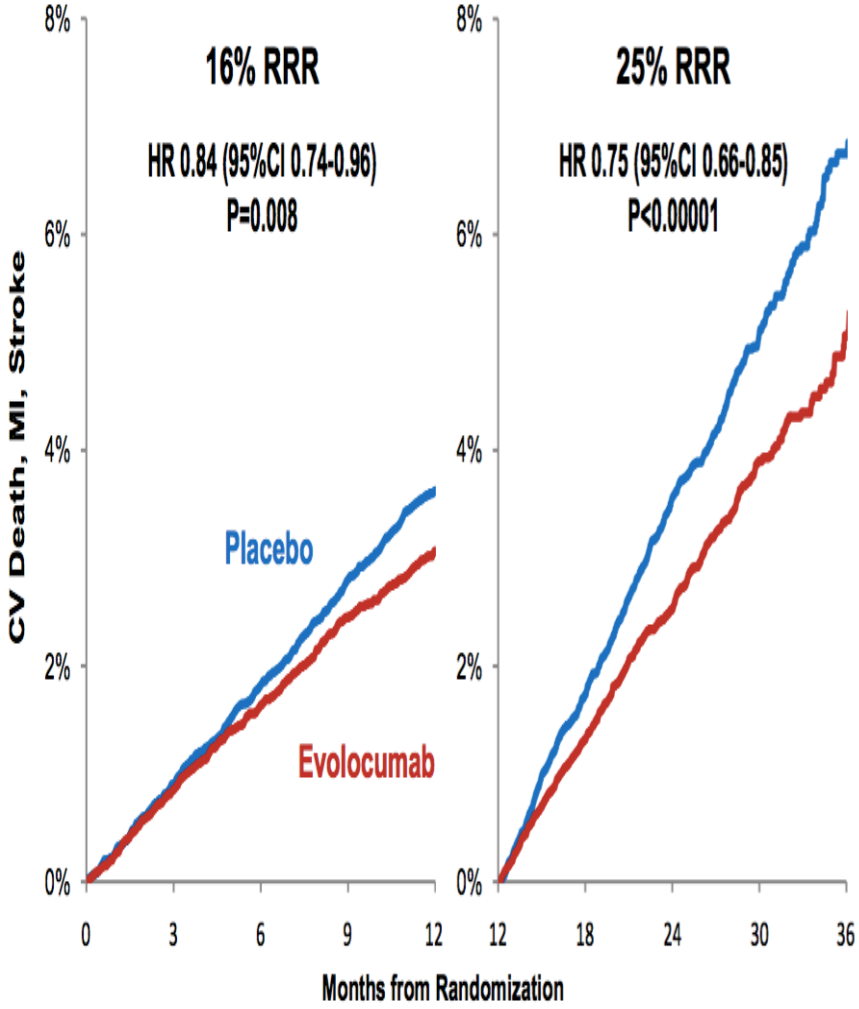
Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

Landmark Analysis



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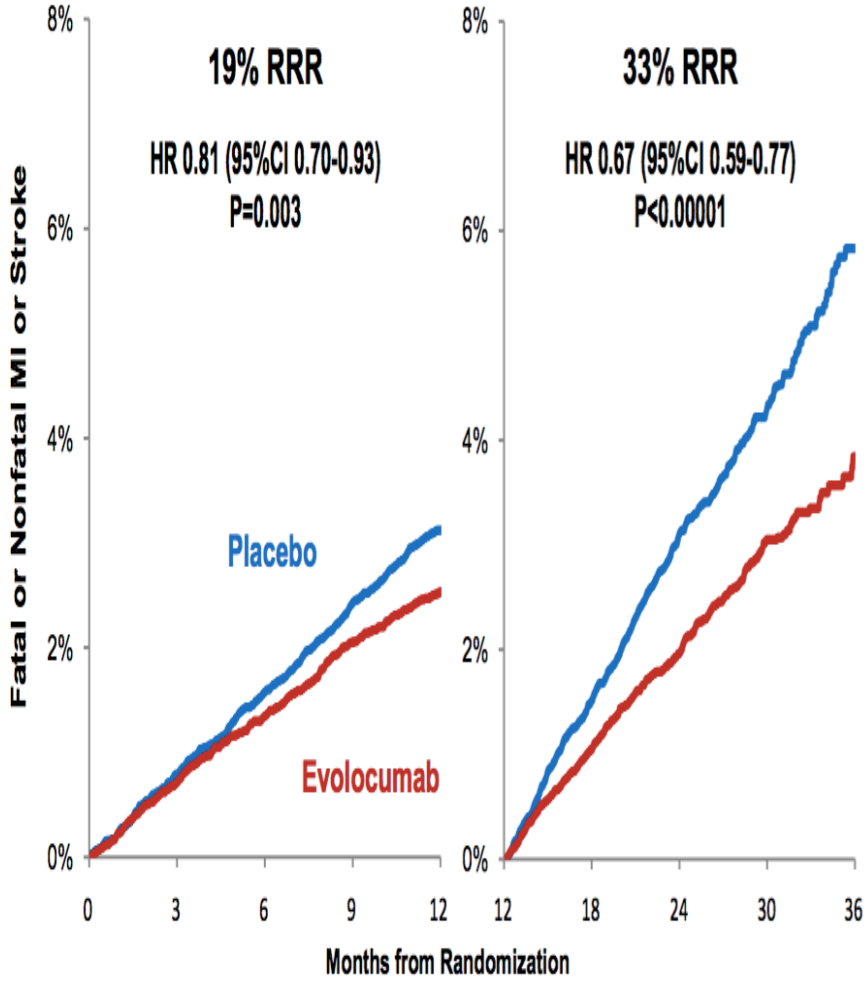
Fatal or Nonfatal MI or Stroke



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Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

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

Sabatine MS et al. nejm.org 3/17/17**DOI: 10.1056/NEJMoa1615664**

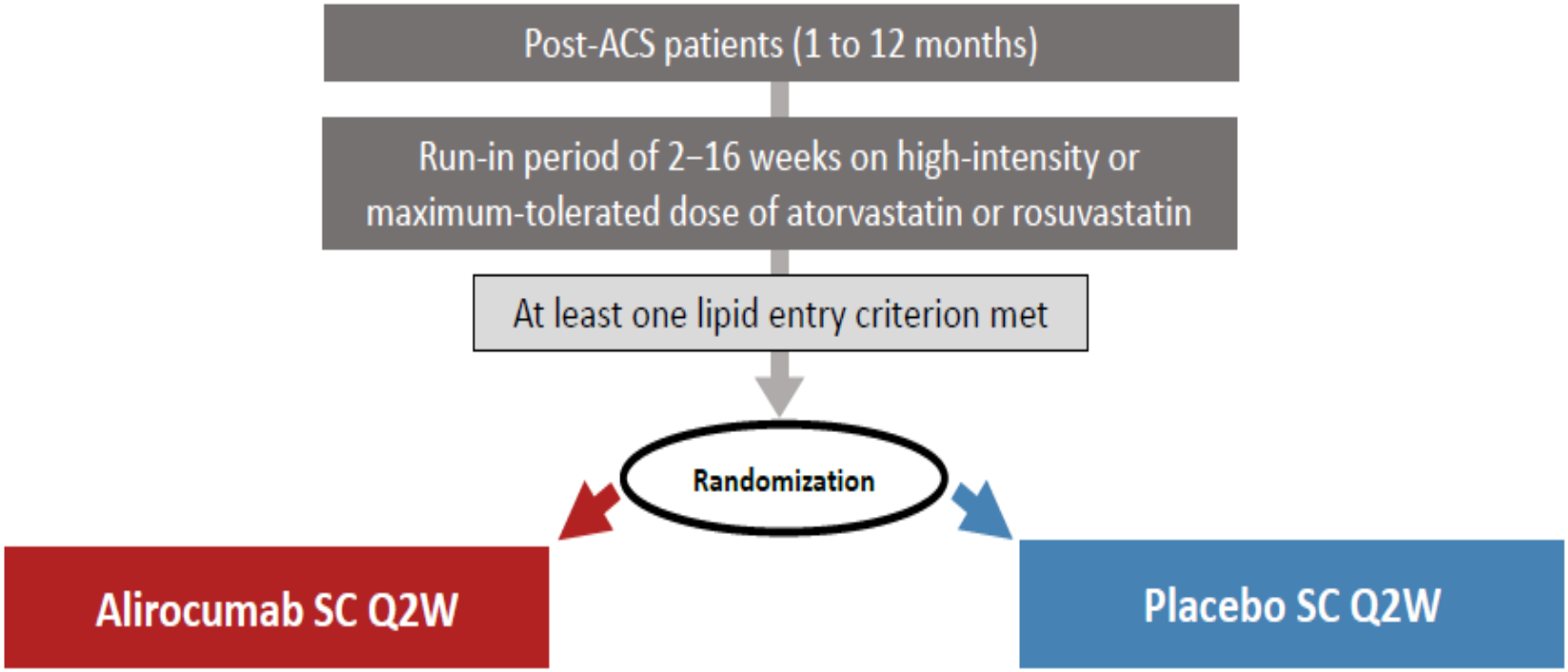
Risk of CV Death or Stroke in FOURIER Subgroups with Prior MI's or Multi-vessel CAD

	Evo	Placebo	NNT	HR (95% CI)
Time From Qualifying MI				
< 2 *Years*	7.9%	10.8%	35	0.76 (0.64-0.89)
≥ 2 *Years*	8.3%	9.3%	101	0.87 (0.76-0.99)
Number of Prior MIs				
≥ 2	12.4%	15.0%	38	0.79 (0.67-0.94)
1	6.6%	8.2%	60	0.84 (0.74-0.96)
Multi-vessel CAD				
Yes	9.2%	12.6%	29	0.70 (0.58-0.84)
No	7.6%	8.9%	78	0.89 (0.79-1.00)

