Lipid Management update 2019

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Disclosures:

Dr. Christopher Cannon

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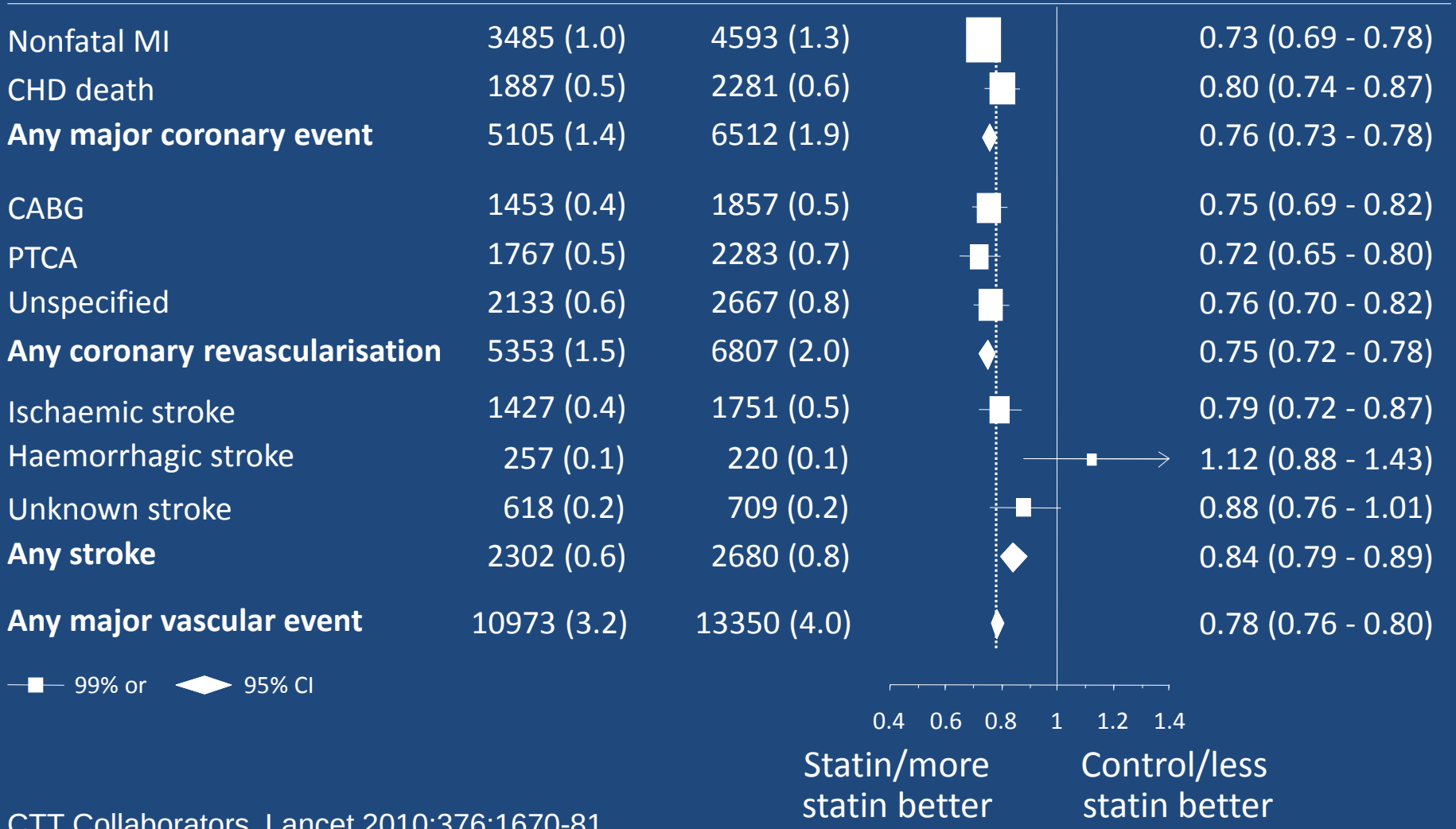
A Half-Century of Research in LDL-C Lowering Drugs for Preventing CV Events

Method	Study	Chol/LDL	CHD↓	P-value
Diet	Oslo I 1970	T-C 14 %	25 %	0.05
Cholestyramine	LRC–CPPT 1984	LDL-C 13 %	19 %	<0.05
Ileal bypass	POSCH 1990	LDL-C 38 %	35 %	<0.001
Statin	4S 1994	LDL-C 35 %	30 %	0.0003
HD Statin	PROVE IT 2004	LDL-C 33mg/dl	16 %	0.005
Fibrates	FIELD 2005	LDL-C 12%	11%	NS
Niacin	HPS2 2014	LDL-C 10mg/dl	4%	NS
Ezetimibe	IMPROVE IT 2016	LDL-C 17mg/dl	6.4 %	0.016
PCSK9	FOURIER 2017	LDL-C 62mg/dl	20%	<0.001
CETP	REVEAL 2017	LDL-C 11mg/dl	9%	0.004

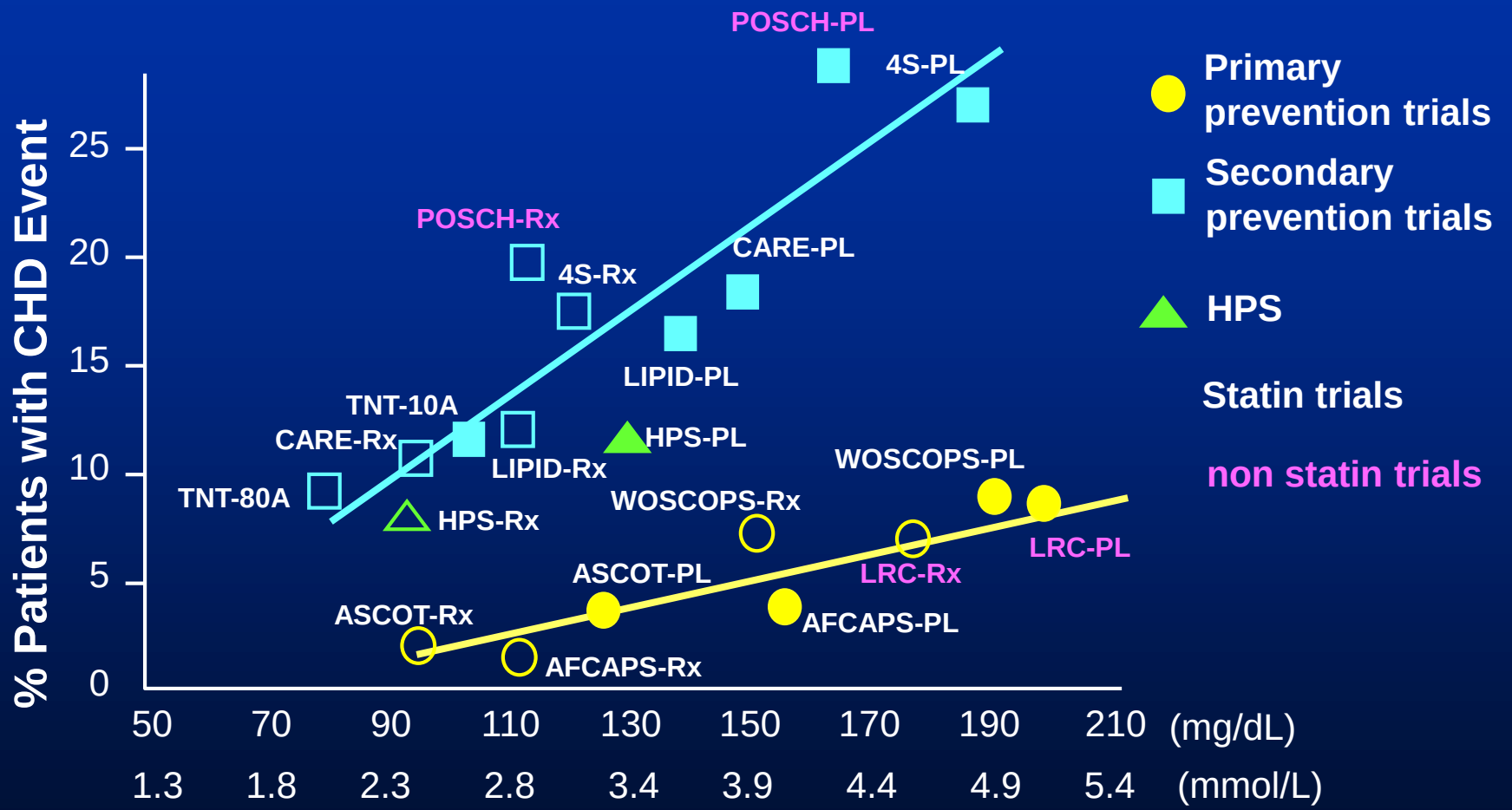
CTT: Benefits of Statins on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol

