What have We Learned in Dyslipidemia Management Since the Publication of the 2013 ACC/AHA Guideline?

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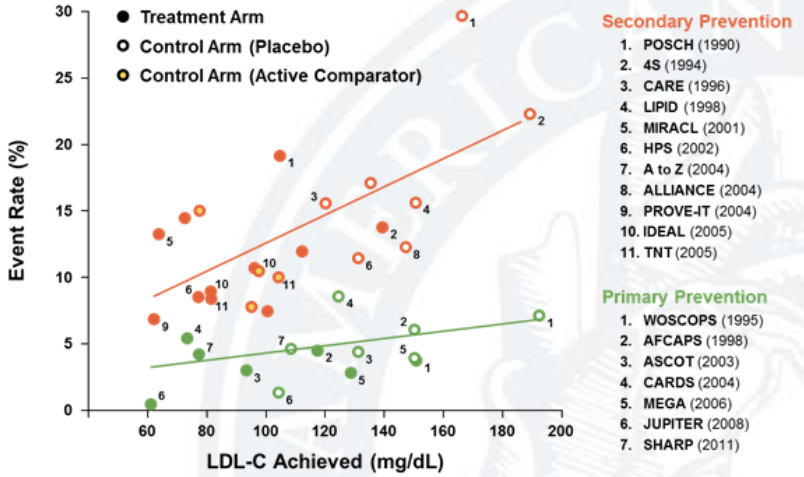
Discussion Points

- What we knew.
- What did the guidelines say and why?
- What have we learned since the guideline publication?
- What are the remaining questions?

What we knew…

- LDL-C is causally related to ASCVD
- Lowering LDL-C with statin therapy, diet, or ileal bypass reduces risk of ASCVD events

Major Lipid Trials: LDL Achieved vs Rates of Coronary Events



Adapted from Raymond C, et al. Clev Clin J Med. 2014;81:11-19.

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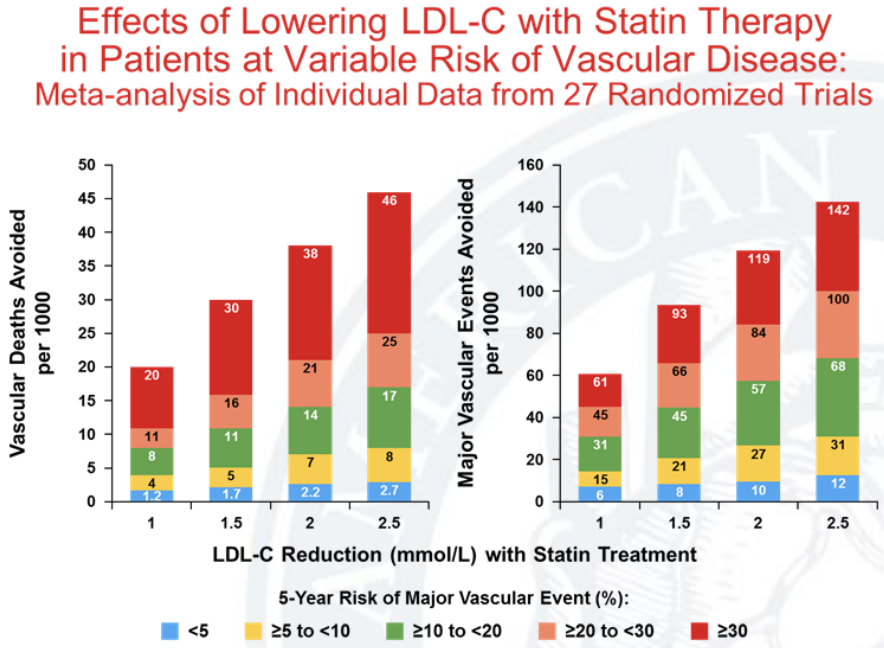
What we knew…

- Reduction in ASCVD events is *proportionally similar* in pts at all levels of risk
- Greatest *absolute* number of events avoided in pts at greatest risk
- Reduction in ASCVD events is related to the extent of LDL-C reduction



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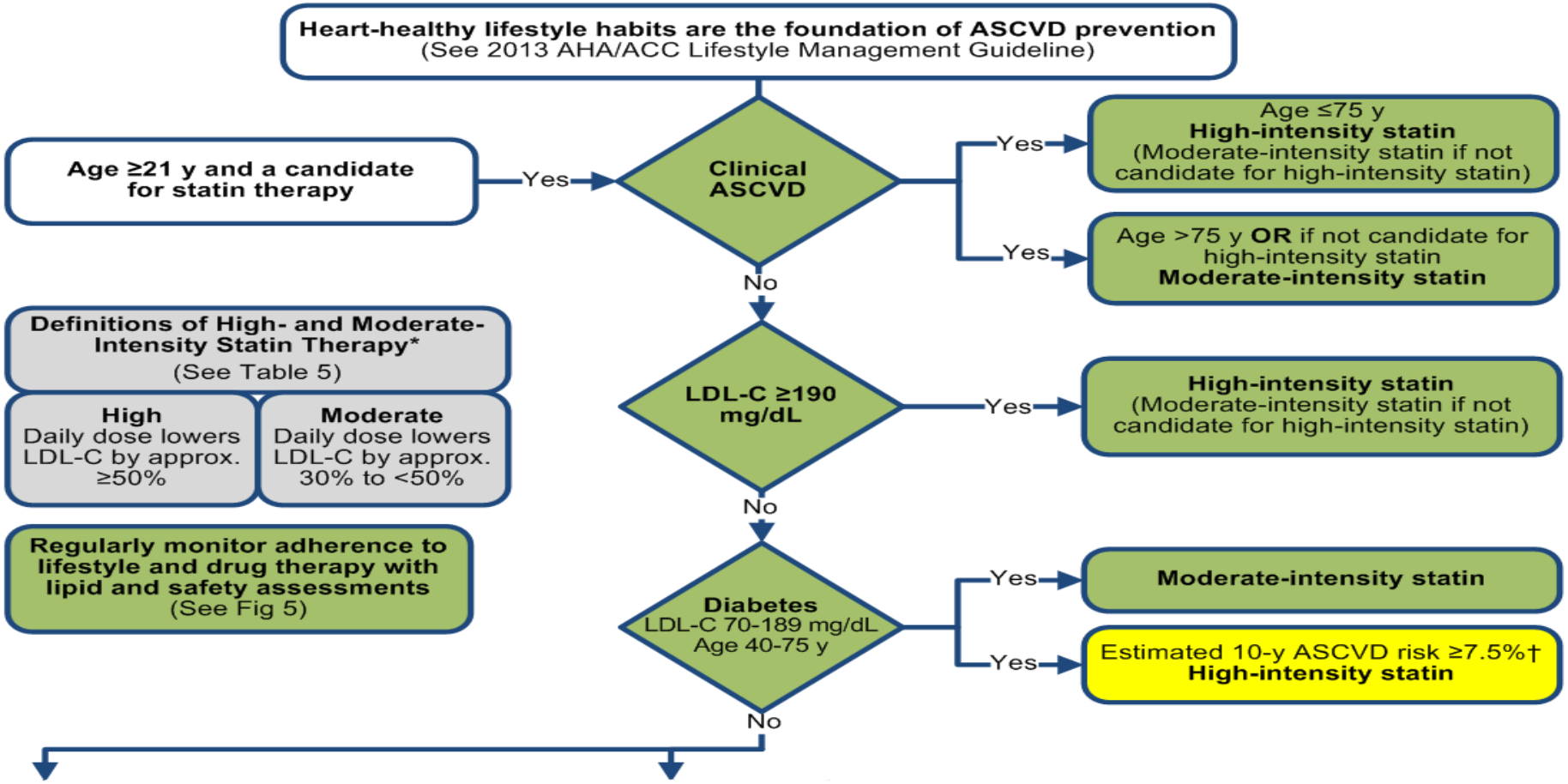
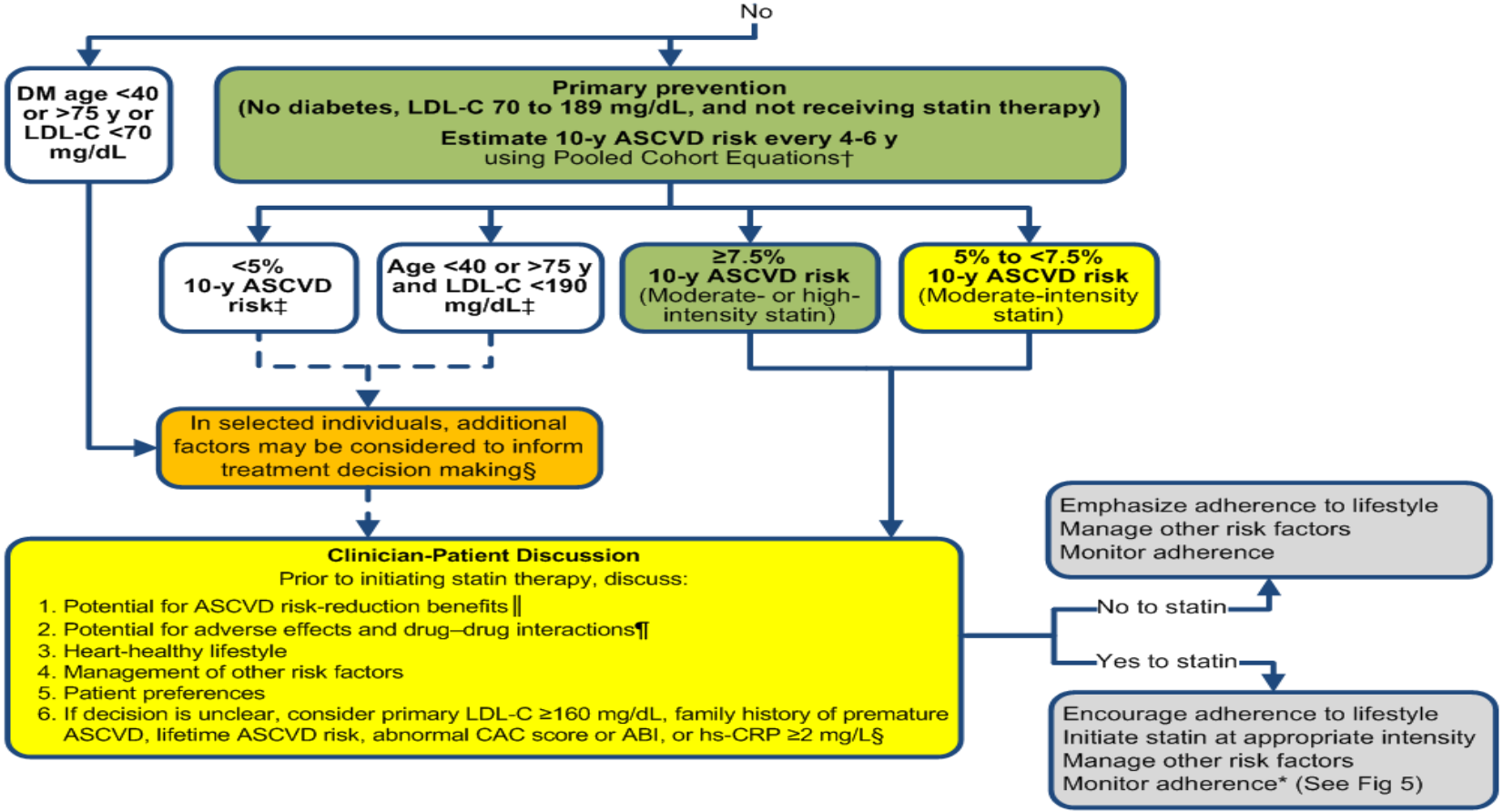
Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)



Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)



What did the guidelines say?