Sabatine M presented at AHA 2017

ODYSSEY OUTCOMES

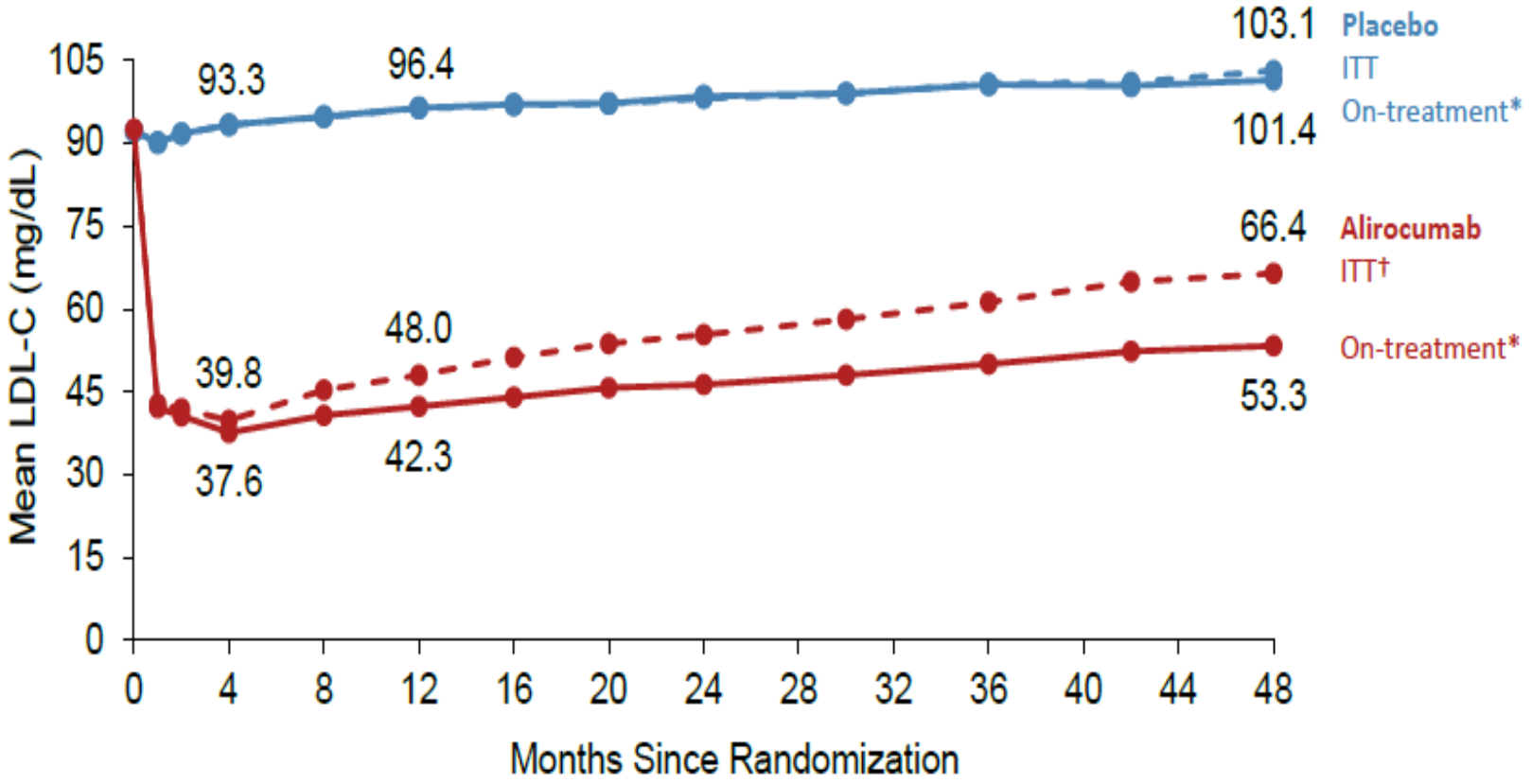
Treatment Assignment



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.

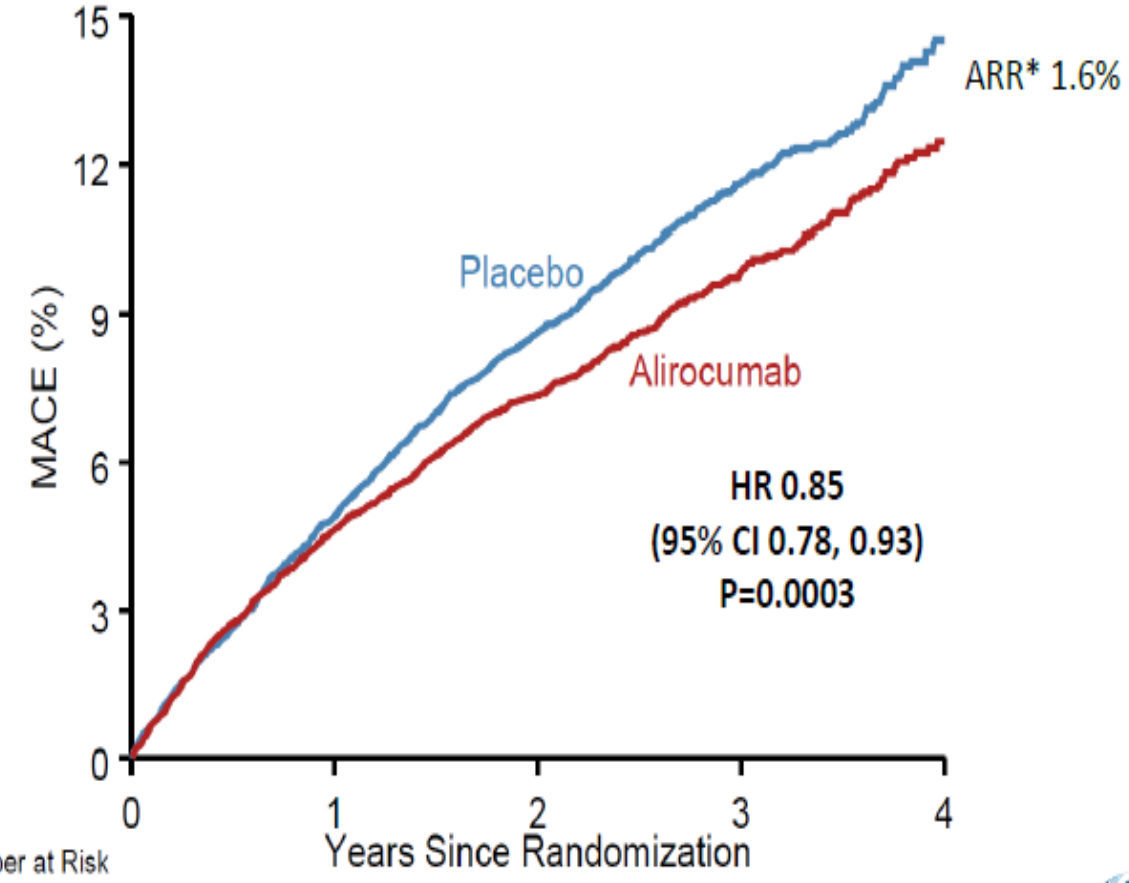
LDL-C: ITT and On-Treatment Analyses



*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

ODYSSEY OUTCOMES 28

Primary Efficacy Endpoint: MACE



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

Number at Risk					
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

*Based on cumulative incidence

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***

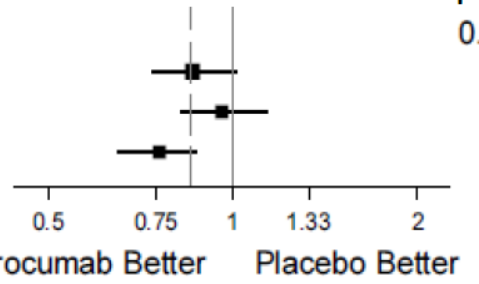
*Nominal P-value

ODYSSEY OUTCOMES

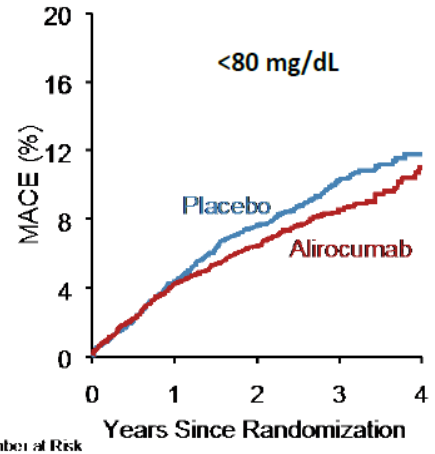
Is There a Sweet Spot Where PCKS9i Have the Most Impact?

Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
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)	

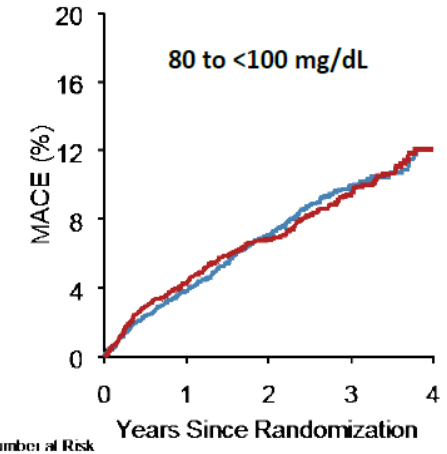


*P-values for interaction



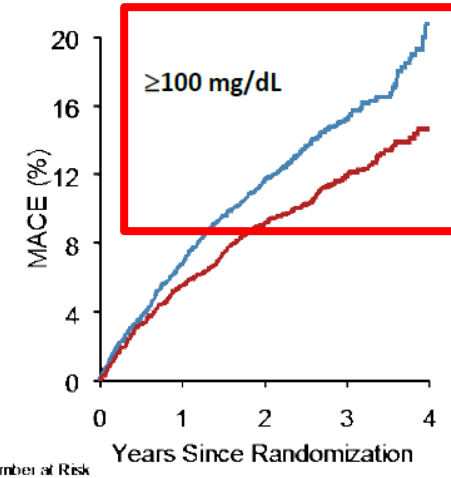
Number at Risk

Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233



Number at Risk

Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213



Number at Risk

Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

1.6% vs. 3.4% ARR, NNT 64 vs. 29

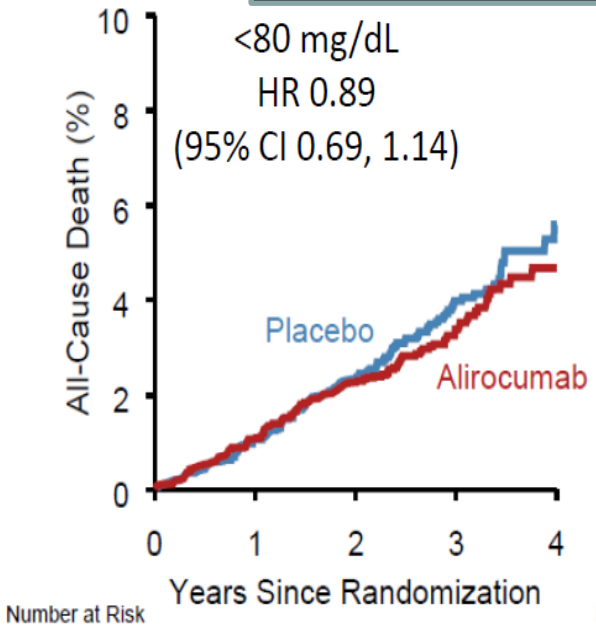
ODYSSEY OUTCOMES

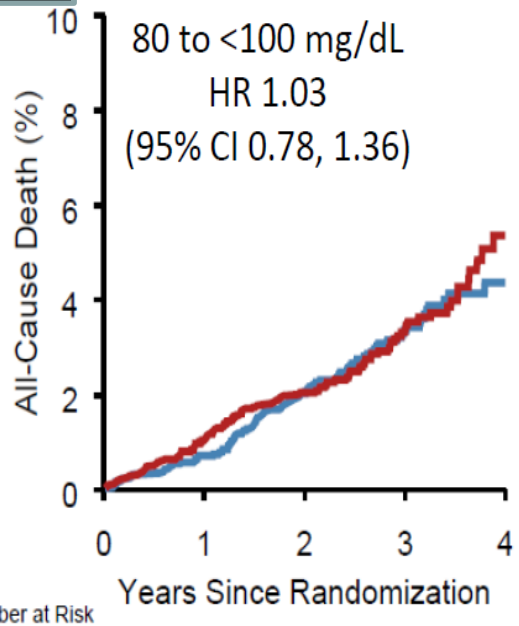
LBCT ACC 2018- Presented by Ph. Gabriel Steg