	No. of events (% per year)		
	Statin/ More statin	Contr ol/ Less statin	Relative risk (CI)
Nonfatal MI	3485 (1.0)	4593 (1.3)	0.73 (0.69 - 0.78)
CHD death	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Any major coronary event	5105 (1.4)	6512 (1.9)	0.76 (0.73 - 0.78)
CABG	1453 (0.4)	1857 (0.5)	0.75 (0.69 - 0.82)
PTCA	1767 (0.5)	2283 (0.7)	0.72 (0.65 - 0.80)
Unspecified	2133 (0.6)	2667 (0.8)	0.76 (0.70 - 0.82)
Any coronary revascularisation	5353 (1.5)	6807 (2.0)	0.75 (0.72 - 0.78)
Ischaemic stroke	1427 (0.4)	1751 (0.5)	0.79 (0.72 - 0.87)
Haemorrhagic stroke	257 (0.1)	220 (0.1)	1.12 (0.88 - 1.43)
Unknown stroke	618 (0.2)	709 (0.2)	0.88 (0.76 - 1.01)
Any stroke	2302 (0.6)	2680 (0.8)	0.84 (0.79 - 0.89)
Any major vascular event	10973 (3.2)	13350 (4.0)	0.78 (0.76 - 0.80)



CTT Collaborators. Lancet 2010;376:1670-81.