- Lack of RCT evidence to support titration of drug therapy to specific LDL-C and/or non–HDL-C goals.
- Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk.
- Available RCT data do not indicate what the target should be.

What Have We Learned Since?

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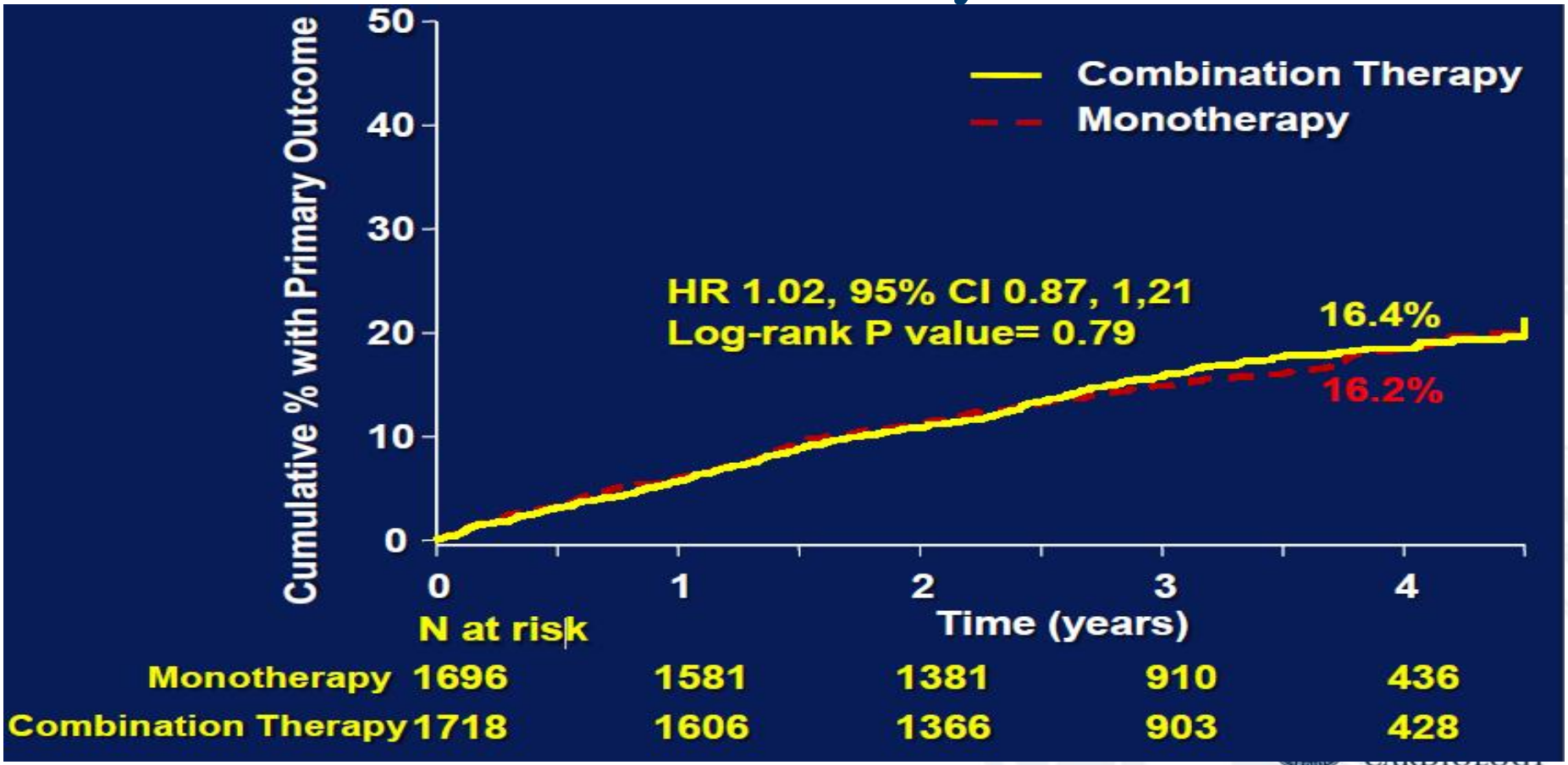
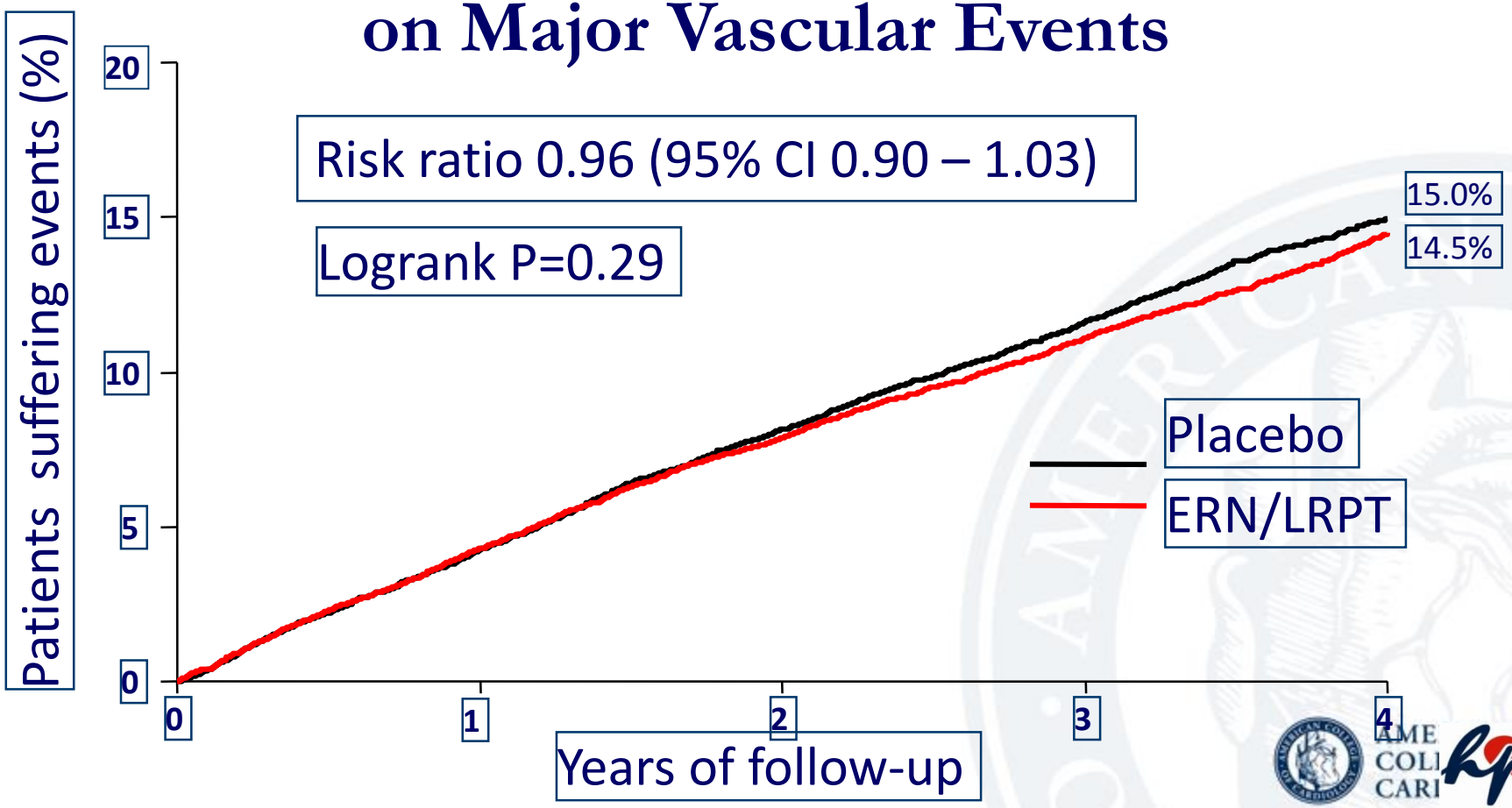
AIM-HIGH: Primary Outcome

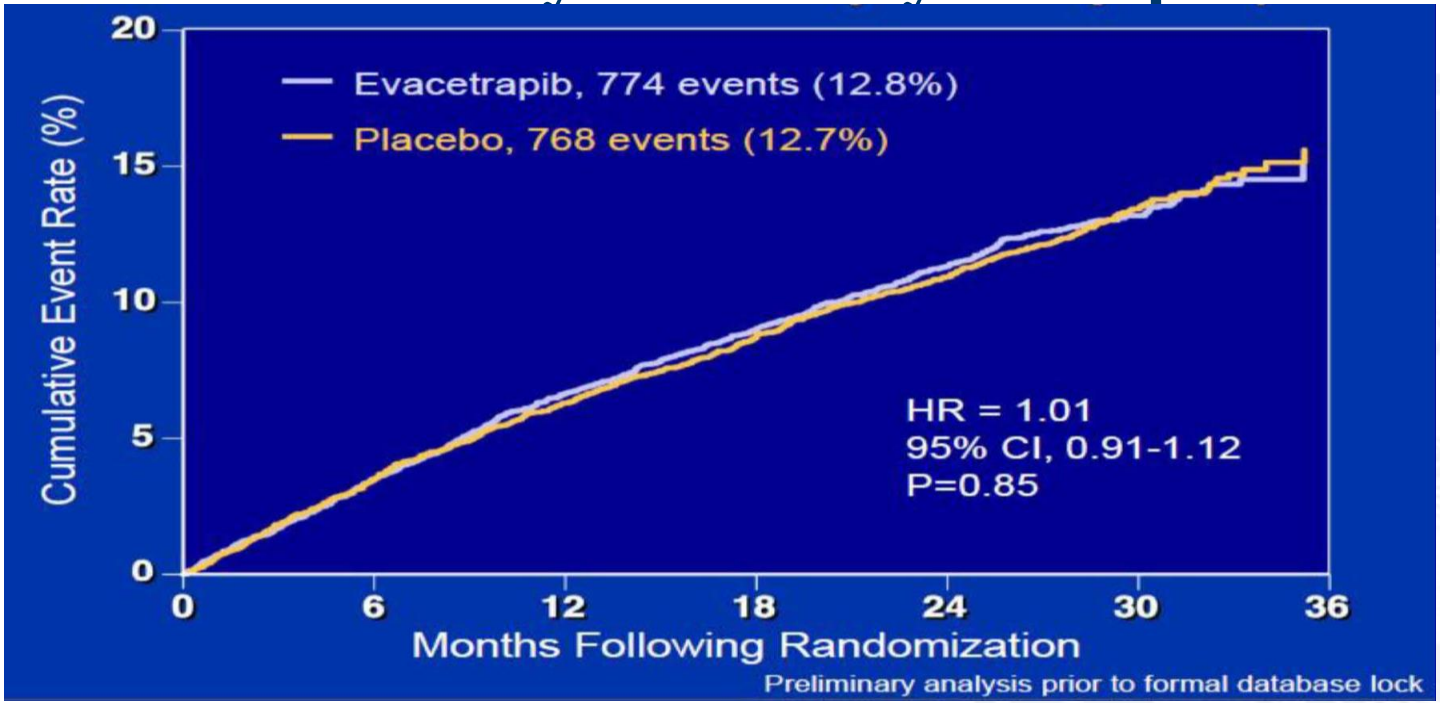


HPS2-THRIVE: Effect of ERN/LRPT on Major Vascular Events



HPS2-THRIVE Collaborative Group. *N Engl J Med.* 2014;371:203-212.