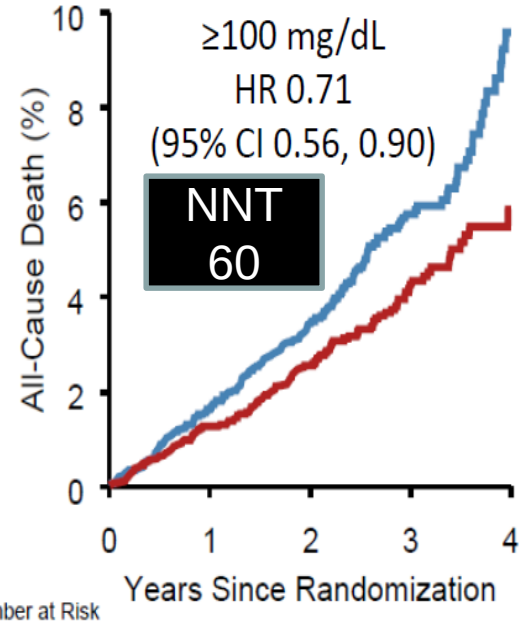
Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR = 0.6% for all patients, NNT 163

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







Number at Risk					
Placebo	3583	3486	3349	1426	285
Alirocumab	3581	3488	3358	1452	269

Number at Risk					
Placebo	3062	3001	2894	1325	228
Alirocumab	3066	2992	2907	1308	237

Number at Risk					
Placebo	2815	2732	2645	1147	224
Alirocumab	2814	2739	2655	1186	240

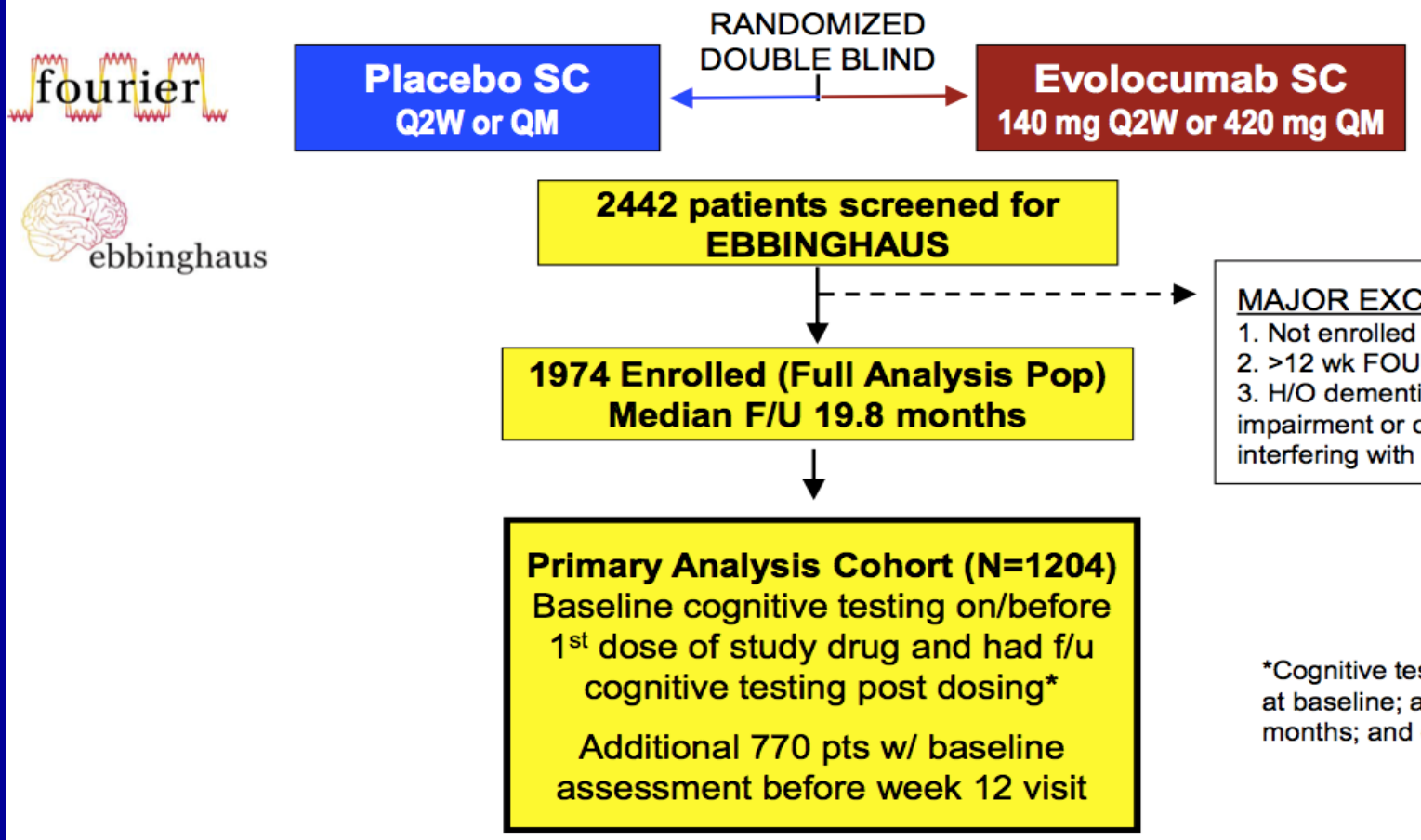
*Based on cumulative incidence

ODYSSEY OUTCOMES

LBCT Presentation. ACC 2018

EBBINGHUAS

Trial Design



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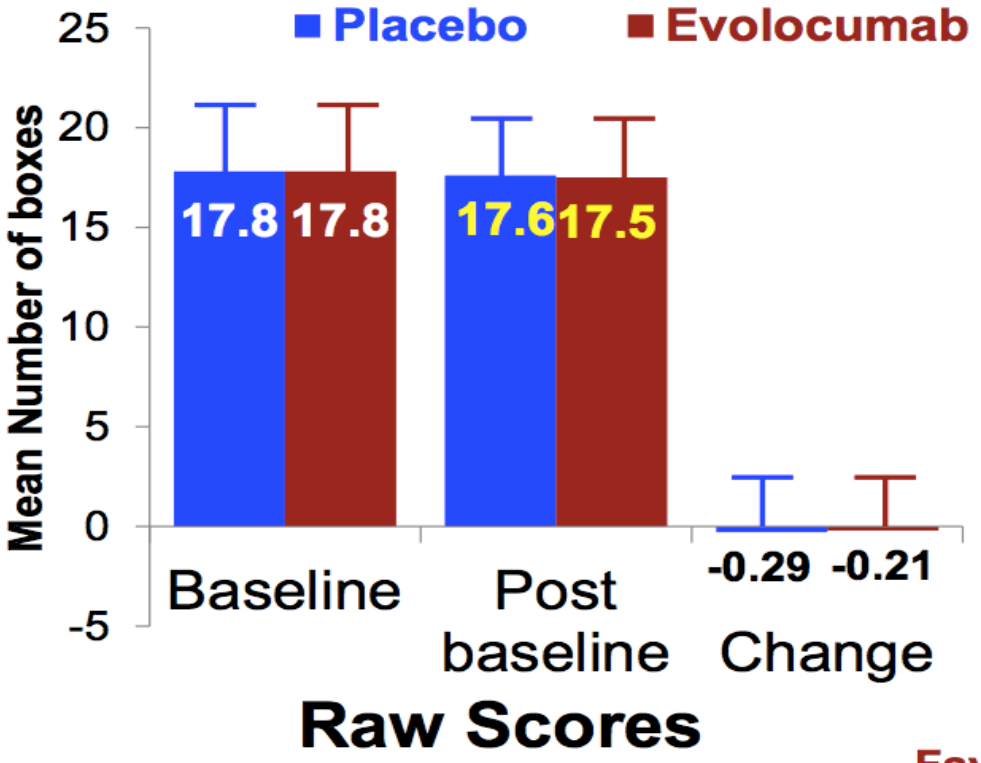
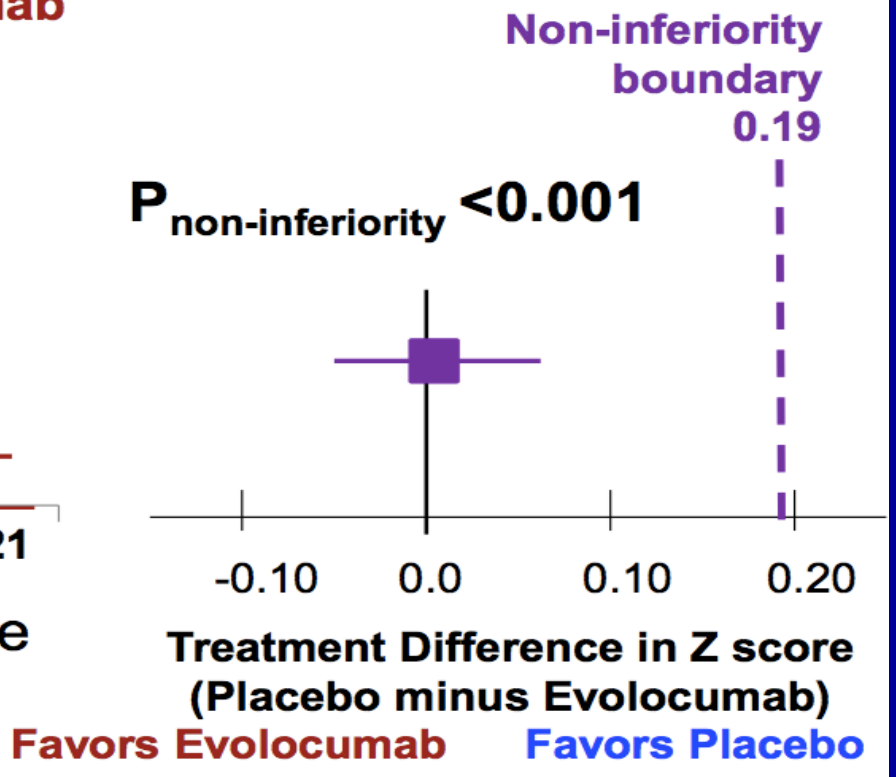
Giugliano RP et al. *Clin Card* 2017;40:59–65