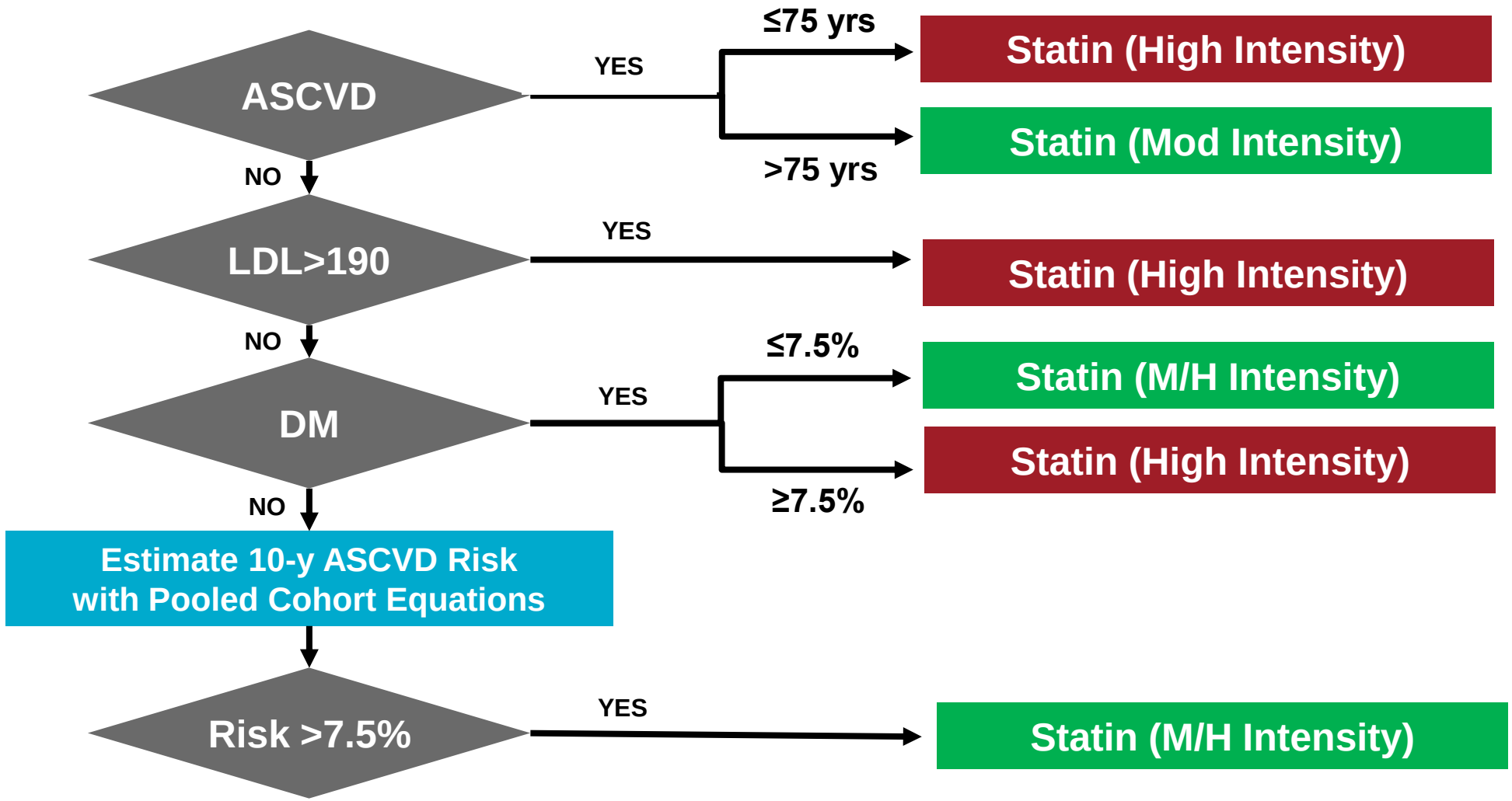
Effect of Lowering LDL-C on CHD Events



Ballantyne CM. Am J Cardiol. 1998
O'Keefe JH et al, JACC 2004

2013 ACC/AHA Cholesterol Guidelines:

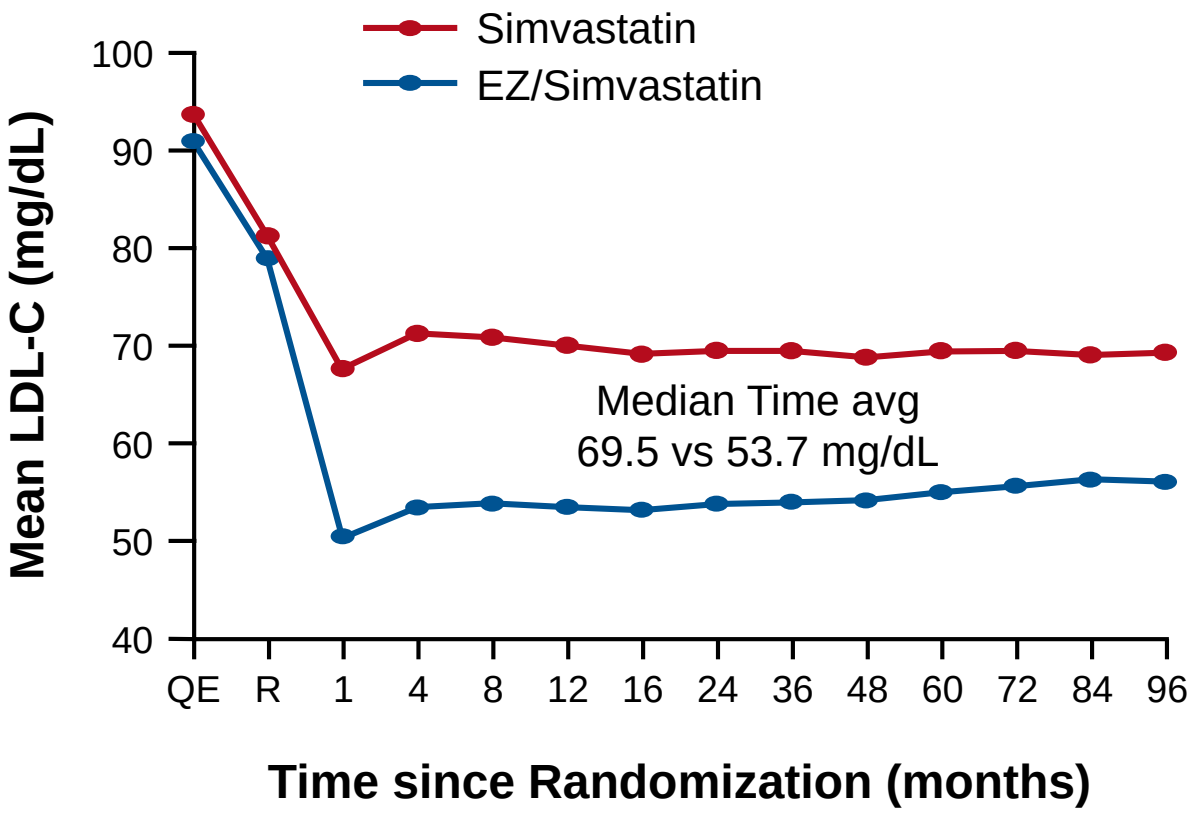
Recommendations for the 4 Statin Benefit Groups

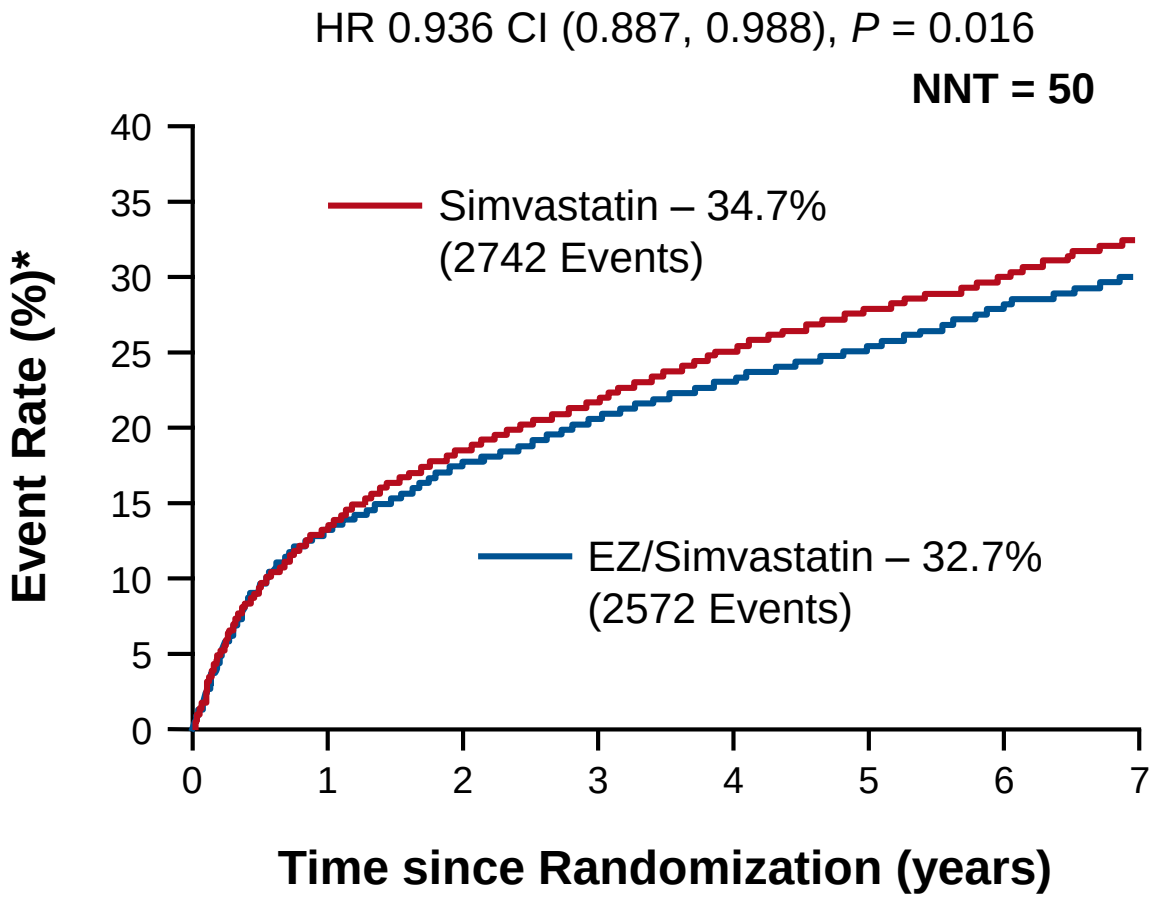


Stone NJ, et al. *Circ.* 2014;129(suppl 25):S1-45.

IMPROVE-IT: Primary Results

18,144 ACS patients randomized to simvastatin alone or ezetimibe (EZ)/simvastatin, median follow-up 6 years