ACCELERATE: Cumulative Incidence of Primary Efficacy Endpoint



Nicholls SJ. Presented at American College of Cardiology 65th Annual Scientific Session, Chicago, IL, 3 April 2016.

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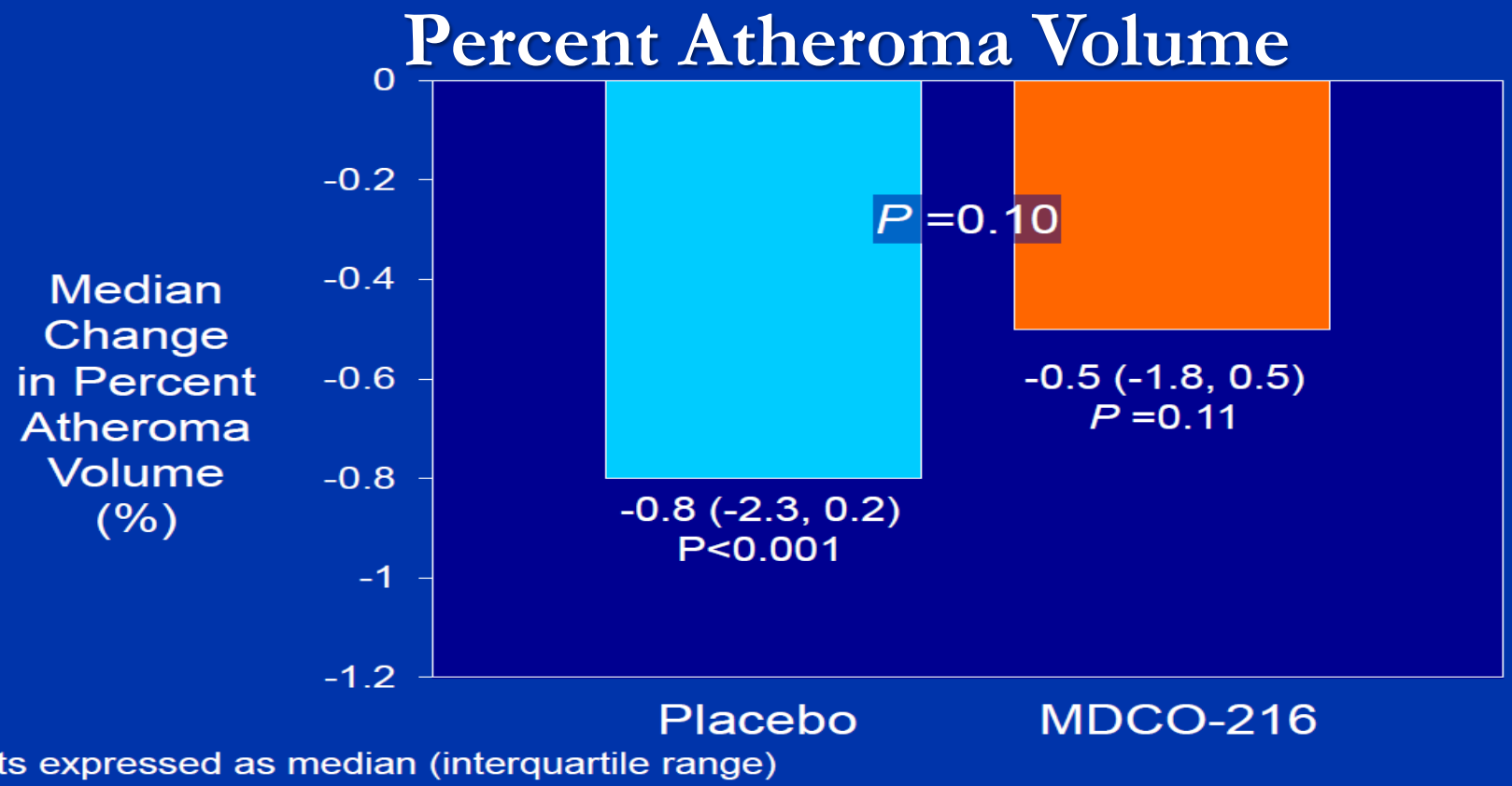
MILANO-PILOT: Primary Endpoint



Results expressed as median (interquartile range)

Nicholls SJ et al. Presented at American Heart Association Scientific Sessions, New Orleans, LA, 15 November 2016

The Million Heart Longitudinal ASCVD Risk Assessment Tool

- Uses 2013 pooled cohort risk equation for estimating “baseline” ASCVD risk.
- Updated 10-year ASCVD risk by instituting “ACBS” in ASCVD primary prevention (multiple combinations allowed).
- Allows assessment of updated ASCVD risk at f/u based on response to therapy.

Lloyd-Jones DM, et al. *J Am Coll Cardiol* 2016 (in press).

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Therapy Choices	Baseline 10-Year ASCVD Risk	Expected (Projected) ASCVD Risk if Therapy Initiated (Optimal floor values applied)	Potential Adverse Events
Start statin (moderate intensity) or intensify statin from moderate to high intensity dose now	30.8%	23.1%	There is moderate quality evidence that statins do not increase the overall risk of adverse events, but that they may increase the risk of diagnosis of type 2 diabetes in certain individuals.
Start (or add) BP-lowering drug now	30.8%	22.6%	Adverse effects of blood-pressure-lowering therapies are generally poorly reported, and vary by drug class.
Stop smoking for 2 years	30.8%	22.5%	Adverse effects of tobacco cessation therapies are generally poorly reported, and vary by drug.
Start or continue aspirin now	30.8%	27.7%	There is high-quality evidence indicating that aspirin may increase the risk of major bleeding.
Start/continue aspirin + start/intensify statin now	30.8%	20.8%	
Start/continue aspirin + start/add BP-lowering drug now	30.8%	20.3%	
Start/intensify statin + start/add BP-lowering drug now	30.8%	16.9%	
Start/intensify statin + stop smoking for 2 years	30.8%	16.8%	
Start/continue aspirin + stop smoking for 2 years	30.8%	20.2%	
Start/add BP-lowering drug + stop smoking for 2 years	30.8%	16.5%	
Start/continue aspirin + start/intensify statin + start/add BP-lowering drug now	30.8%	15.2%	
Start/continue aspirin + start/add BP-lowering drug + stop smoking for 2 years	30.8%	14.8%	
Start/intensify statin + start/add BP-lowering drug + stop smoking for 2 years	30.8%	12.4%	
Start/continue aspirin + start/intensify statin + stop smoking for 2 years	30.8%	15.2%	
Start all 4	30.8%	11.1%	

70 year old AA male, +smoker, no DM, TC 240 m/dL, HDL-C 40 mg/dL, LDL-C 170 mg/dL), SBP 160 mm Hg.

Smoking cessation and BP control

Baseline 10-Year ASCVD Risk	Risk at Follow-Up if Nothing Had Been Done	Composite updated ASCVD Risk (based on all updated values compared with baseline risk, with floor and ceiling values applied)
30.8%	31.7%	11.4%

+ Mod Intensity Statin

Baseline 10-Year ASCVD Risk	Risk at Follow-Up if Nothing Had Been Done	Composite updated ASCVD Risk (based on all updated values compared with baseline risk, with floor and ceiling values applied)
30.8%	31.7%	8.5%

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Lloyd-Jones DM, et al. *J Am Coll Cardiol* 2016 (in press).

Primary Prevention: Intermediate Risk HOPE-3

- 2-by-2 factorial
- 12,705 particip
  intermediate ris
  not have CVD
- Randomly assig
  mg per day or p
- Median follow-u

sed on lipid

127.8 mg/dl

DL-C 93.2 mg/dl

34.6 mg/dl

ing

Yusuf S, et al. N Engl J Med. 2016;374:2021-2031

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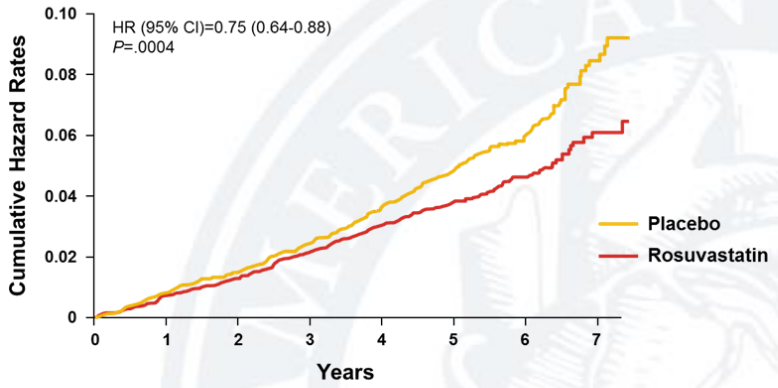
Primary Prevention: Intermediate Risk HOPE-3

- Rosuvastatin 10 mg/d reduced:
  - LDL-C by 34.6 mg/dL
  - CVD by 25%
  - Greater than 18% predicted by CTTC

CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure



Rosuva	6361	6241	6039	2122
Placebo	6344	6192	5970	2073

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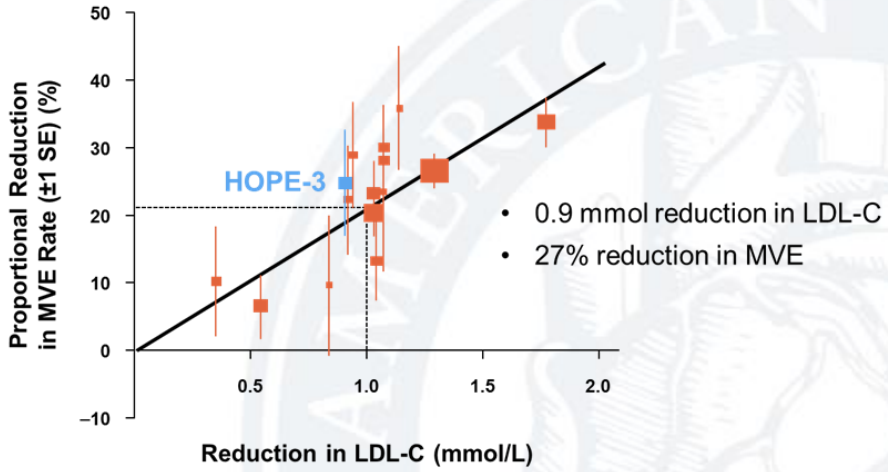
Yusuf S, et al. N Engl J Med. 2016;374:2021-2031