N Engl J Med. 2017 Aug 17;377(7):633-643

Primary Endpoint
Spatial Working Memory Strategy Index





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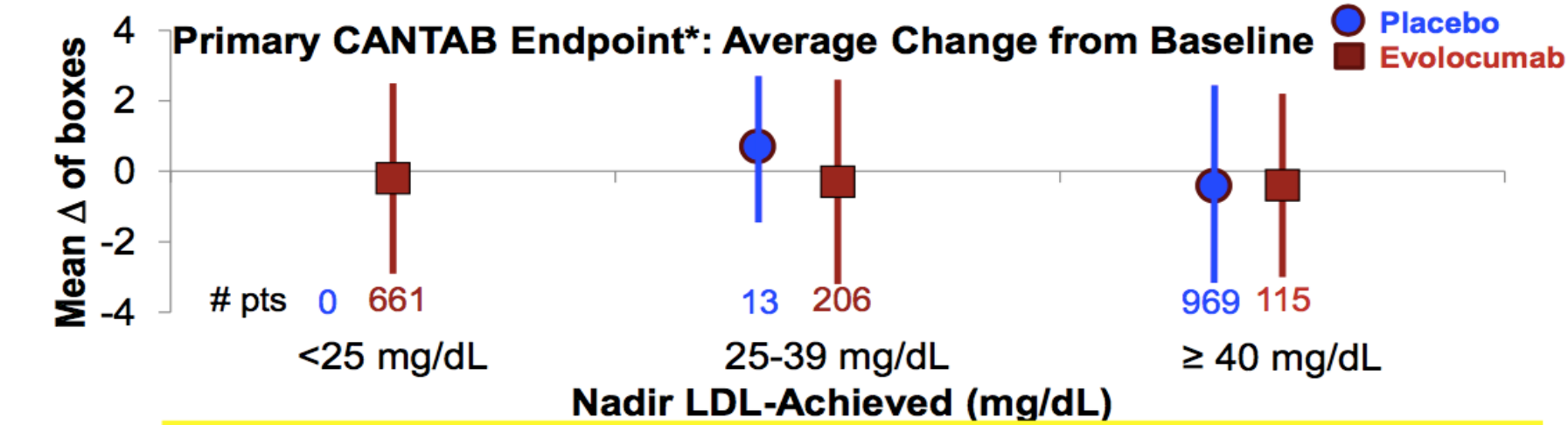
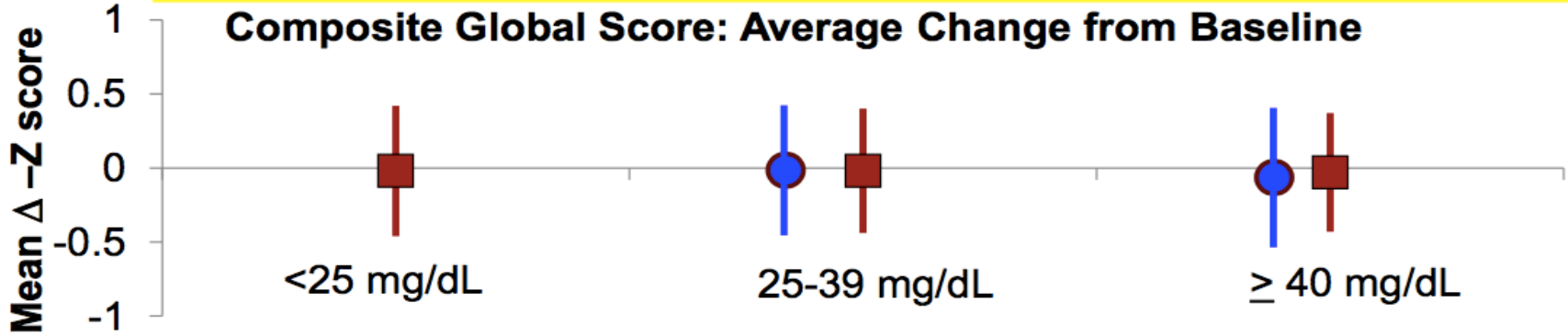
P_{NI} is from fixed estimate

N Engl J Med. 2017 Aug 17;377(7):633-643

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)



P=NS across LDL values achieved and also between treatments



Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

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N Engl J Med. 2017 Aug 17;377(7):633-643

Patient Self-Report: 23 Questions Regarding Everyday Cognition

ebbinghaus

All Patients	Placebo (N=781) Mean (SD)	Evolocumab (N=800) Mean (SD)	P-Value
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
Total Score	**1.13 (0.33)**	**1.14 (0.33)**	**0.42**

Patient self-report at end of study as compared to randomization, graded as

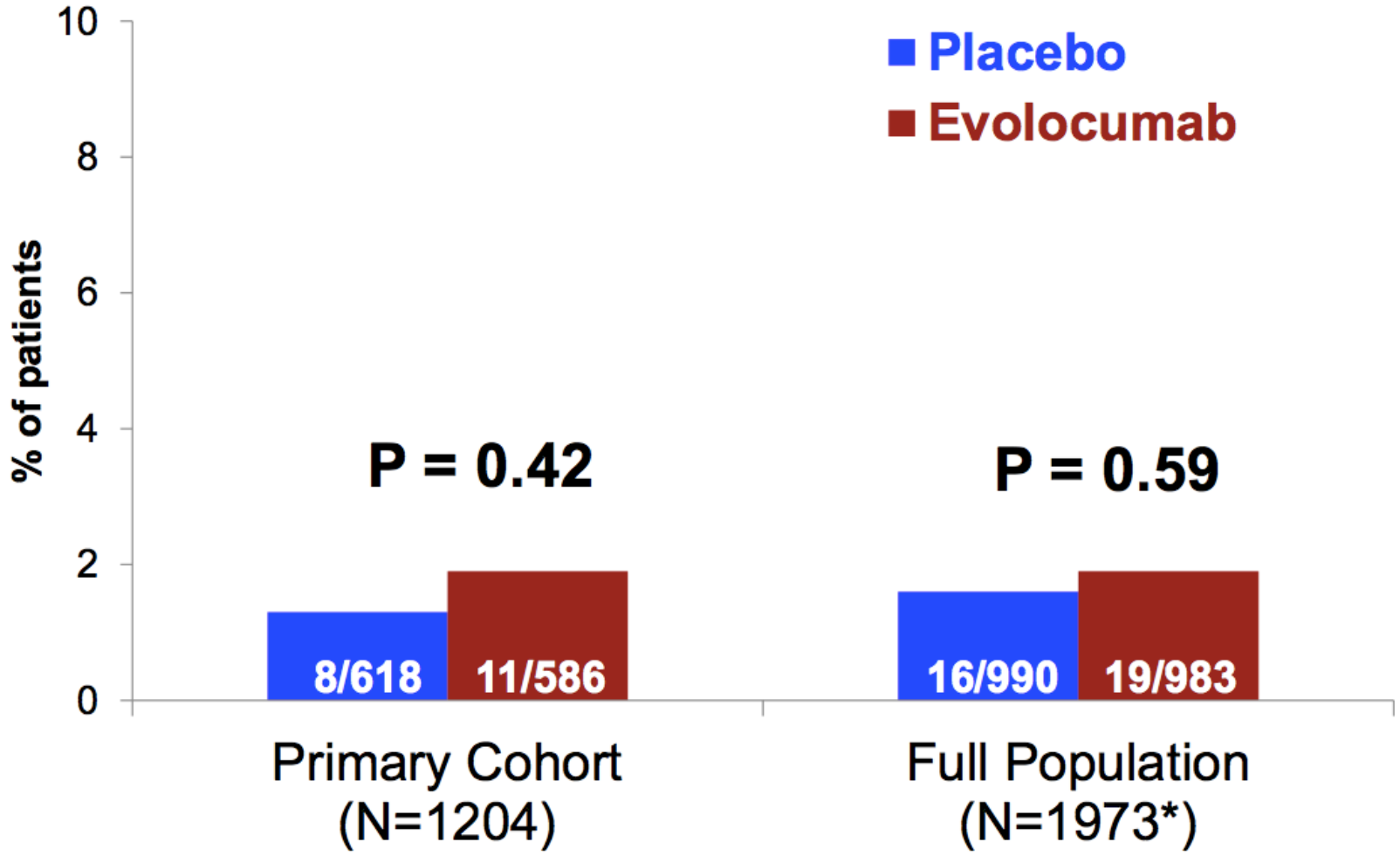
1. *Better or no change*
2. *Questionable / occasionally worse*
3. *Consistently a little worse*
4. *Consistently much worse*