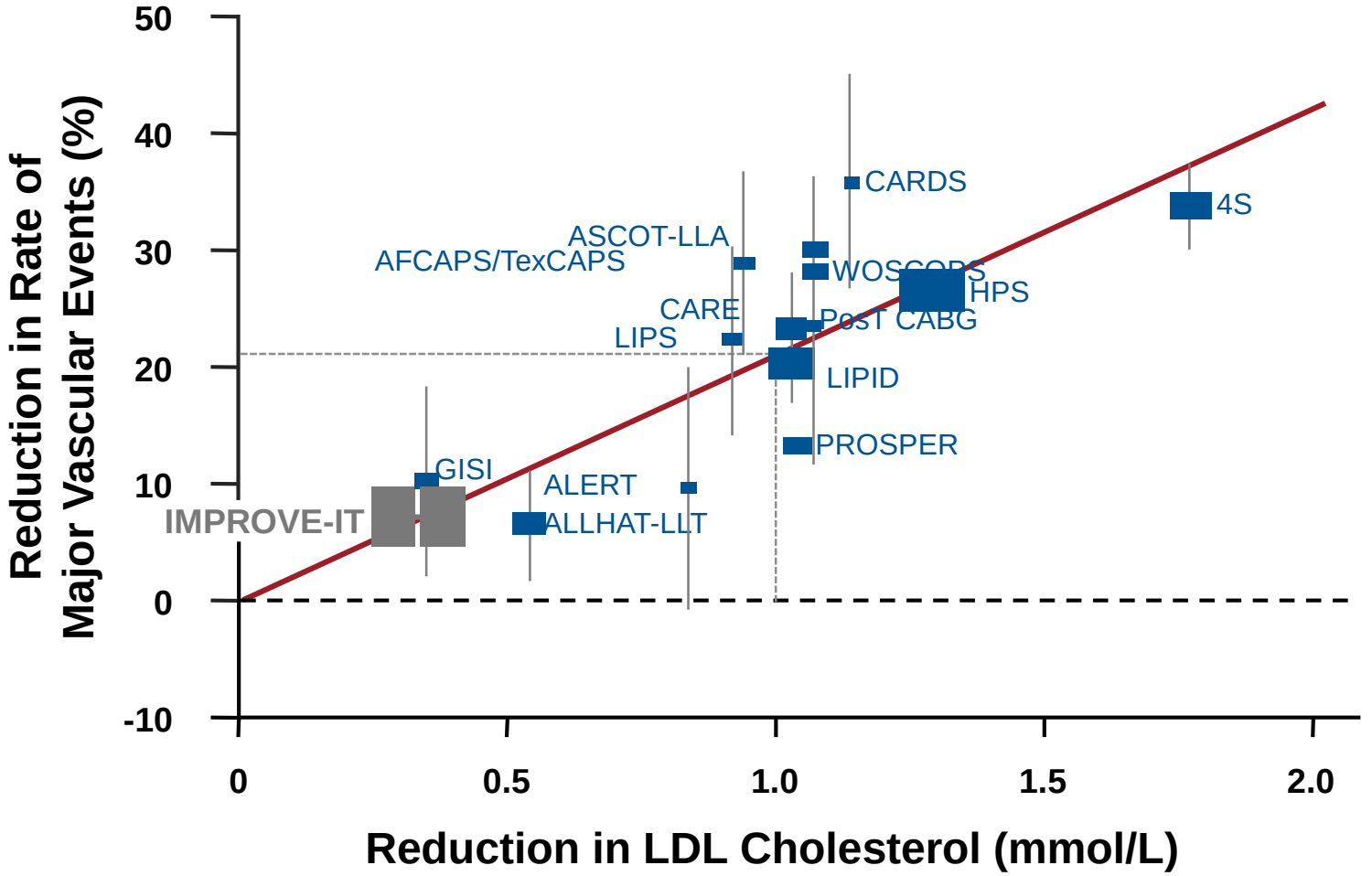




***Primary end point (cardiovascular death, MI, unstable angina, coronary revascularization, or stroke).**

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

IMPROVE-IT vs CTT: CV Benefit Proportional to LDL-C for Both Ezetimibe and Statins



***Using CTT methods: LDL difference between groups using baseline LDL for Pts without blood samples. Endpoint of CV Death, MI, stroke or revascularization >30days post Rand. Cox HR reported.**

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

IMPROVE-IT: Safety (mean 6 years F/U)

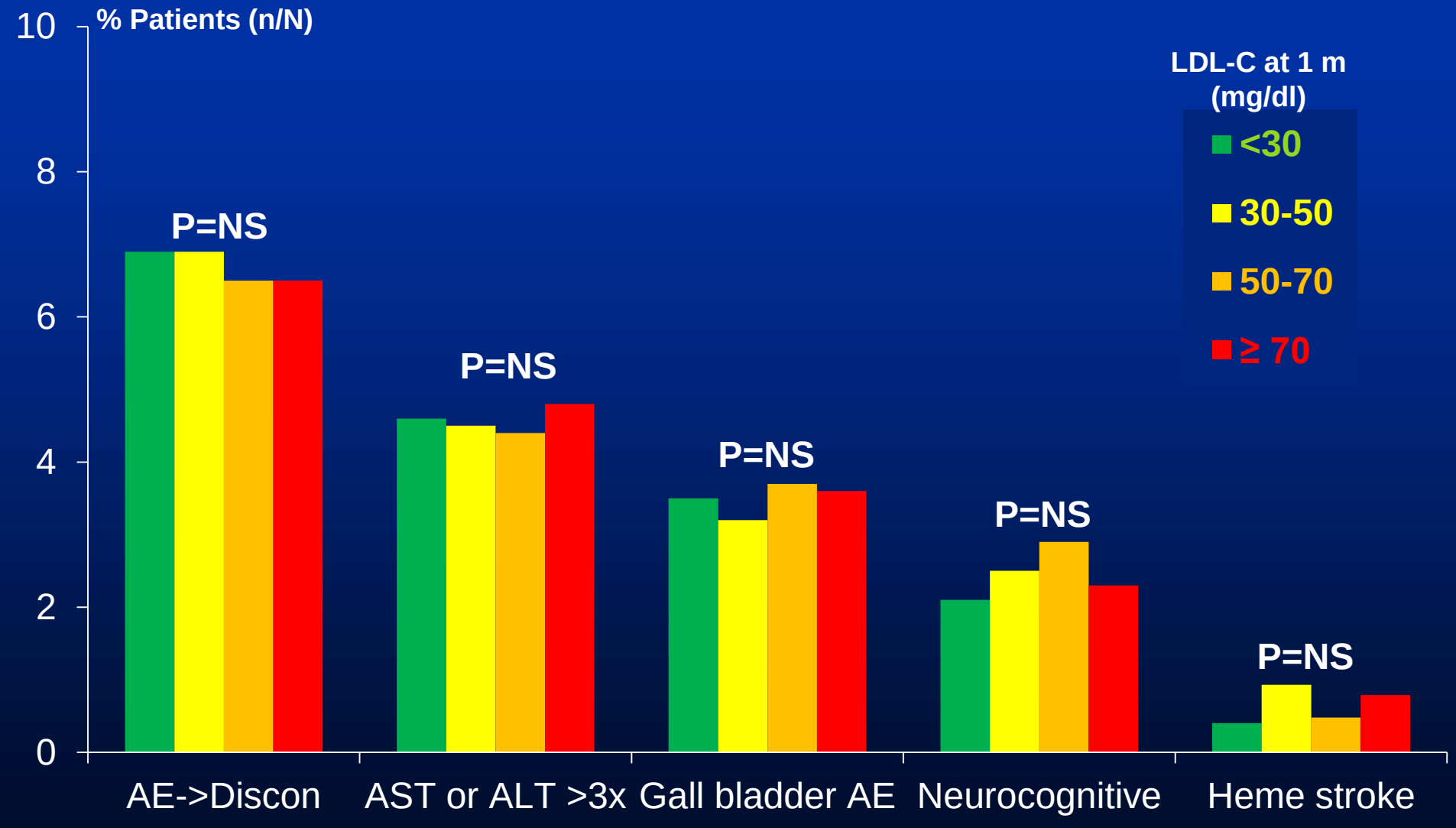
No statistically significant differences in cancer or muscle- or gallbladder-related events

Adverse Event	Simva n=9077 (%)	EZ/Simva n=9067 (%)	P-value
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