Primary Prevention: Intermediate Risk
HOPE-3

- Consistent benefits regardless of:
  - LDL-C
  - Systolic blood pressure
  - Risk
  - C-reactive protein
  - Ethnicity

HOPE-3 Results: MVE Reduction vs LDL-C (mg/dL) Lowering in RCTs



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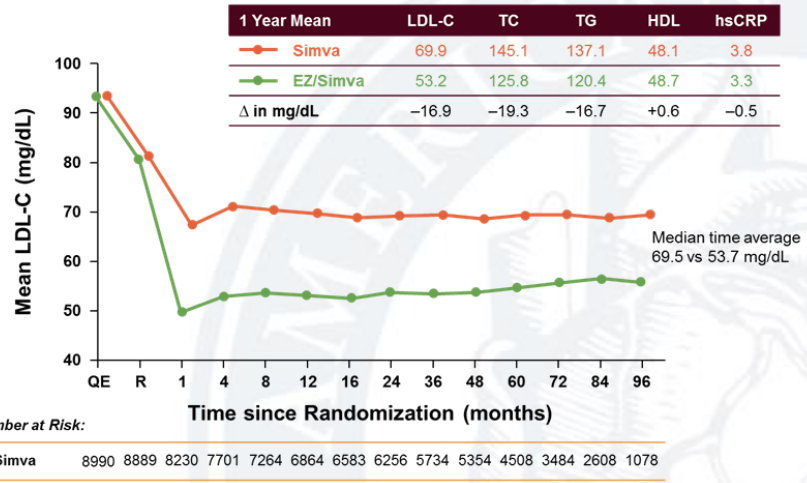
Yusuf S, et al. N Engl J Med. 2016;374:2021-2031

IMPROVE-IT: ASCVD risk reduction post-ACS

Ezetimibe + simvastatin vs. simvastatin monotherapy

- Addition of ezetimibe to simvastatin 40 mg resulted in additional 16.9 mg/dl reduction in LDL-C

NPC1L1 Inhibition and ASCVD Risk Reduction: IMPROVE-IT



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N Engl J Med 2015; 372:2387-2397

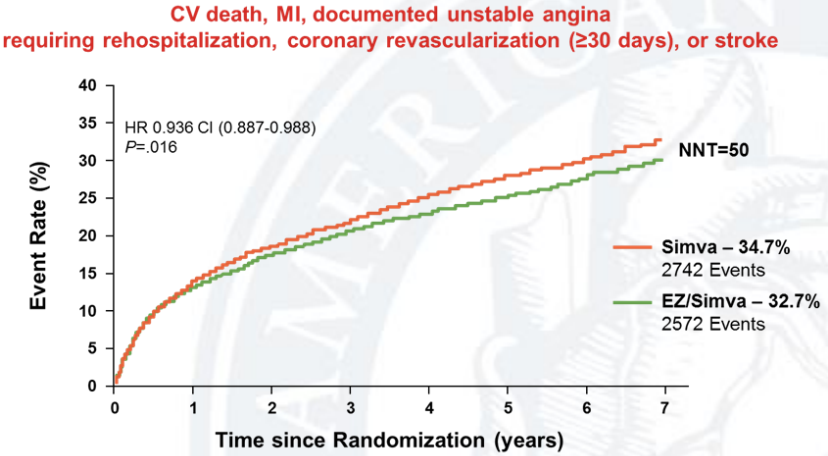
IMPROVE-IT: ASCVD risk reduction post-ACS

Ezetimibe + simvastatin vs. simvastatin monotherapy

- Addition of ezetimibe to simvastatin 40 mg resulted in statistically significant reduction in ASCVD events

- HR 0.936 CI (0.887-0.988)

Primary Endpoint: ITT



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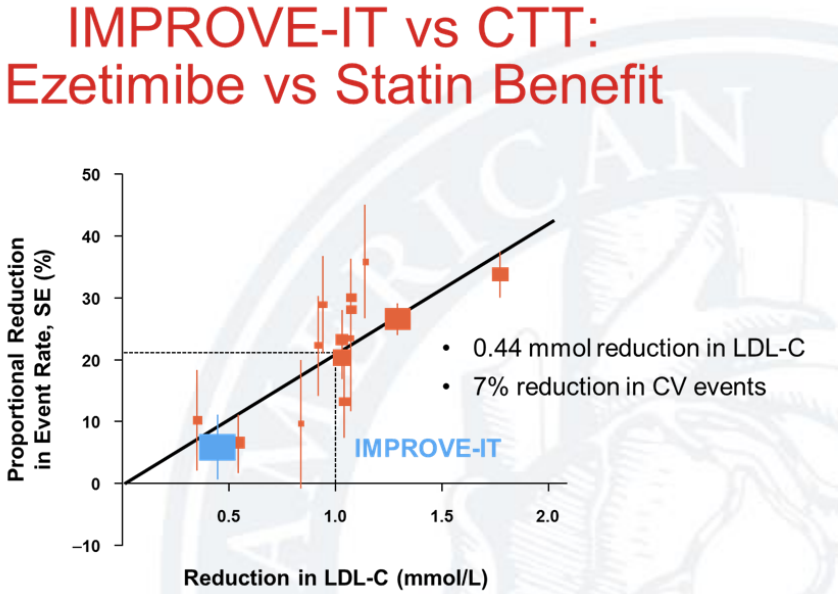
N Engl J Med 2015; 372:2387-2397

IMPROVE-IT: ASCVD risk reduction post-ACS

Ezetimibe + simvastatin vs. simvastatin monotherapy

- CTTC
  - Every 1 mmol/L (38.7 mg/dl) reduction in LDL-C results in approximate 20% reduction in ASCVD
- IMPROVE-IT
  - 0.44 mmol/l reduction in LDL-C
  - 7% reduction in CV events



N Engl J Med 2015; 372:2387-2397

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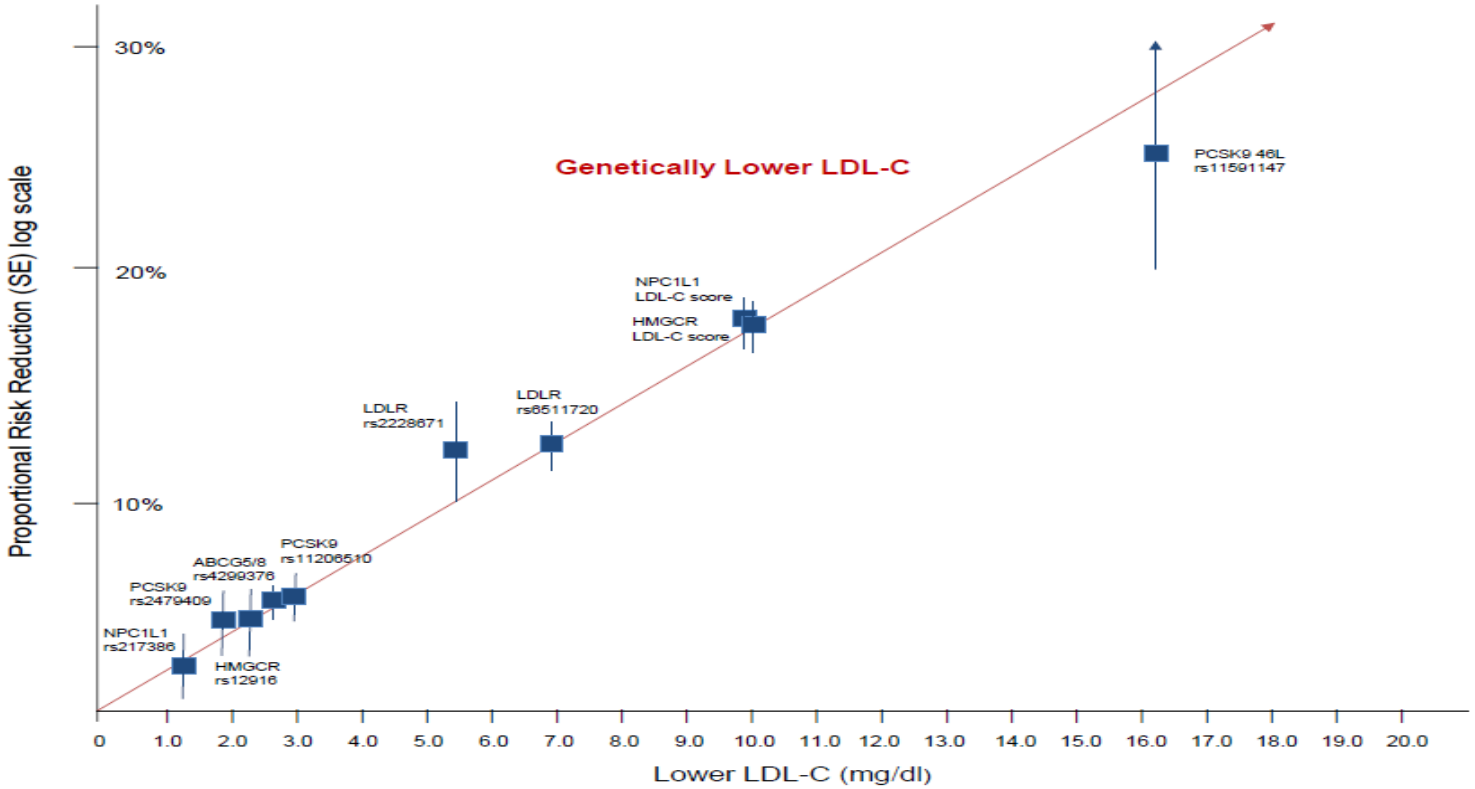
Log-Linear Effect of Lower LDL-C on CHD