Lower scores represent better cognition

Results shown are in the full study population

N Engl J Med. 2017 Aug 17;377(7):633-643

Investigator Reported Cognitive Adverse Events



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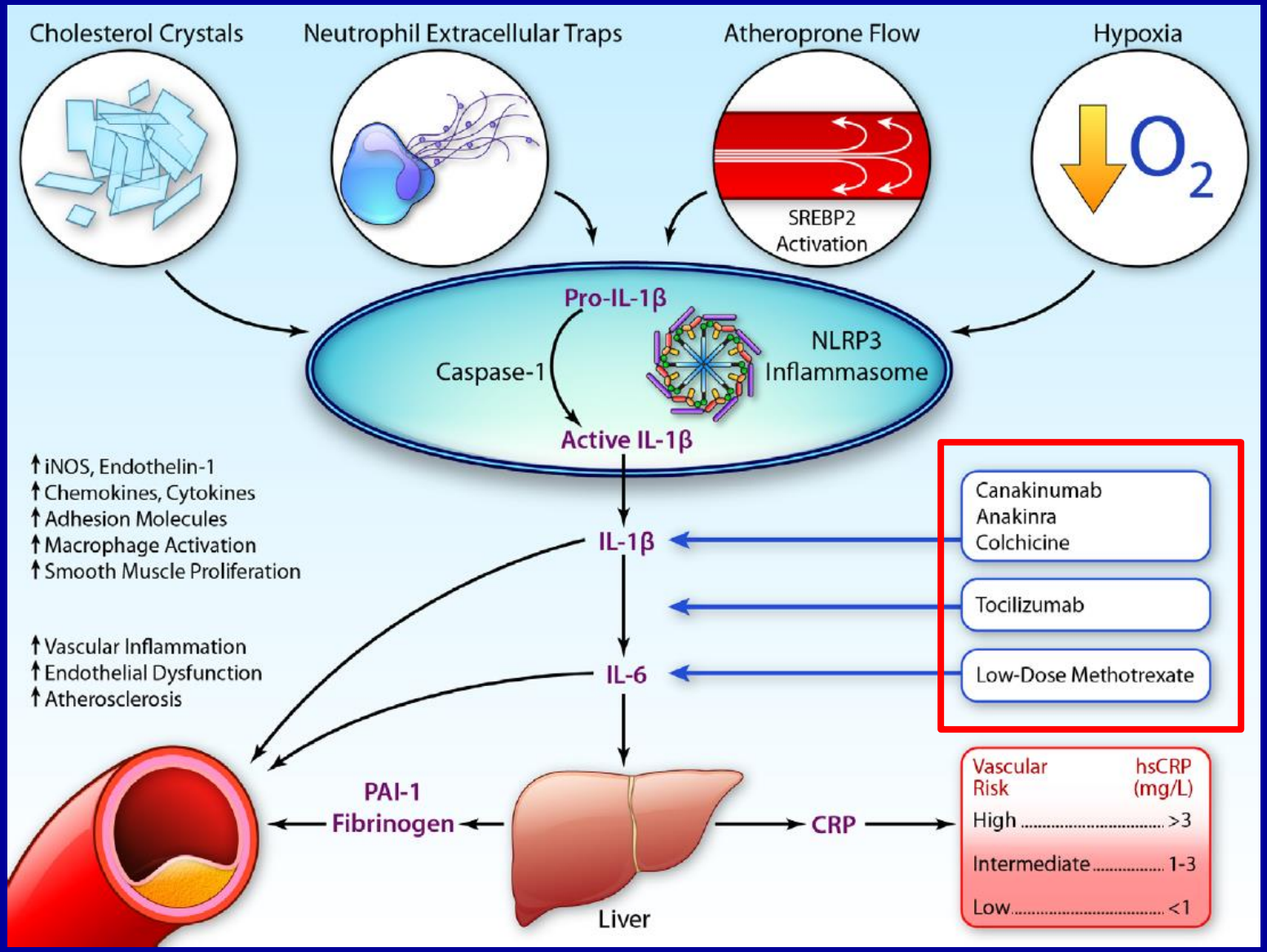
Data shown are % of patients with at least 1 event
*1 patient who did not take study drug is excluded from the evolocumab group

N Engl J Med. 2017 Aug 17;377(7):633-643

CANTOS

From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection



Ridker PM. Circ Res 2016;118:145-156.

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

Randomized
Canakinumab 50 mg
SC q 3 months

Randomized
Canakinumab 150 mg
SC q 3 months

Randomized
Canakinumab 300 mg
SC q 3 months*

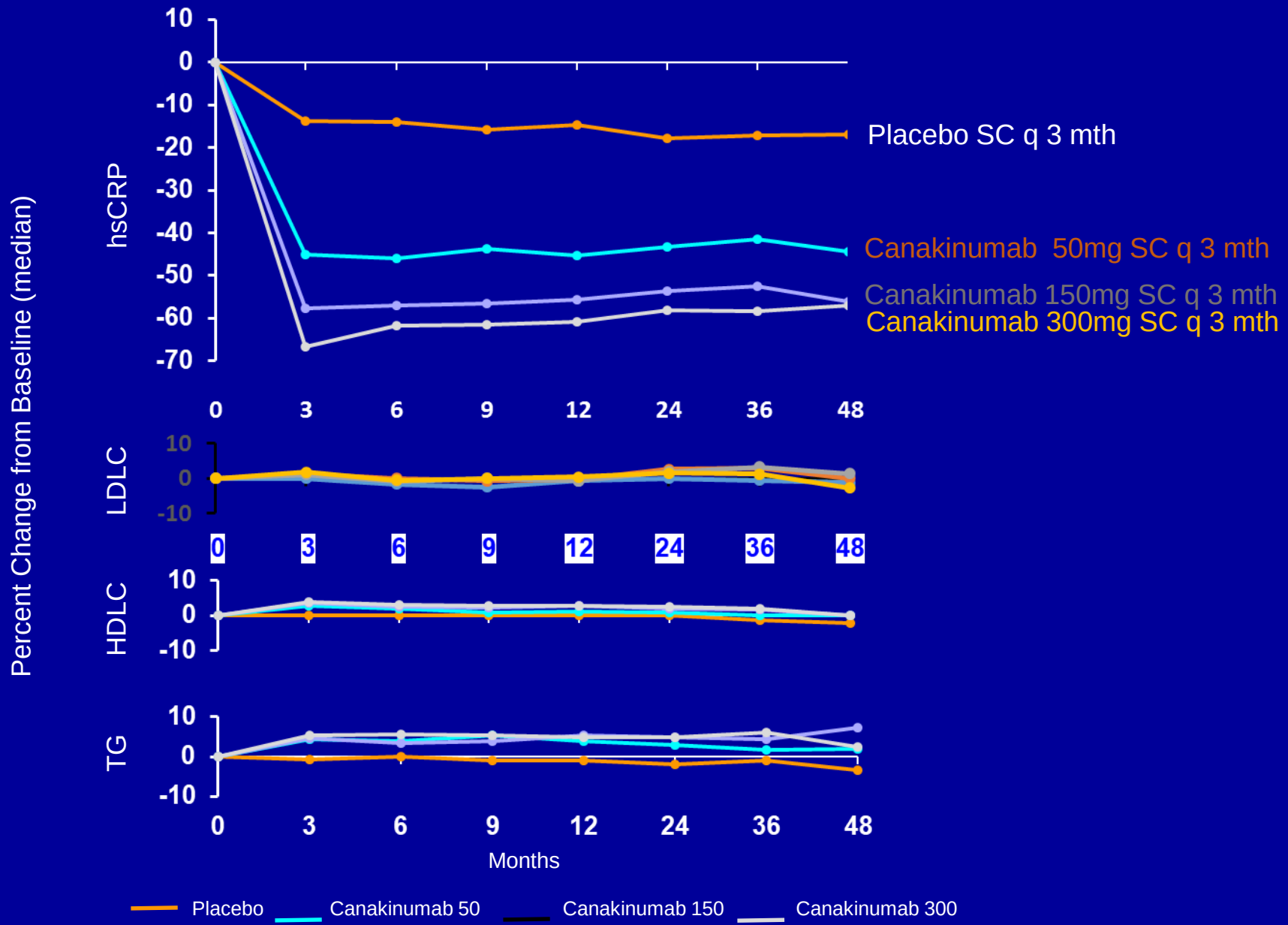
Randomized
Placebo
SC q 3 months

Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Key Secondary CV Endpoint: MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+)

Critical Non-Cardiovascular Safety Endpoints: Cancer and Cancer Mortality, Infection and Infection Mortality

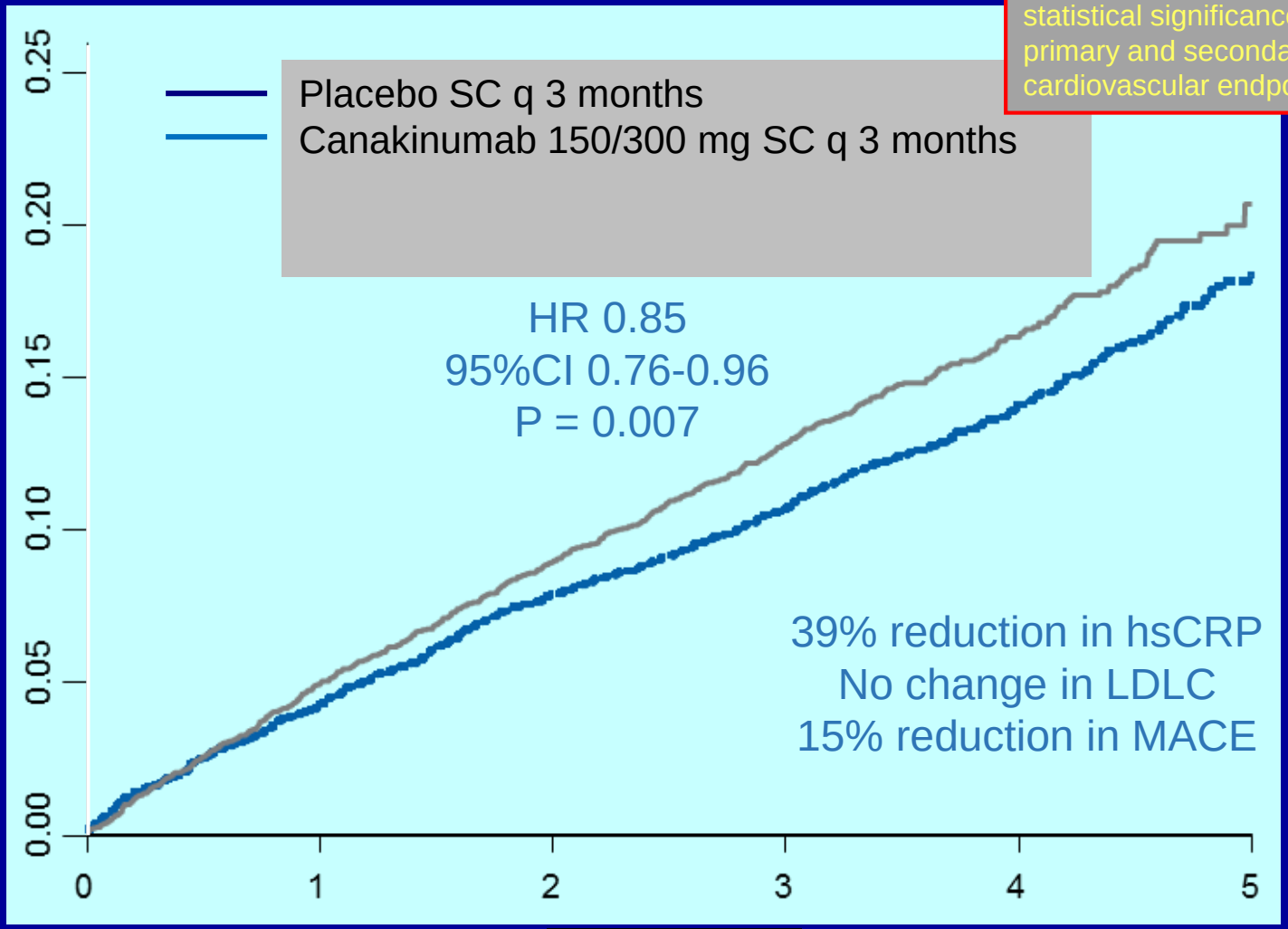
CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)