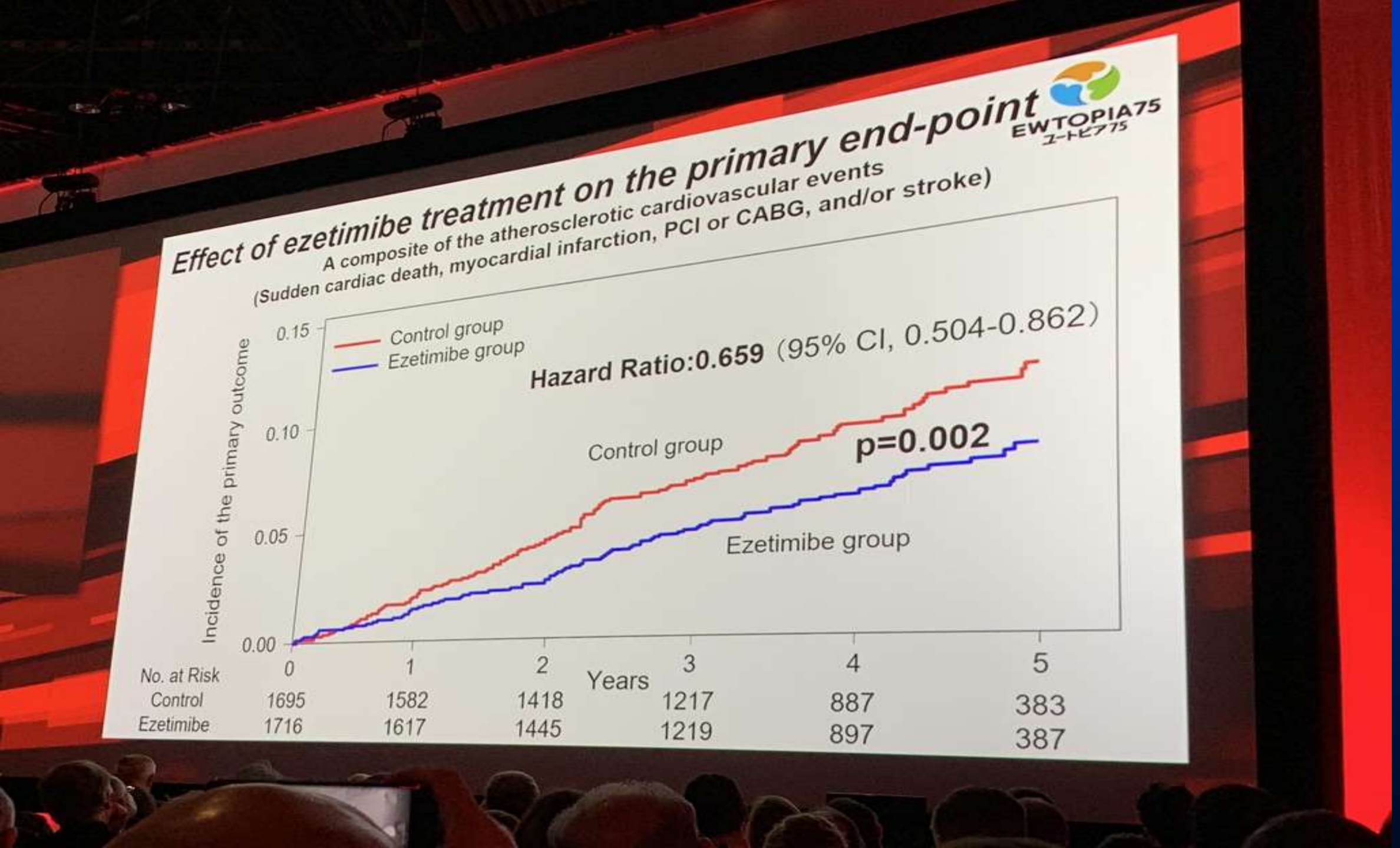
***% = n/N for the trial duration.**

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

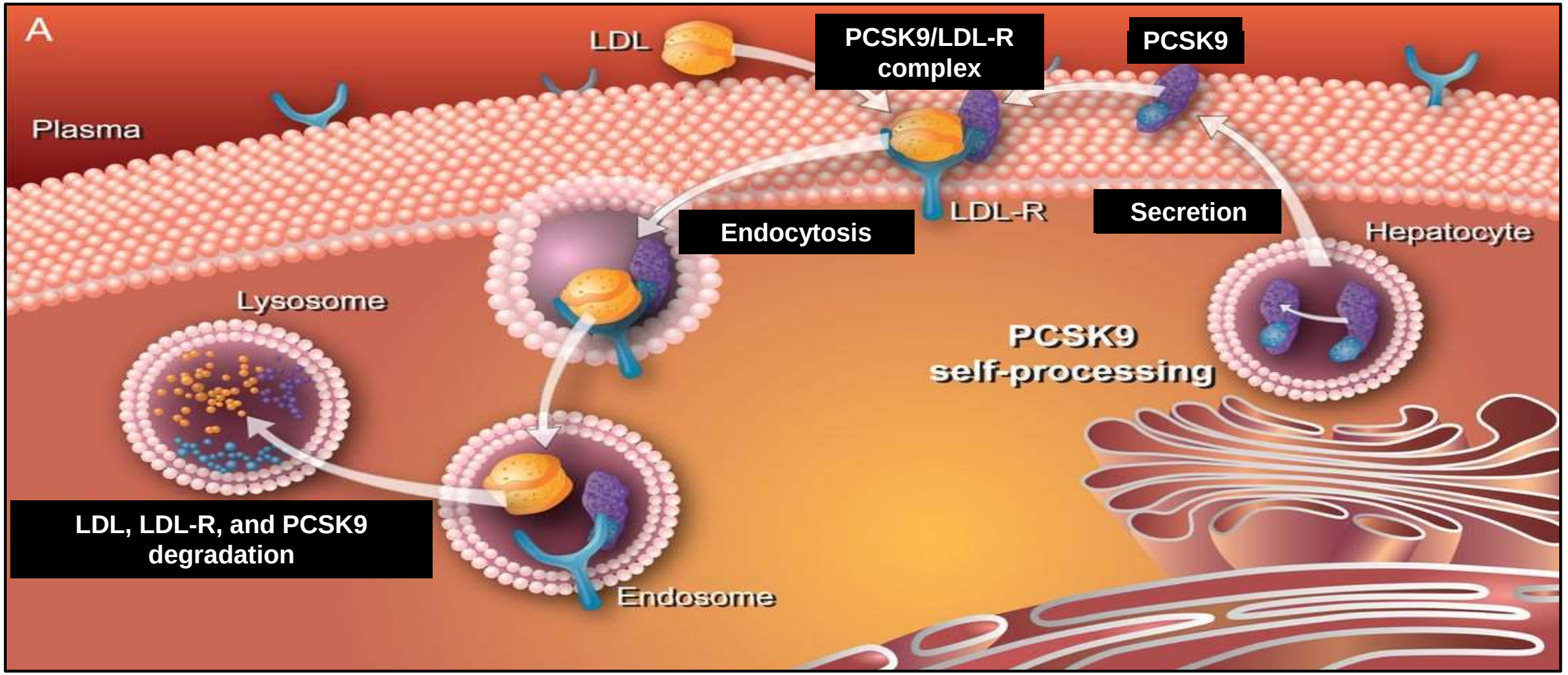
Safety Events – 6 years f/u



Giugliano RP et al. JAMA Cardiology March 2017

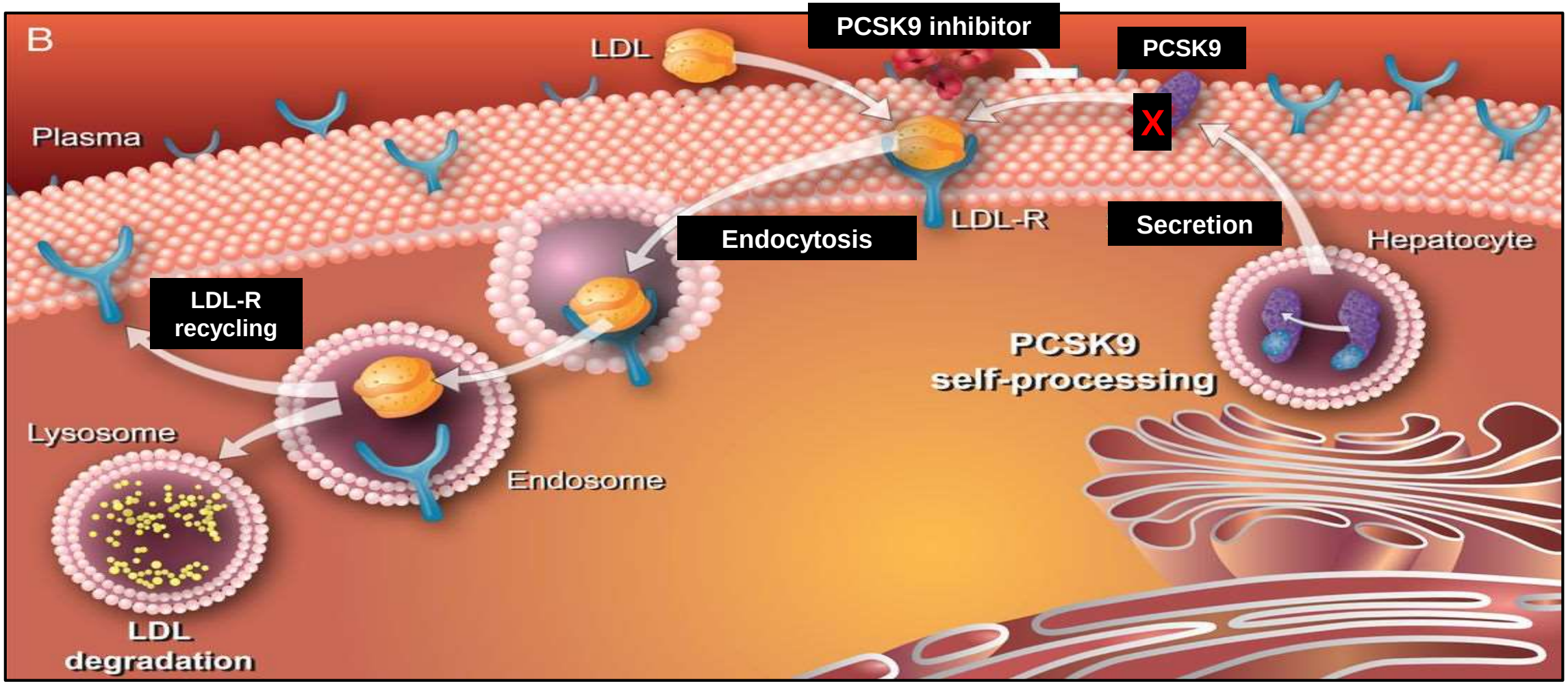

Effect of ezetimibe treatment on the primary end-point
A composite of the atherosclerotic cardiovascular events
(Sudden cardiac death, myocardial infarction, PCI or CABG, and/or stroke)