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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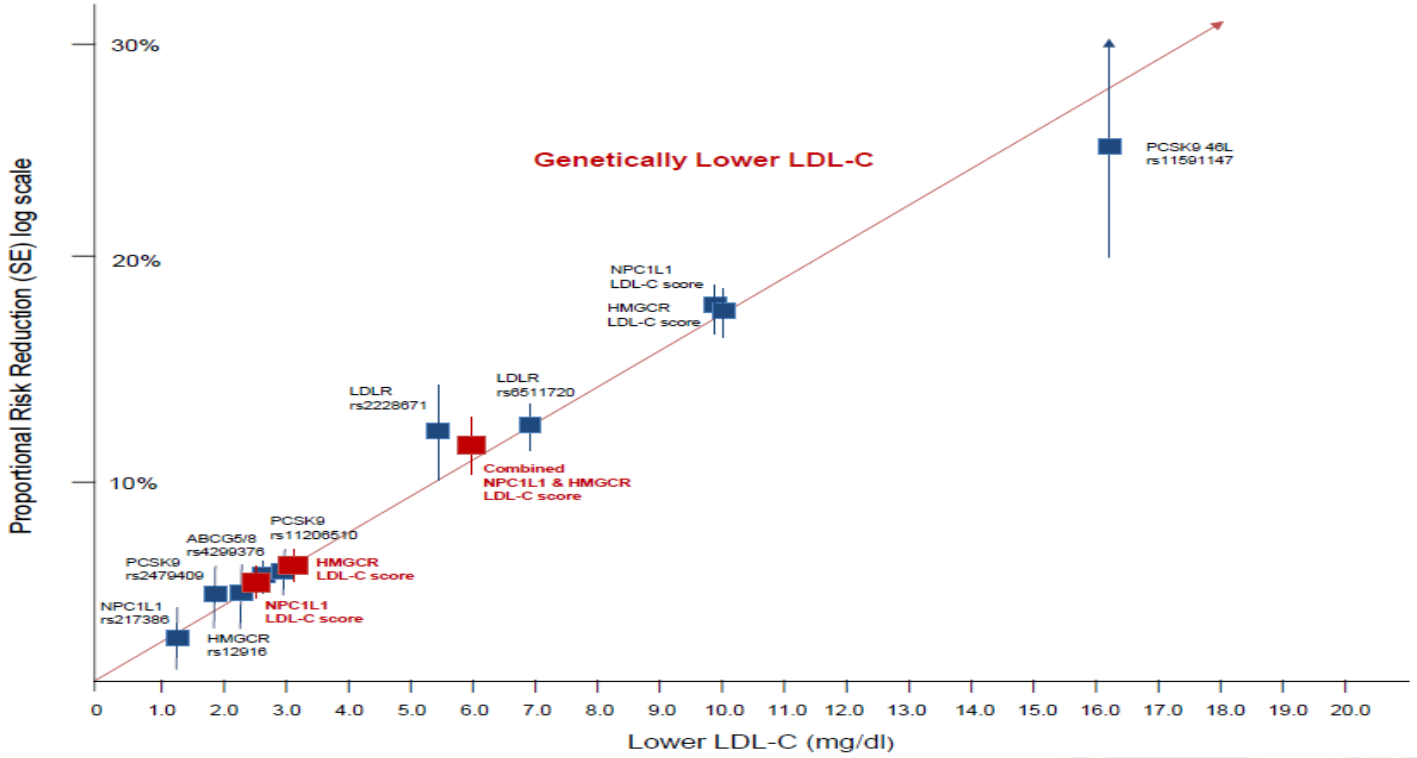

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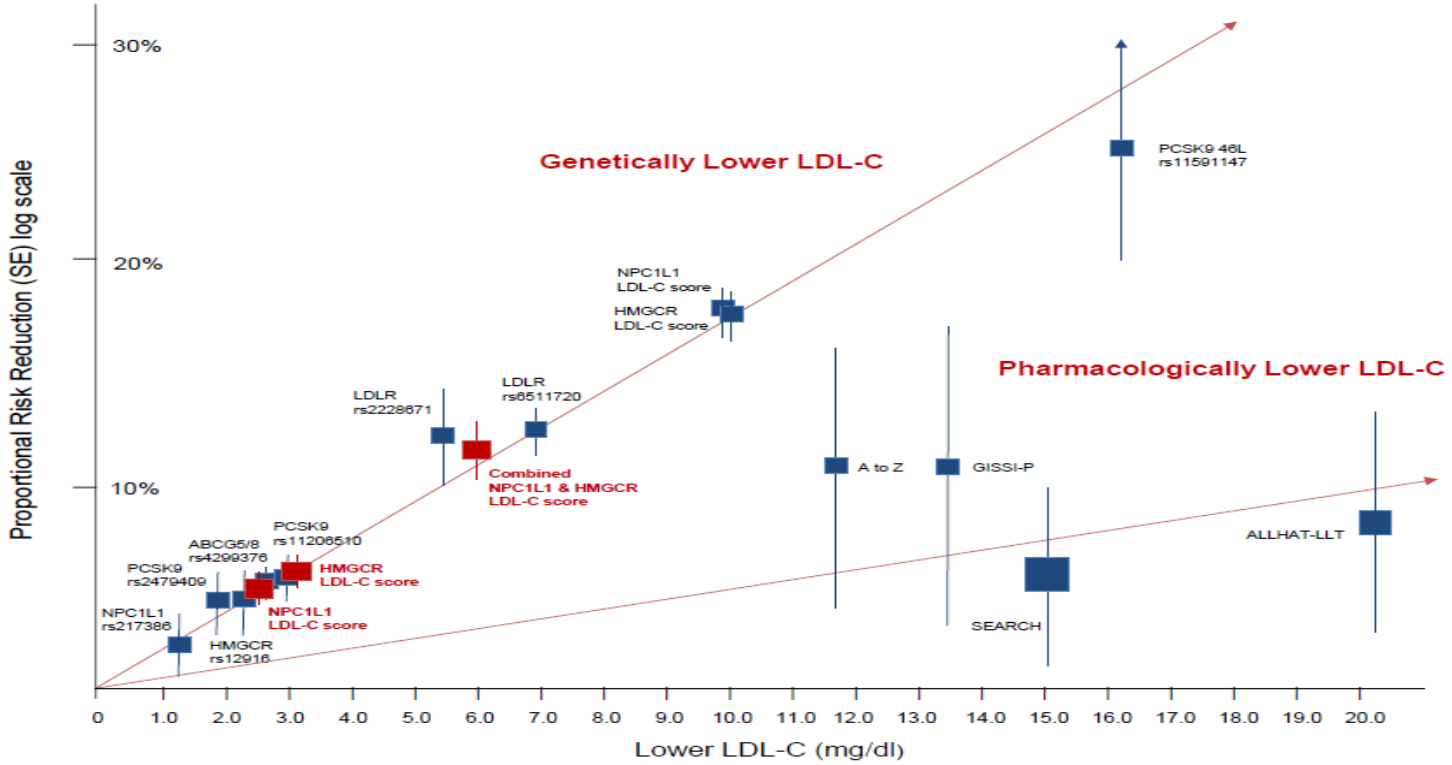

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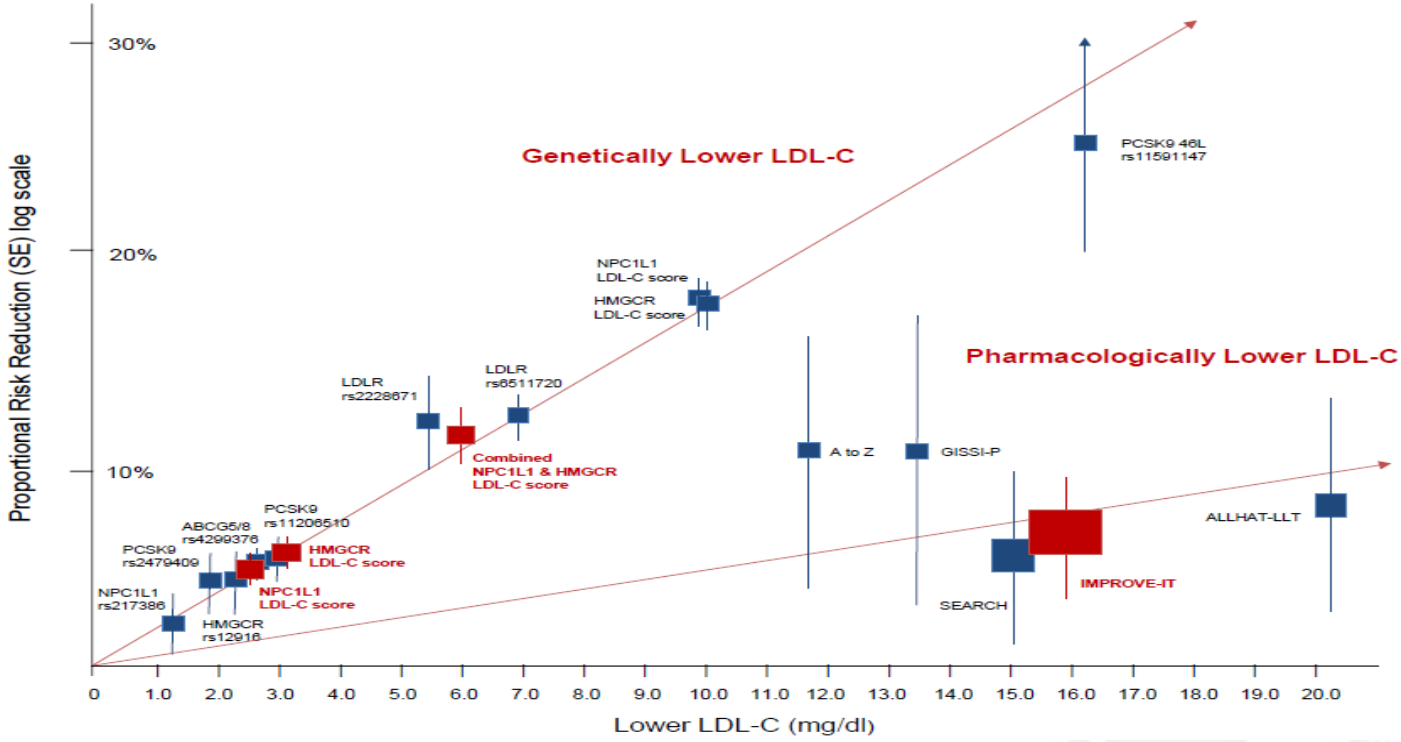