Ridker PM, et al. NEJM. 2017;DOI: 10.1056/NEJMoa1707914

CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150 mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



Ridker PM, et al. NEJM. 2017;DOI: 10.1056/NEJMoa1707914

CANTOS: Additional Outcomes (per 100 person years of exposure)

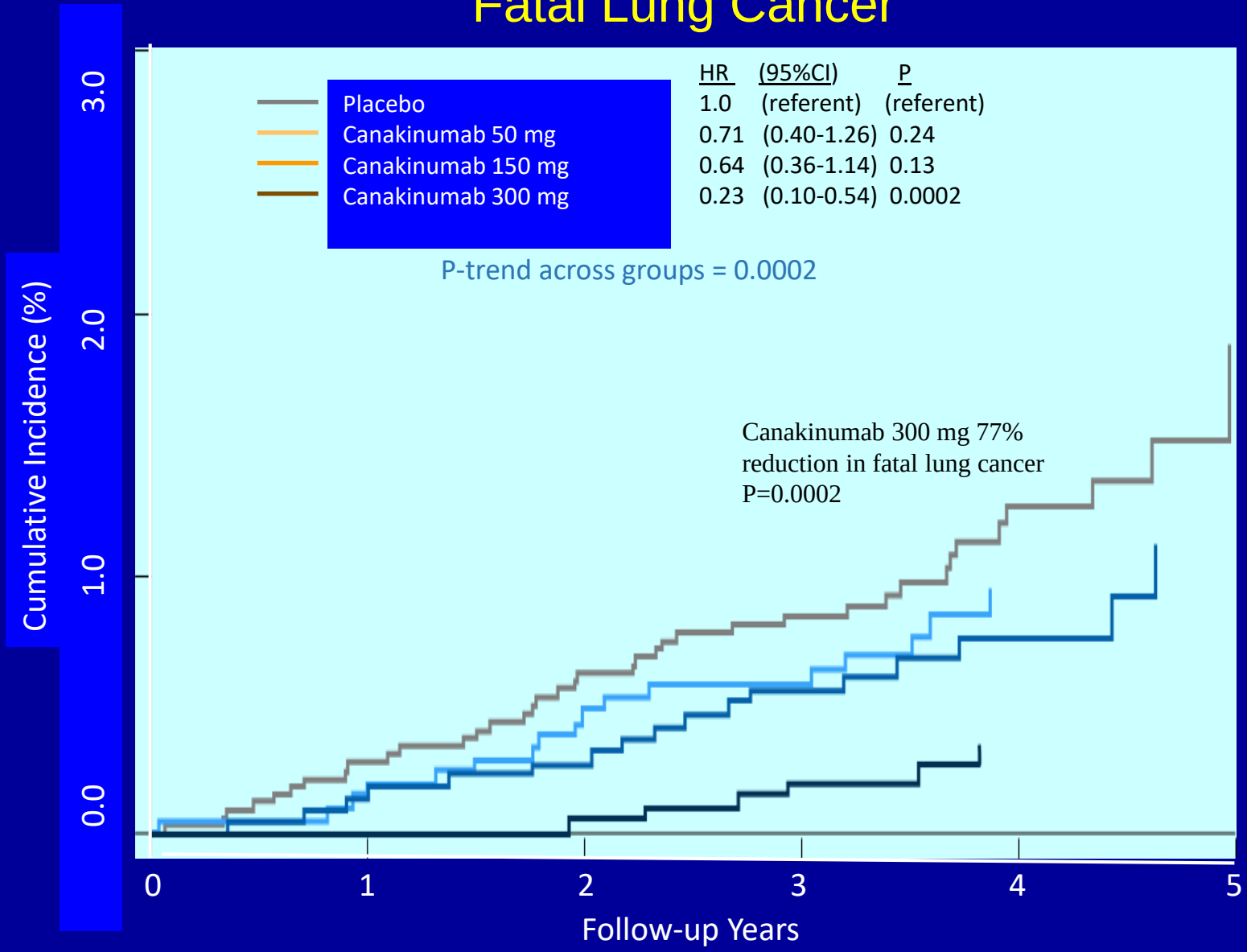
		Canakinumab SC q 3 months			
Adverse Event	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Any SAE	12.0	11.4	11.7	12.3	0.43
Leukopenia	0.24	0.30	0.37	0.52	0.002
Any infection	2.86	3.03	3.13	3.25	0.12
Fatal infection	0.18	0.31	0.28	0.34	0.09/0.02*
Injection site reaction	0.23	0.27	0.28	0.30	0.49
Any Malignancy	1.88	1.85	1.69	1.72	0.31
Fatal Malignancy	0.64	0.55	0.50	0.31	0.0007
Arthritis	3.32	2.15	2.17	2.47	0.002
Osteoarthritis	1.67	1.21	1.12	1.30	0.04
Gout	0.80	0.43	0.35	0.37	0.0001
ALT > 3x normal	1.4	1.9	1.9	2.0	0.19
Bilirubin > 2x normal	0.8	1.0	0.7	0.7	0.34

* P-value for combined canakinumab doses vs placebo

ALT, alanine aminotransferase;
SAE, serious adverse event; SC, subcutaneous

Ridker PM, et al. NEJM. 2017;DOI: 10.1056/NEJMoa1707914

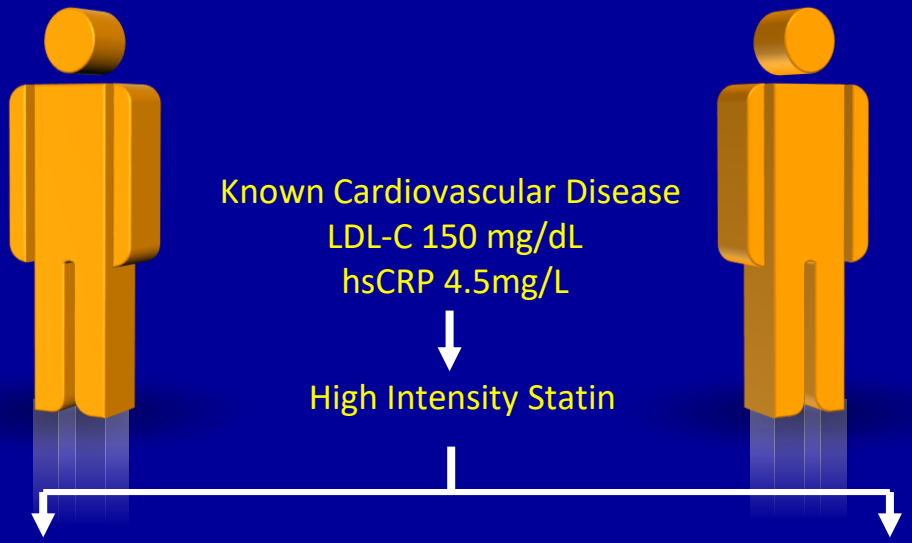
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Fatal Lung Cancer



Ridker PM, et al. Lancet. 2017;DOI: 10.1016/S0140-6736(17)32247-X

Where Are We Going With All this for Treatment of Atherosclerosis?

Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin



Known Cardiovascular Disease
LDL-C 150 mg/dL
hsCRP 4.5mg/L

High Intensity Statin

"Residual Cholesterol Risk"

LDL-C 110 mg/dL
hsCRP 1.8 mg/L

Additional
LDL-C Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/ODYSSEY/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

"Residual Inflammatory Risk"

LDL-C 80 mg/dL
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

No Prior Proof of Concept
Canakinumab 150mg SC q 3 months 15%RRR

Ridker PM. Eur Heart J 2016;37:1720-22

Conclusion

- Multiple non-statins showing benefits in ASCVD outcomes (ezetimibe, PCSK9i).
- Targeting inflammation appears to be promising for ASCVD risk reduction.
- Signal on common inflammatory pathway for ASCVD and Cancer initiation/progression. Can we have therapies now that target both?

Genetically Altered LDL, TG, and Risk for CHD[1-3]