EWTOPIA75
Control group
Ezetimibe group
Hazard Ratio:0.659 (95% CI, 0.504-0.862)
p=0.002
Incidence of the primary outcome
0.15
0.10
0.05
0.00
Years
0
1
2
3
4
5
No. at Risk
Control 1695 1582 1418 1217 887 383
Ezetimibe 1716 1617 1445 1219 897 387

PCSK9 Regulates LDL-R Expression



Shimada YJ, Cannon CP. Eur Heart J. 2015;36:2415–2424.

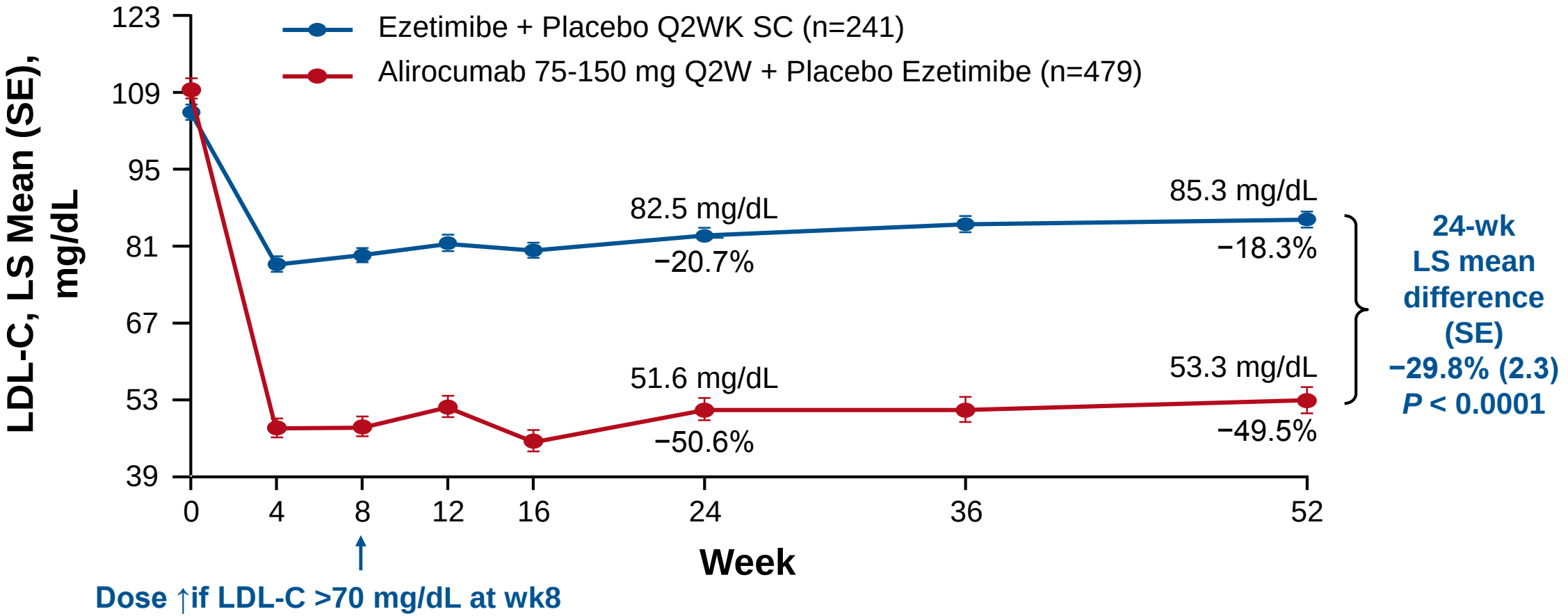
LDL-C Reduction via PCSK9 Inhibition



Shimada YJ, Cannon CP. *Eur Heart J.* 2015;36:2415–2424.