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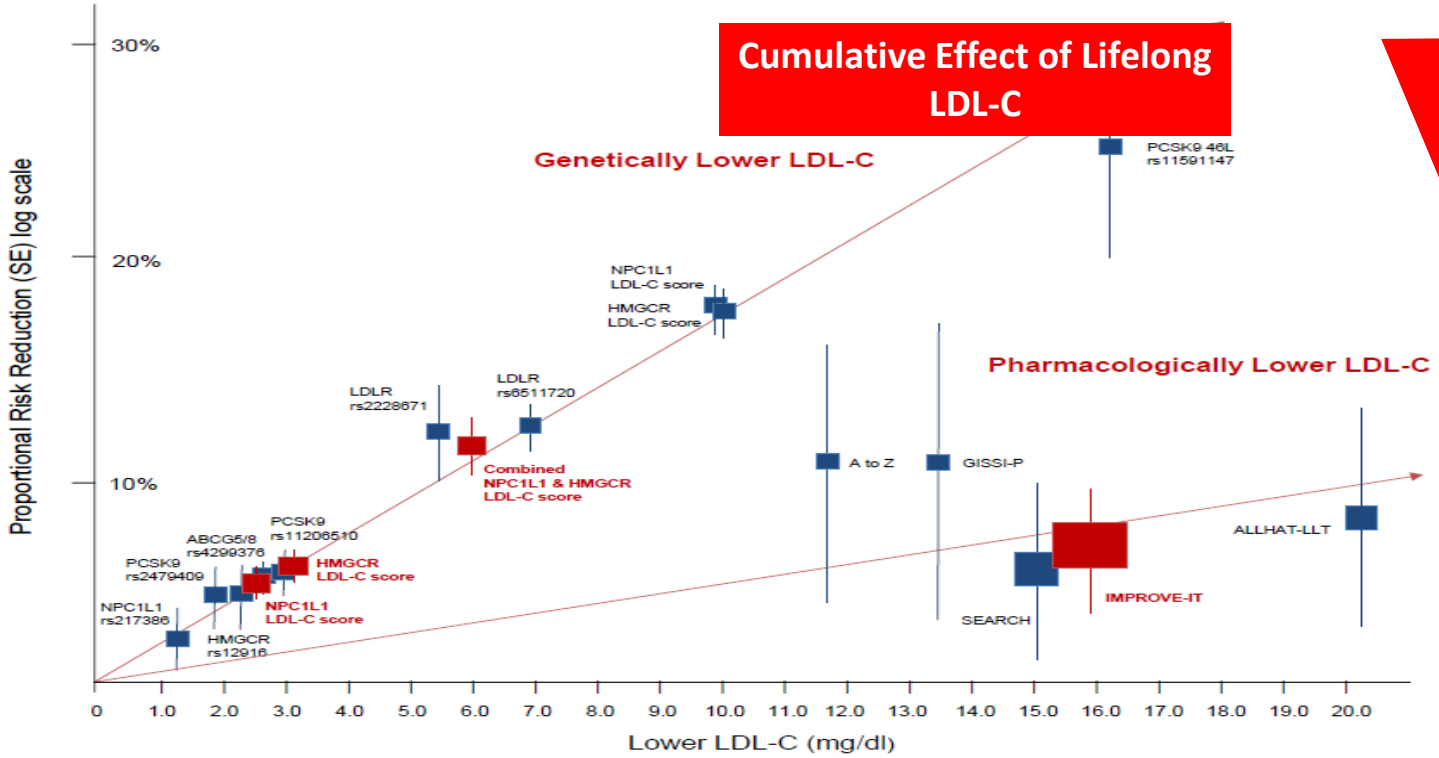
Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

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

Log-Linear Effect of Lower LDL-C on CHD



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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Safety and efficacy of lower levels of LDL-C…

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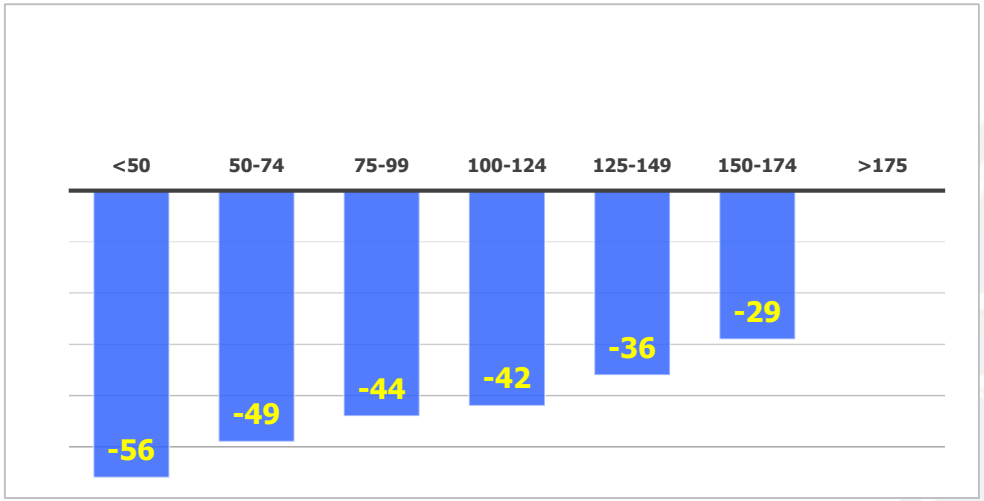
Individual Level Meta-Analysis: No Lower LDL-C Limit For ASCVD Risk Reduction

N= 38,253 from 14 DRBCTs

Relative reduction CVD Risk by Achieved LDL-C level (mg/dl)



Can LDL-C values of <100 mg/dl or <70 mg/dl be considered a minimal goal of therapy?

Boekholdt SM, et al. JACC 2014; 64:485-494

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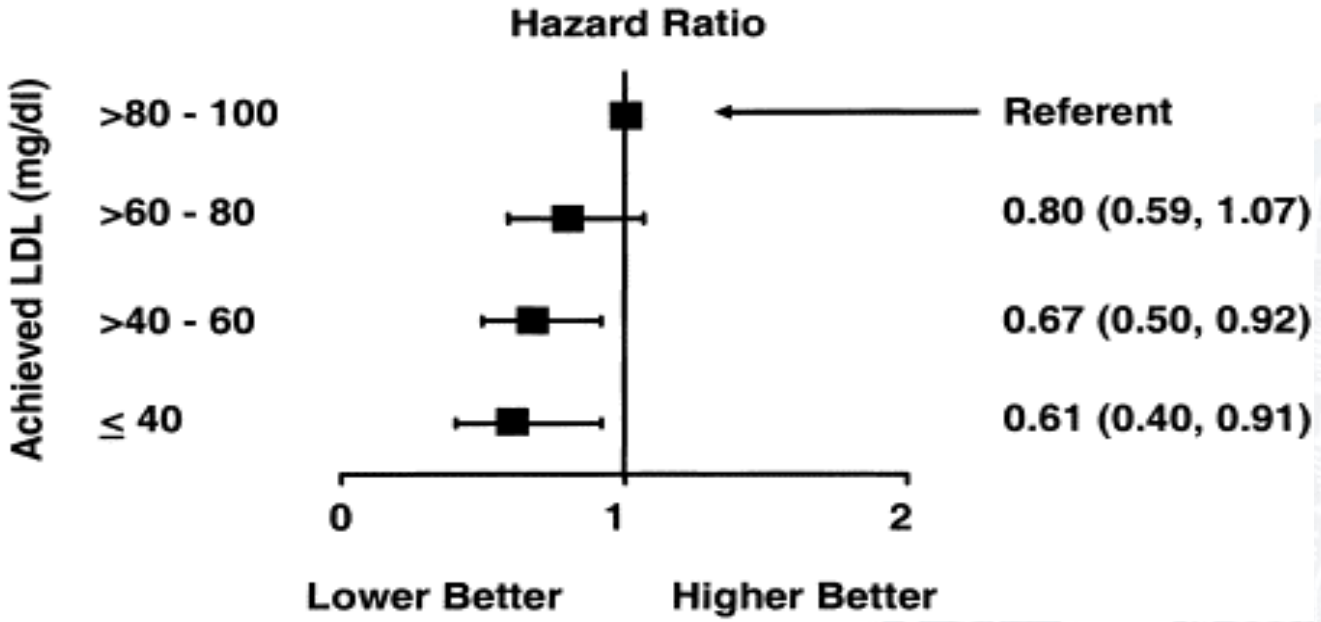
Hazard ratio of the primary end point compared with achieved LDLC 80 to 100 mg/dl (PROVE-IT)



adjusted for age, gender, baseline calculated low-density lipoprotein, diabetes mellitus, and prior myocardial infarction

Stephen D. Wiviott, Christopher P. Cannon, David A. Morrow, Kausik K. Ray, Marc A. Pfeffer, Eugene Braunwald
Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin
Journal of the American College of Cardiology, Volume 46, Issue 8, 2005, 1411–1416

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LDL-C–Lowering Efficacy of PCSK9 Inhibitors: OSLER and ODYSSEY Long-Term

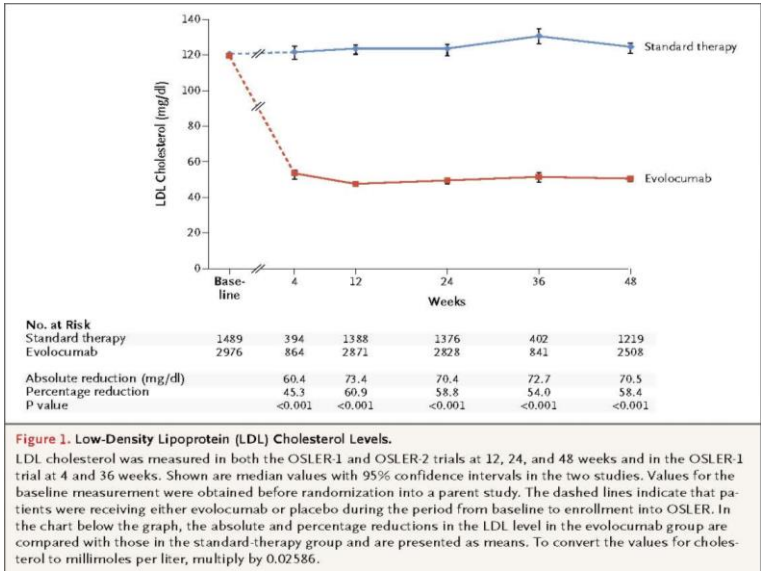

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.

LDL cholesterol was measured in both the OSLER-1 and OSLER-2 trials at 12, 24, and 48 weeks and in the OSLER-1 trial at 4 and 36 weeks. Shown are median values with 95% confidence intervals in the two studies. Values for the baseline measurement were obtained before randomization into a parent study. The dashed lines indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER. In the chart below the graph, the absolute and percentage reductions in the LDL level in the evolocumab group are compared with those in the standard-therapy group and are presented as means. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

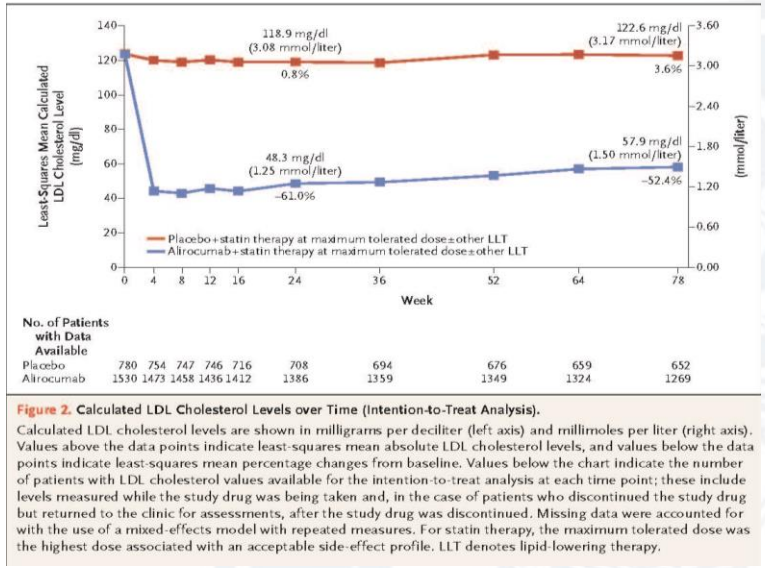

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

Calculated LDL cholesterol levels are shown in milligrams per deciliter (left axis) and millimoles per liter (right axis). Values above the data points indicate least-squares mean absolute LDL cholesterol levels, and values below the data points indicate least-squares mean percentage changes from baseline. Values below the chart indicate the number of patients with LDL cholesterol values available for the intention-to-treat analysis at each time point; these include levels measured while the study drug was being taken and, in the case of patients who discontinued the study drug but returned to the clinic for assessments, after the study drug was discontinued. Missing data were accounted for with the use of a mixed-effects model with repeated measures. For statin therapy, the maximum tolerated dose was the highest dose associated with an acceptable side-effect profile. LLT denotes lipid-lowering therapy.