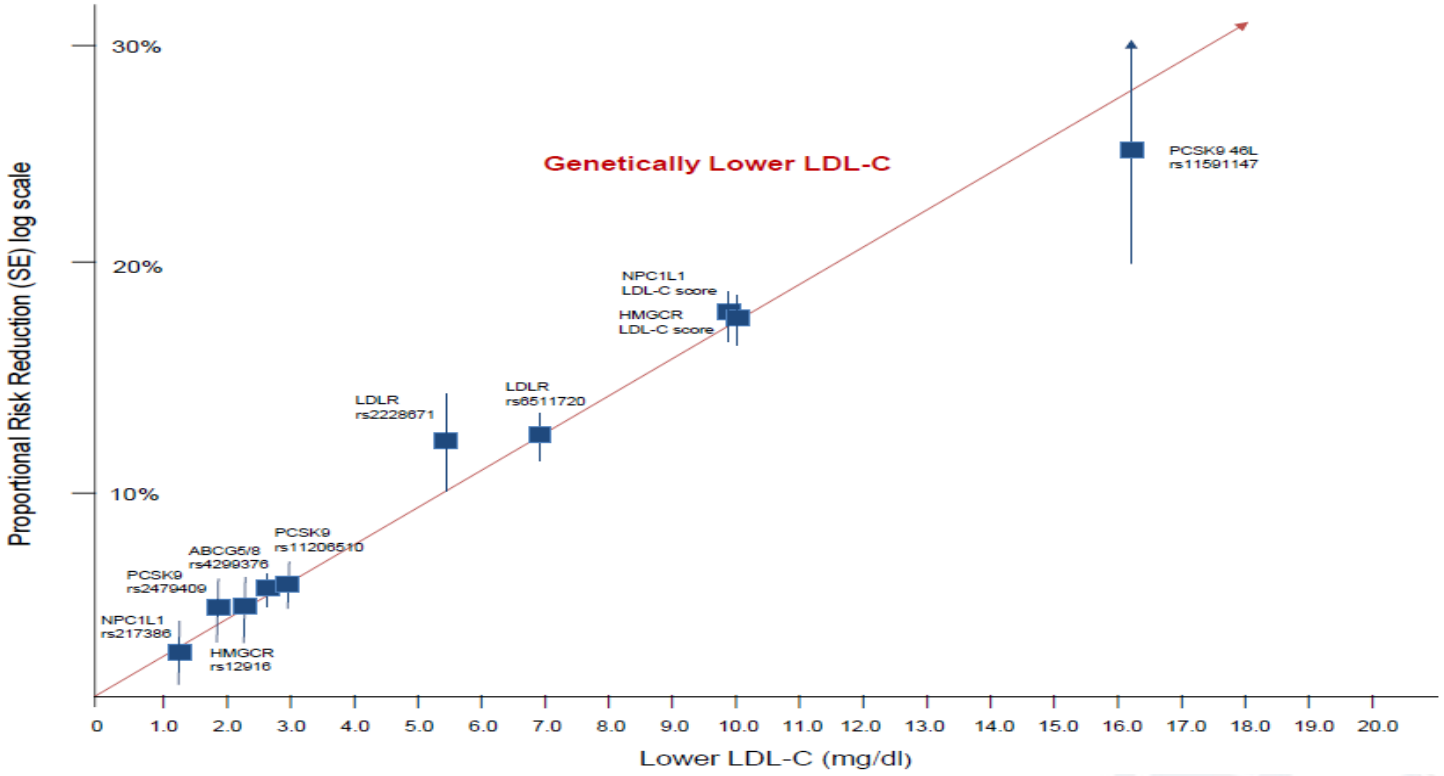
For every 1 SD change (~35 mg/dL) in genetically altered LDL, 50% increase in risk for CHD

For every 1 SD change (~90 mg/dL) in genetically altered TG, 50% increase in risk for CHD

Predictor	Effect size	P
$\beta_{LDL\text{-}C}$	0.39	1×10^{-22}
$\beta_{HDL\text{-}C}$	0.04	0.32
β_{TG}	0.40	2×10^{-10}

1. Do R et al. *Nat Genet*. 2013;45(11):1345-1352; 2. Ballantyne CM. Are triglycerides a cardiovascular risk factor? Presented at: 2014 National Lipid Association Fall Clinical Lipid Updates Session; August 22–24, 2014; Indianapolis, IN. https://www.lipid.org/node/1273. Accessed January 19, 2015;
3. Slide courtesy of Sekar Kathiresan, MD.

Effect of Lower LDL-C on CHD: Importance of Primordial Prevention



Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

Ference, BA et al. J Am Coll Cardiol 2012;60:2631-9.

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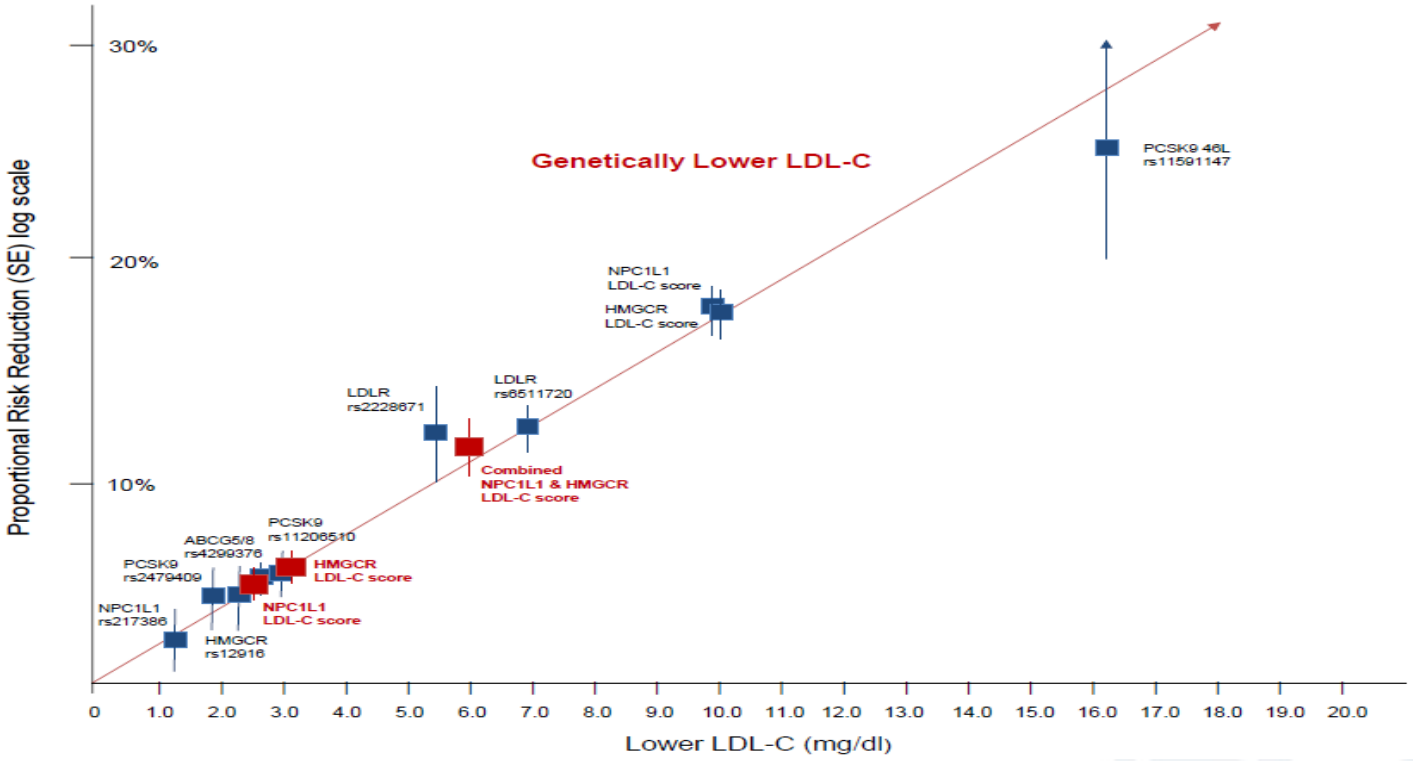
Effect of Lower LDL-C on CHD: Importance of Primordial Prevention



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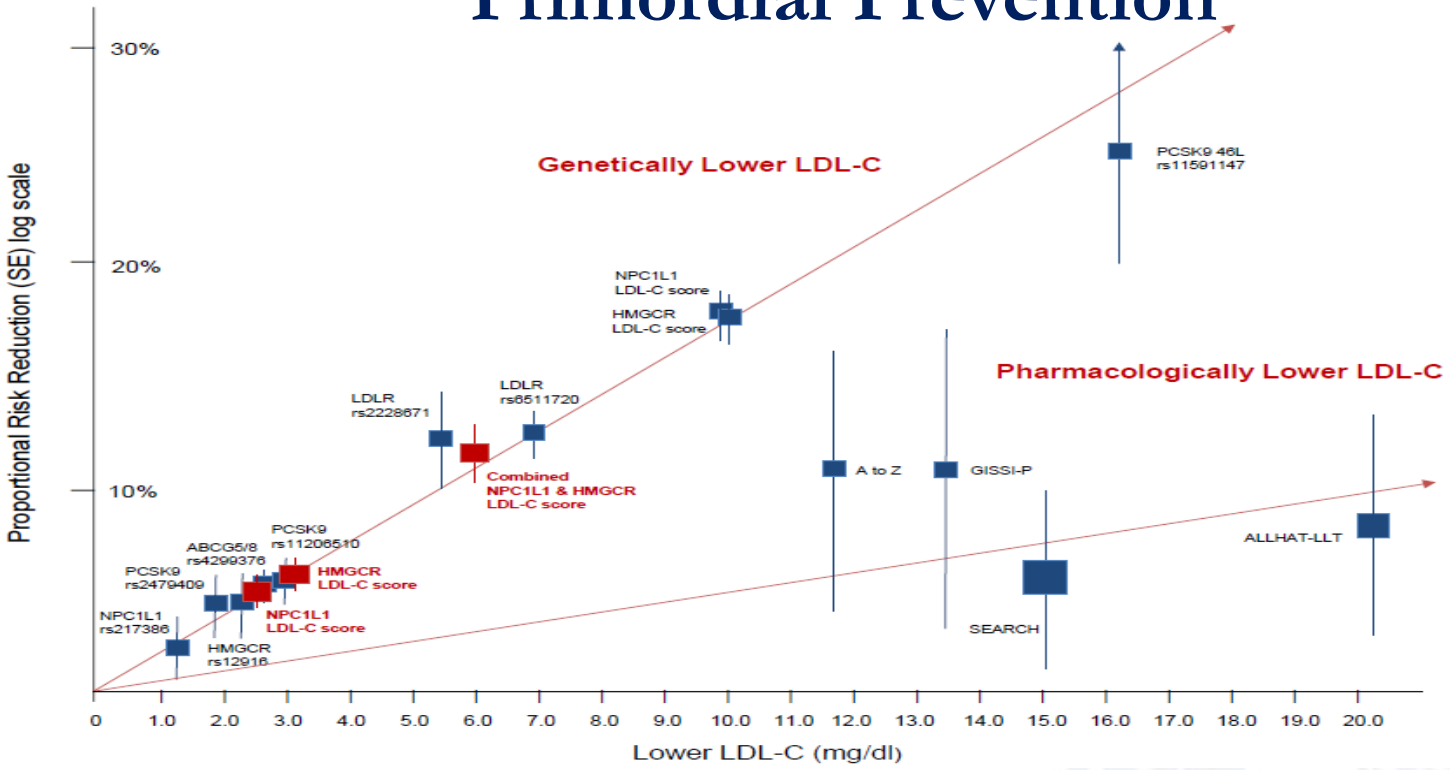