COMBO II: PCSK9i Alirocumab vs Ezetimibe Added to Max-tolerated Statin in High CV-Risk Patients

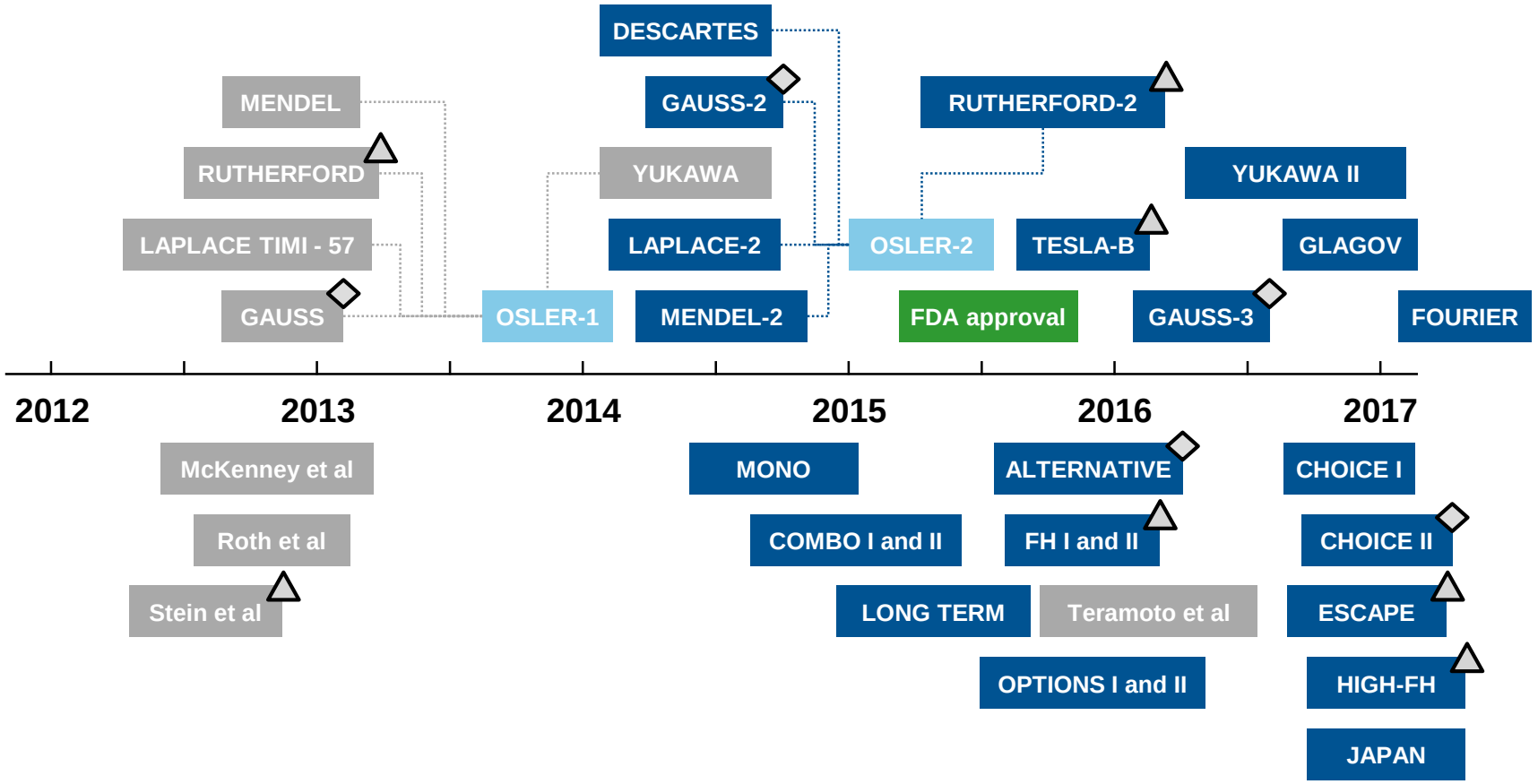
LDL-C reduction over 52 weeks on background of max-tolerated statin



Cannon CP, et al. *Eur Heart J.* 2015;36(19):1186-94.

Impact of PCSK9 Inhibition on Lipid Levels

Meta-analysis of 35 randomized controlled trials comparing treatment with and without PCSK9 inhibitors



Lipoprotein	Δ (%)
LDL-C	↓ 54.7
TC	↓ 34.9
HDL-C	↑ 6.9
apoB	↓ 45.5
Lp(a)	↓ 26.5

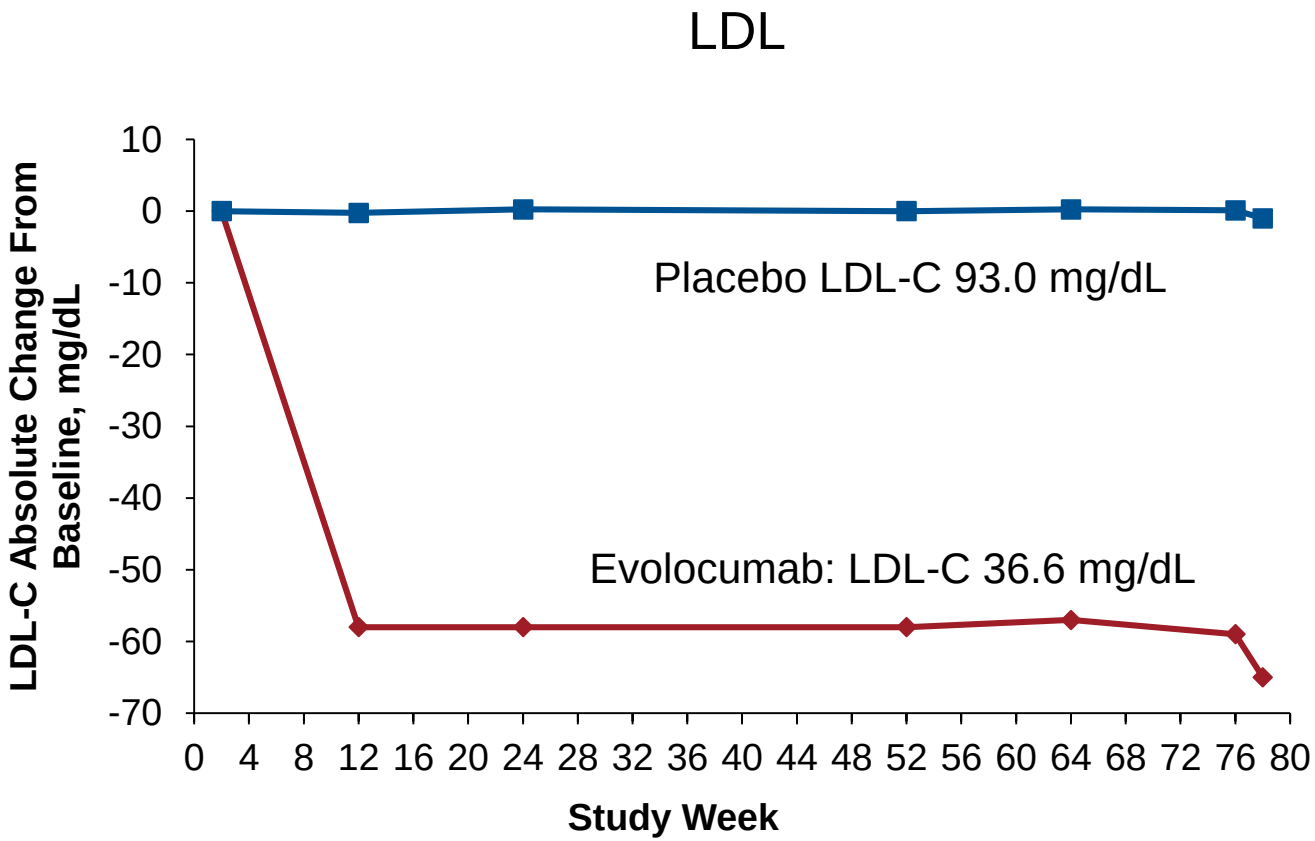
Phase 2 (n=9) | Phase 3 (n=24) | Open-label (n=2)