Sabatine MS et al. *N Engl J Med* 2015;372:1500-9.

Robinson JG et al. *N Engl J Med* 2015;372:1489-99

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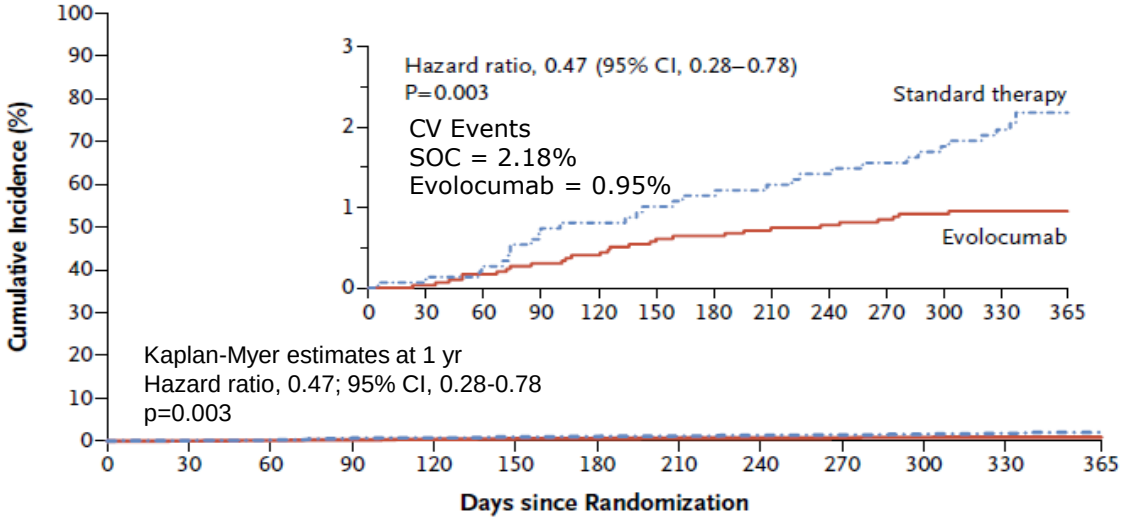
Impact Of Evolocumab vs Placebo on MACE in 4465 Patients in the Osler Study

Osler: Open label study of 4465 patients randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) or SOC for 48 wks

CV Events
- Death
- MI
- UA requiring hospitalization
- CVA
- TIA
- Hosp w CHF



Sabatine et al NEJM 2015; 372:1500-9

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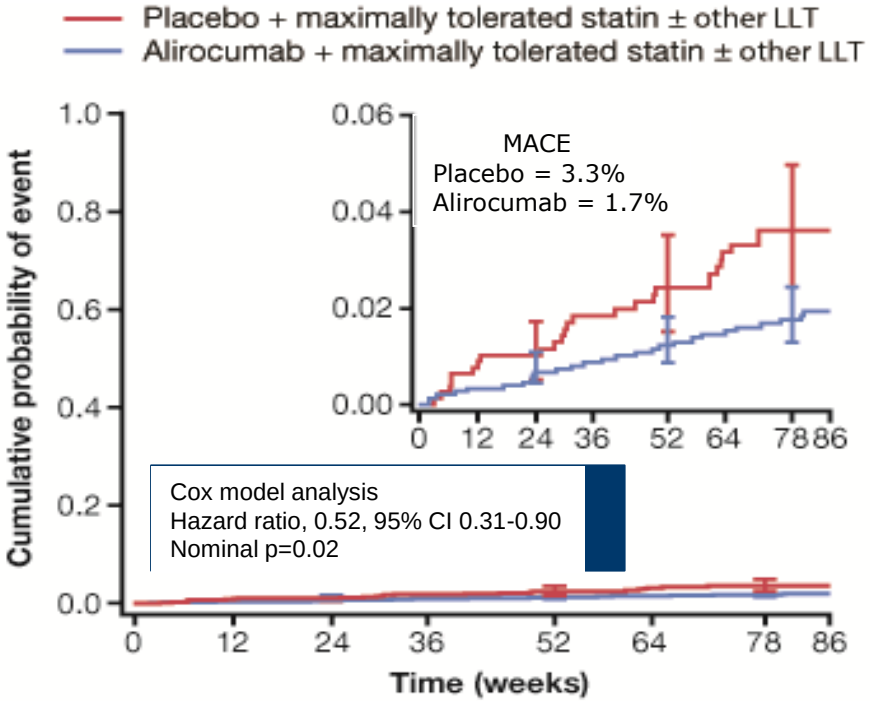
Impact Of Alirocumab vs Placebo on MACE in 2341 Patients in the Odyssey Long Term Study

Odyssey Long Term: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized receiving alirocumab 150 mg or placebo SC Q2W for 78 wks

MACE
- CHD death
- Nonfatal MI
- Fatal/nonfatal ischemic CVA
- UA requiring hospitalization



Robinson et al NEJM 2015; 16;372:1489-99.

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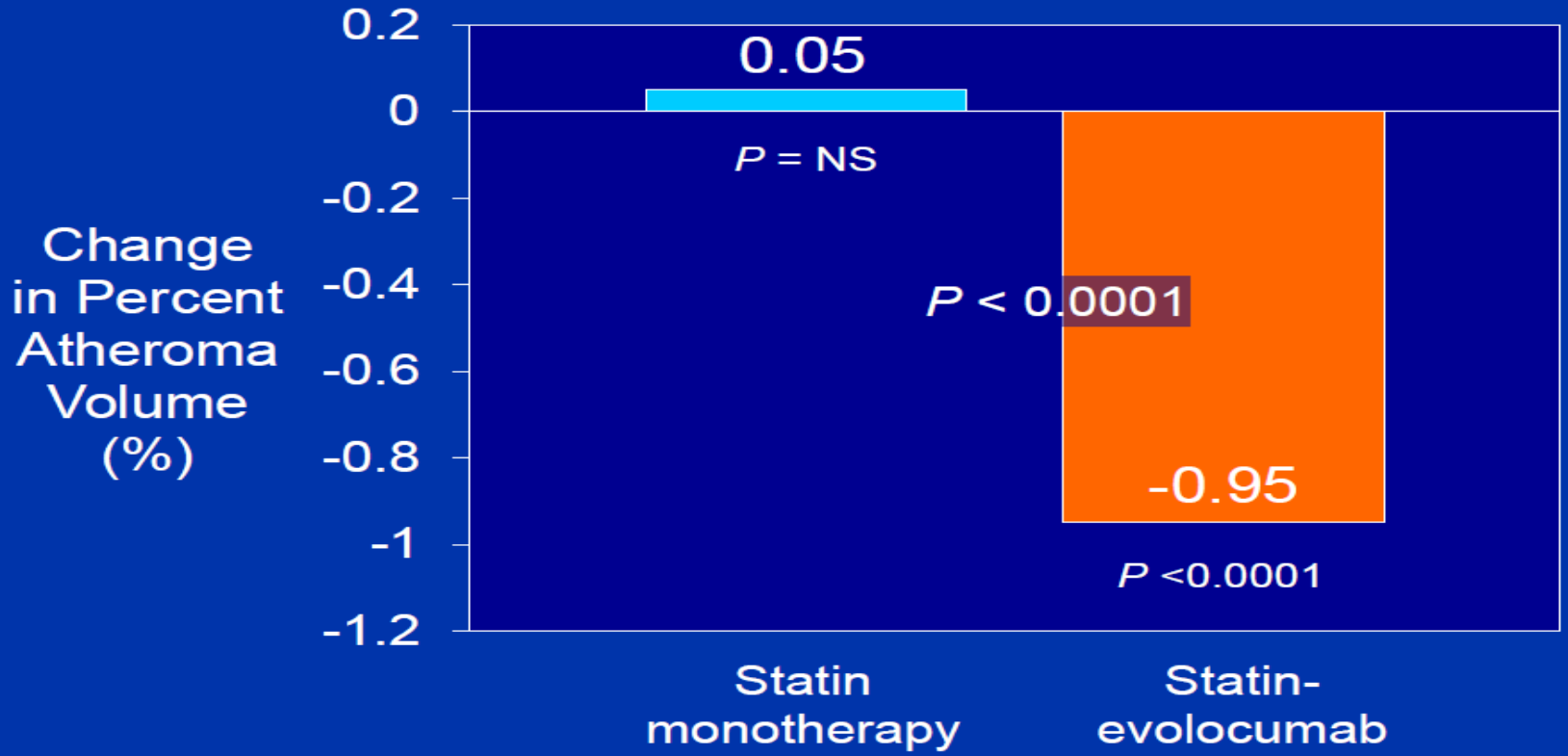
GLAGOV: Primary Endpoint
Percent Atheroma Volume



Nissen SE et al. Presented at American Heart Association Scientific Sessions, New Orleans, LA, 15 November 2016

Statin and high intensity statin use in a National Cohort of CVD patients receiving care in the VA system

Medication use or lipid parameter	Female CVD patients n = 13,371	Male CVD patients n = 959161	*p*
Any statin use, n (%)	7696 (57.6)	621309 (64.8)	<.0001
High intensity statin use*, n (%)	2828 (21.1)	226609 (23.6)	<.0001
Total cholesterol (mg/dL), mean/SD	178.6/45.2	153.9/37.2	<.0001
LDL-C (mg/dL), mean/SD	99.2/38	85/30.4	<.0001
HDL-C (mg/dL), mean/SD	51.3/16.8	42/12.4	<.0001
Triglycerides (mg/dL), mean/SD	153.5/123	147.5/106.7	<.0001
Non-HDL-C (mg/dL), mean/SD	128/44.2	112.5/35.8	<.001

Virani SS et al. Am J Cardiol. 2015 Jan 1;115(1):21-6.