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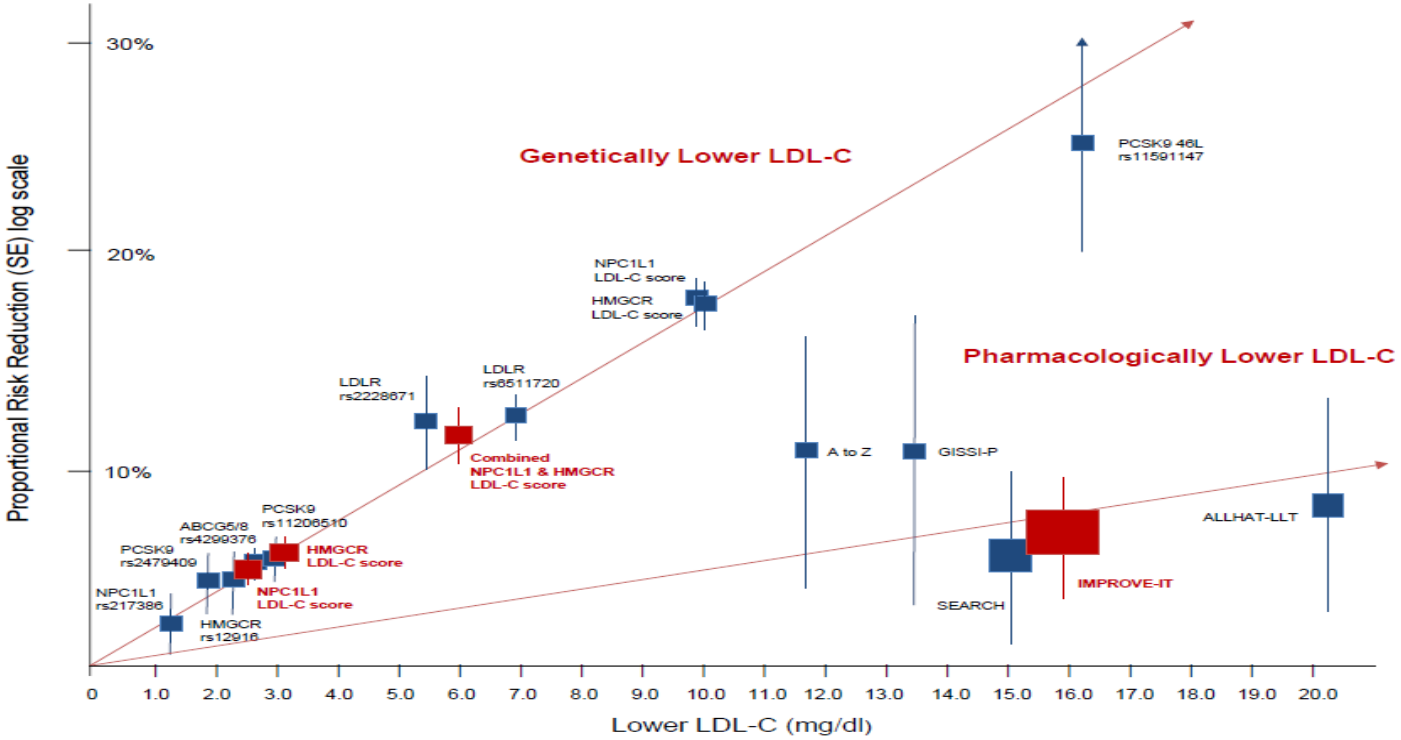
Effect of Lower LDL-C on CHD: Importance of Primordial Prevention



Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

Cannon CP, et al. AHA, November, 17 2014.

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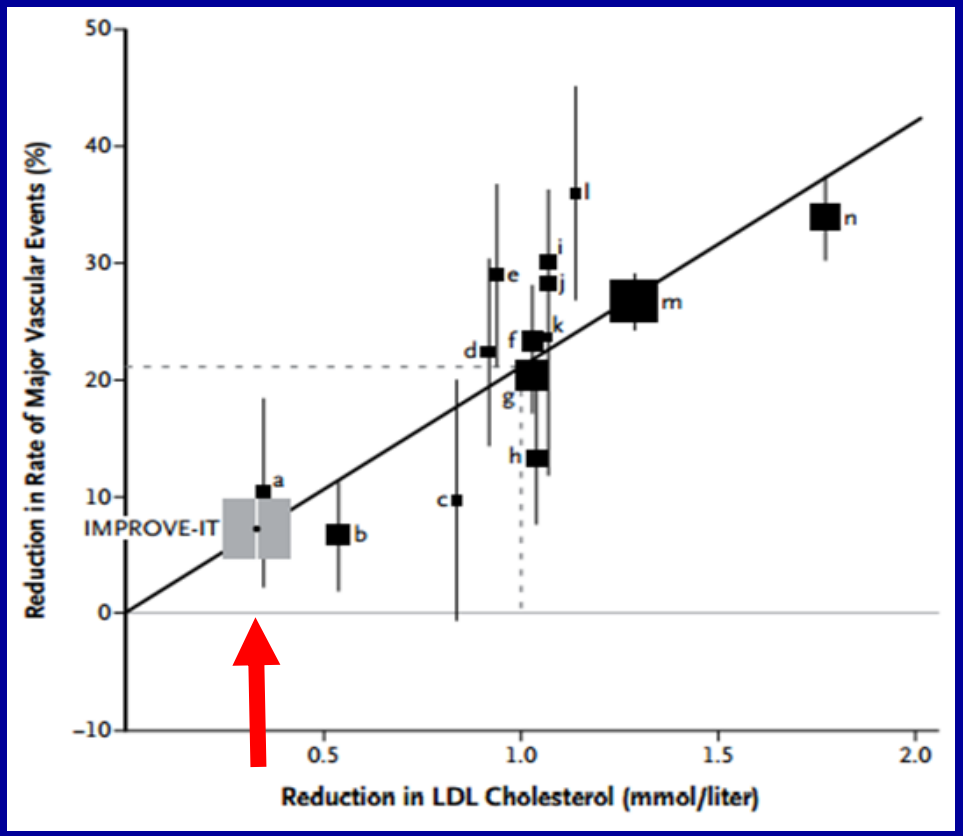
IMPROVE-IT

LDL Reduction – CVD Event Reduction



The RR reduction per 1 mmol/L lowering of LDL-C in the simva + ezetimibe group was nearly the same as expected from statin monotherapy trials

Cannon CP et al. N Engl J Med. 2015;372(25):2387-97

EBBINGHAUS: Hypothesis

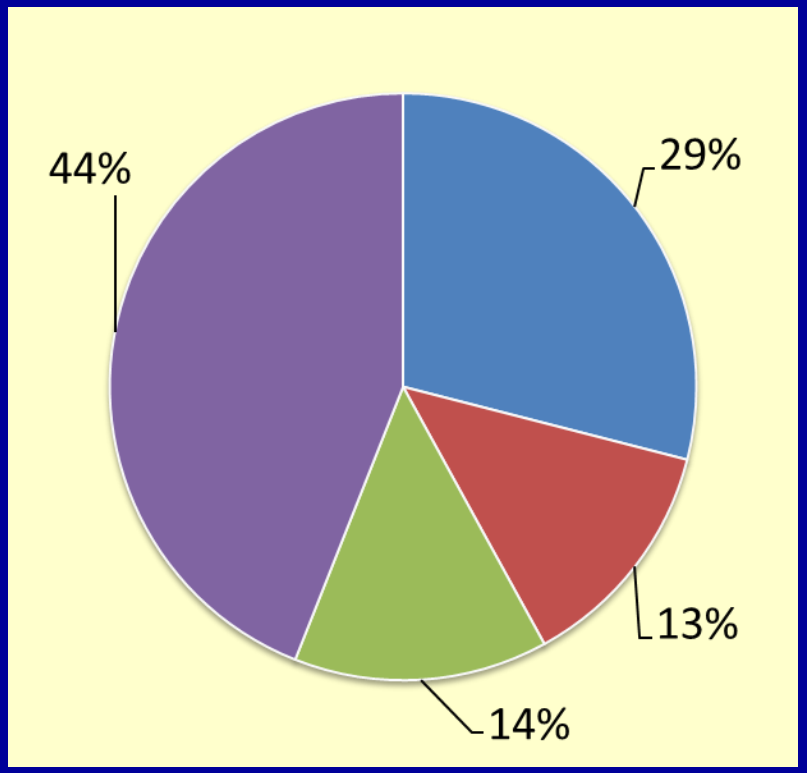
The addition of evolocumab to statin therapy in patients with clinically evident cardiovascular disease does not adversely affect cognitive function

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

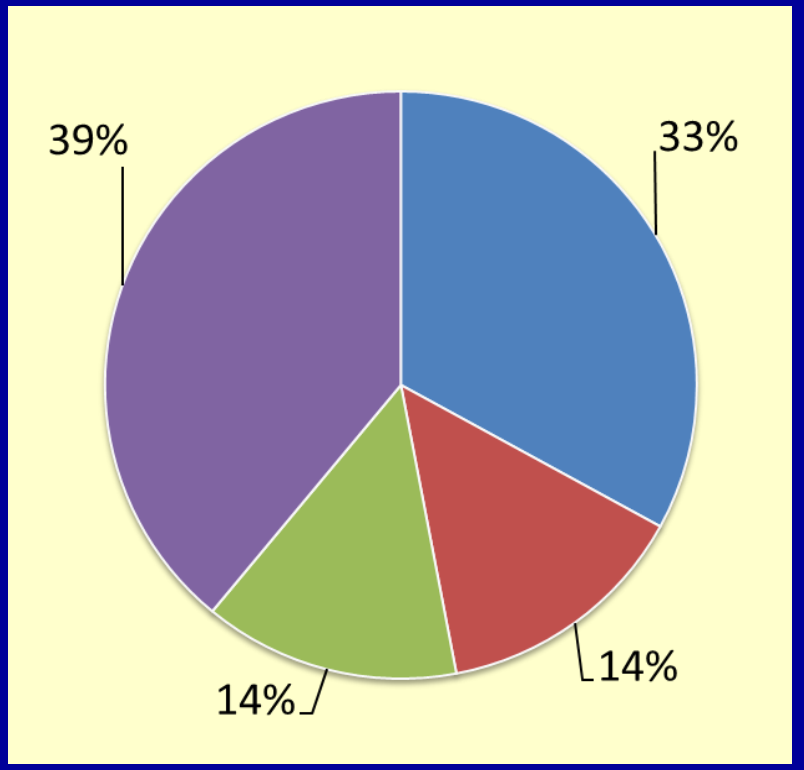
N Engl J Med. 2017 Aug 17;377(7):633-643

How Common is Residual Inflammatory Risk?

PROVE-IT



IMPROVE-IT



Residual Inflammatory Risk	Residual Cholesterol Risk	Both	Neither
hsCRP ≥ 2 mg/L LDLC < 70 mg/dL	hsCRP < 2 mg/L LDLC ≥ 70 mg/dL	hsCRP ≥ 2 mg/L LDLC ≥ 70 mg/dL	hsCRP < 2 mg/L LDLC < 70 mg/dL

Ridker PM. Circulation Res 2017;120:617-9.