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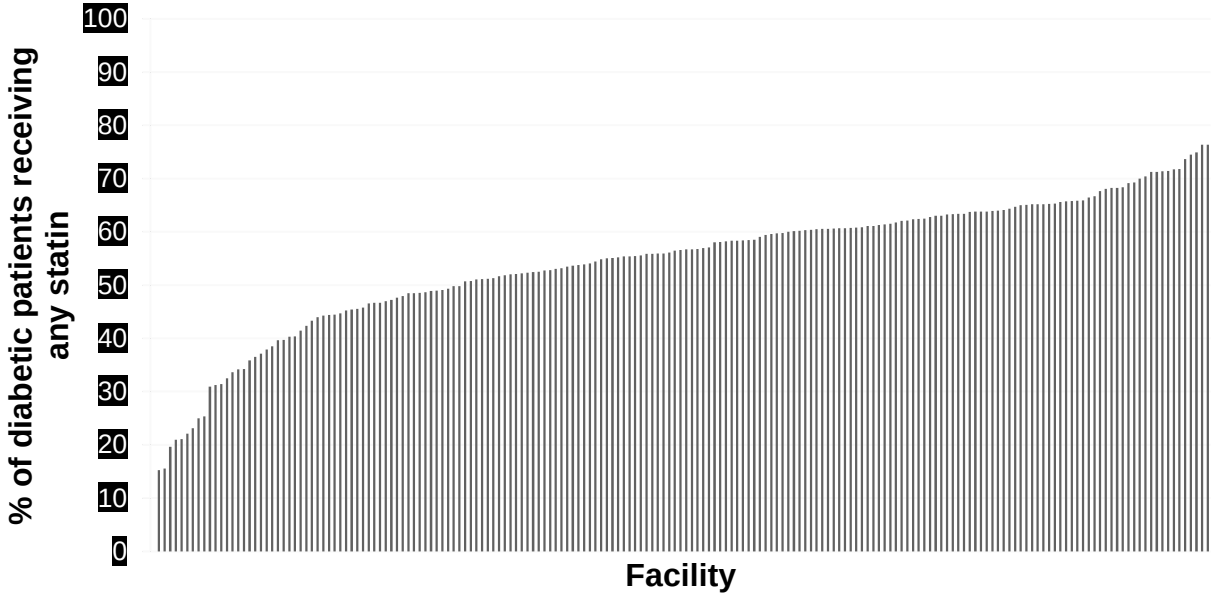
40-75 years old diabetic patients (n=215,193) without CVD in 204 cardiology practices participating in the ACC PINNACLE registry

- Statin use documented in 61.6% of patients.
- Median practice statin prescription rate was 62.3% (IQR: 55.7%-68.7%), with no noticeable change over time. The adjusted MRR was 1.62 (95% CI: 1.57-1.67).



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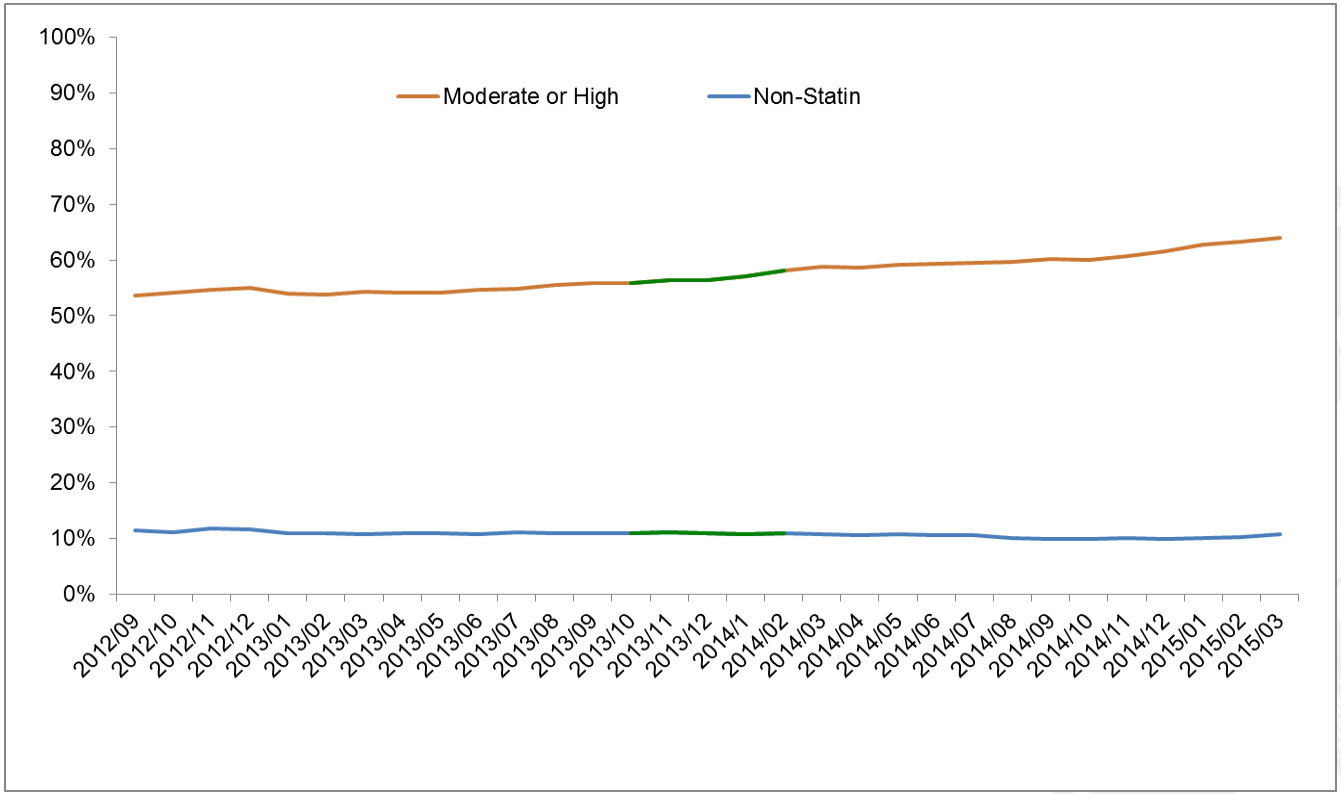
Pokharel Y et al. *J Am Coll Cardiol*. 2016 Sep 20;68(12):1368-9.

Impact of the 2013 ACC/AHA Cholesterol Guidelines on Cholesterol Management in Cardiology Practices



Pokharel Y et al. *Circ Cardiovasc Qual Outcomes*. 2016;9:A14.

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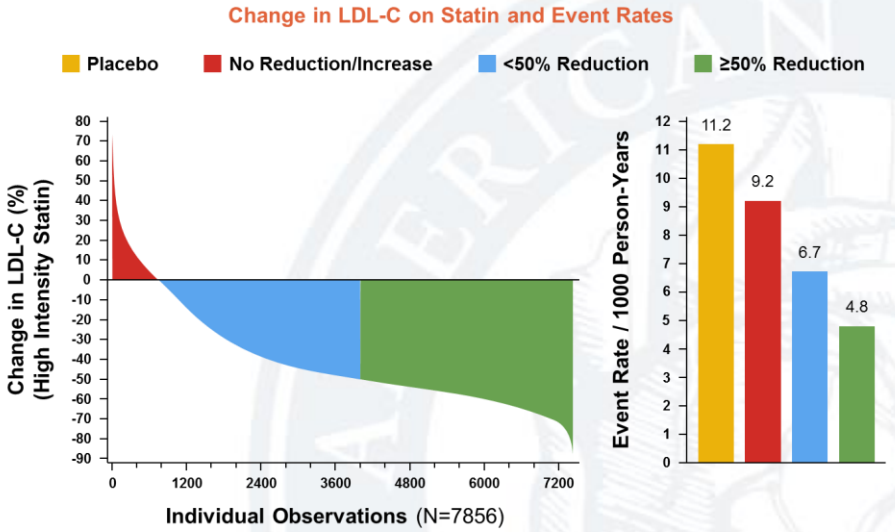
Variation in Response to Statins

- JUPITER trial participants receiving rosuvastatin 20 mg
  - Marked inter-individual variability in response to therapy
  - Reduction in ASCVD events greatest in those with greatest % reduction in LDL-C

LDL-C Response Variability to High-Intensity Statin Therapy



Ridker PM, et al. Eur Heart J. 2016. doi:10.1093/eurheartj/ehw046.

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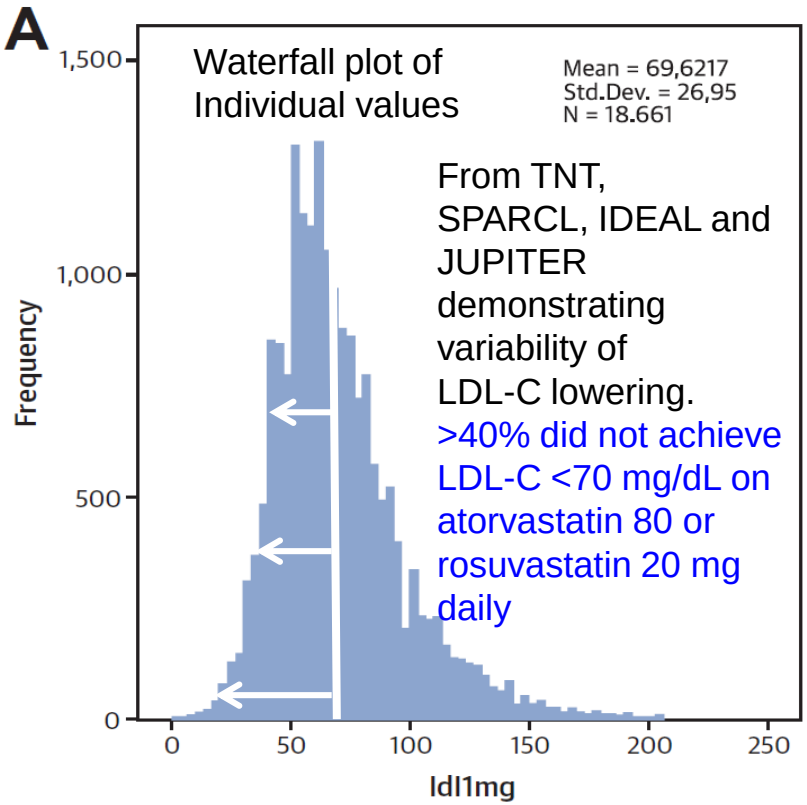
Variability of Achieved LDL-C With High-Intensity Statin Therapy

Meta analysis of 8 statin RCT involving 38,153 subjects of whom 5,387 had 6,286 major CV events and had baseline and 1 year lipids and lipoproteins



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What we know…

- ASCVD reduction is proportional to LDL-C reduction.
- Statins are the first-line therapy for LDL-C lowering, although, their use still remains suboptimal.
- There is considerable inter-individual variability in response to statin therapy.
- Lowering LDL-C with statin therapy, ezetimibe, and *possibly* PCSK9 inhibitors is associated with ASCVD risk reduction.
- High risk patients on maximally tolerated statin therapy may be candidates for additional non-statin therapies.

Questions Waiting to be Answered

- Benefit/risk of very low levels of atherogenic lipoproteins?
- Is lowering of atherogenic lipoproteins with PCSK9 inhibitors associated with reduction in ASCVD events?
- What is the role of the only remaining CTEP inhibitor (anacetrapib/REVEAL) in clinical studies in ASCVD risk reduction?
- Will we *ever* understand and/or modify HDL-C to reduce ASCVD risk?
- Meanwhile, how do we use non-statin lipid lowering therapies?

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