◇ Statin intolerant (n=5)

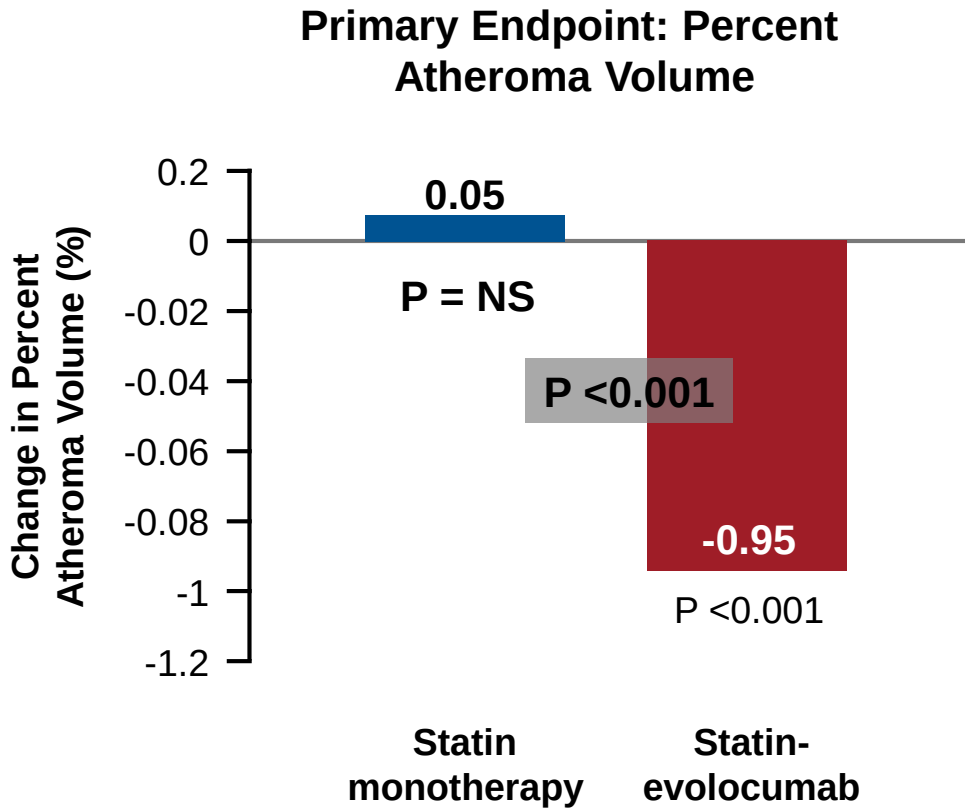
△ HeFH / HoFH (n=8)

Karatasakis A, et al. *J Am Heart Assoc*. 2017;6(12):pii: e006910. doi: 10.1161/JAHA.117.006910.

GLAGOV: Evolocumab Added to Statins



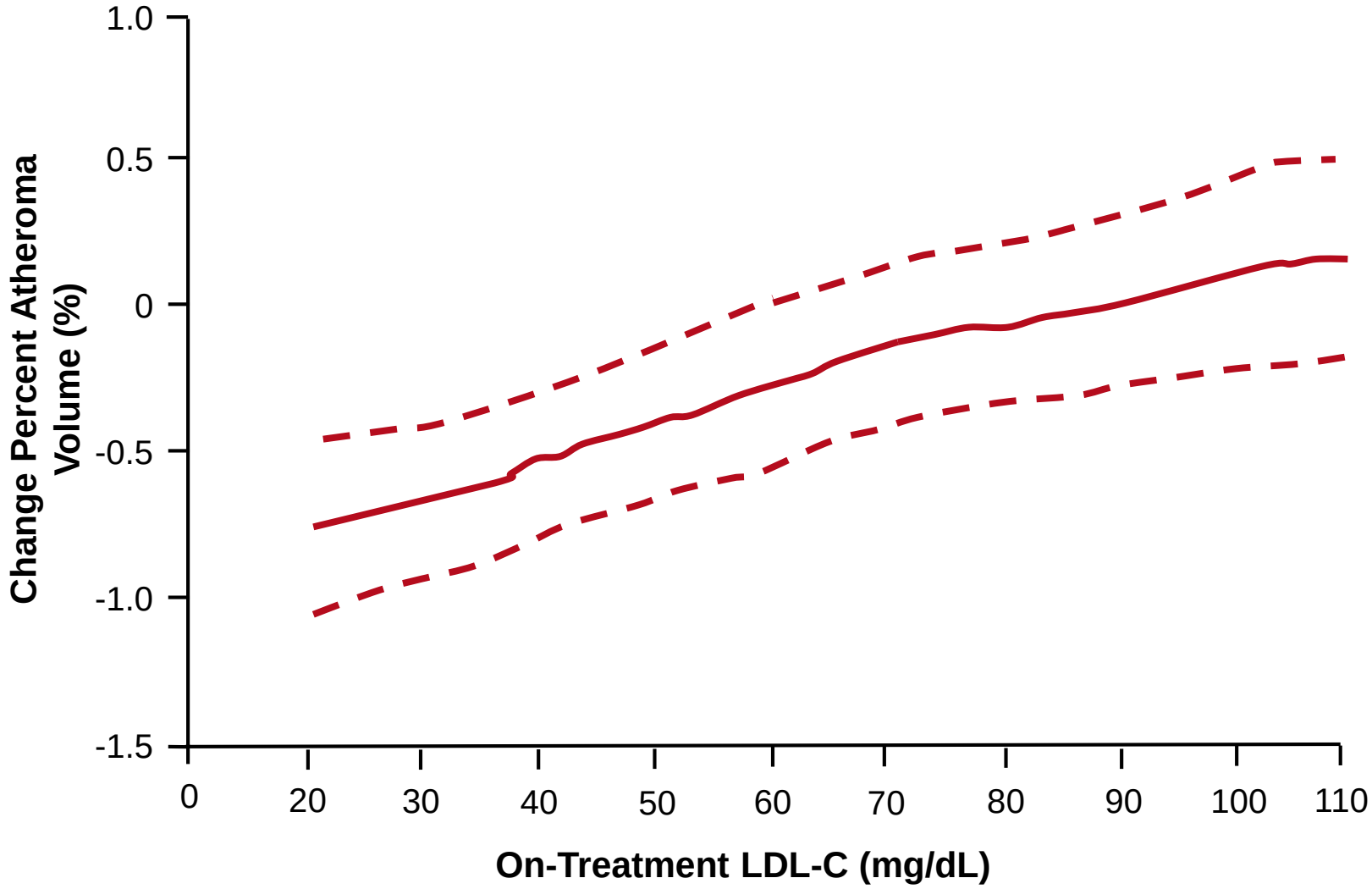
# of Patients								
Placebo	484	446	441	447	441	425	418
Allrocumab	484	456	452	444	449	449	434



Nicholls SJ, et al. *JAMA.* 2016;316(22):2373-2384.

GLAGOV: Evolocumab added to statin

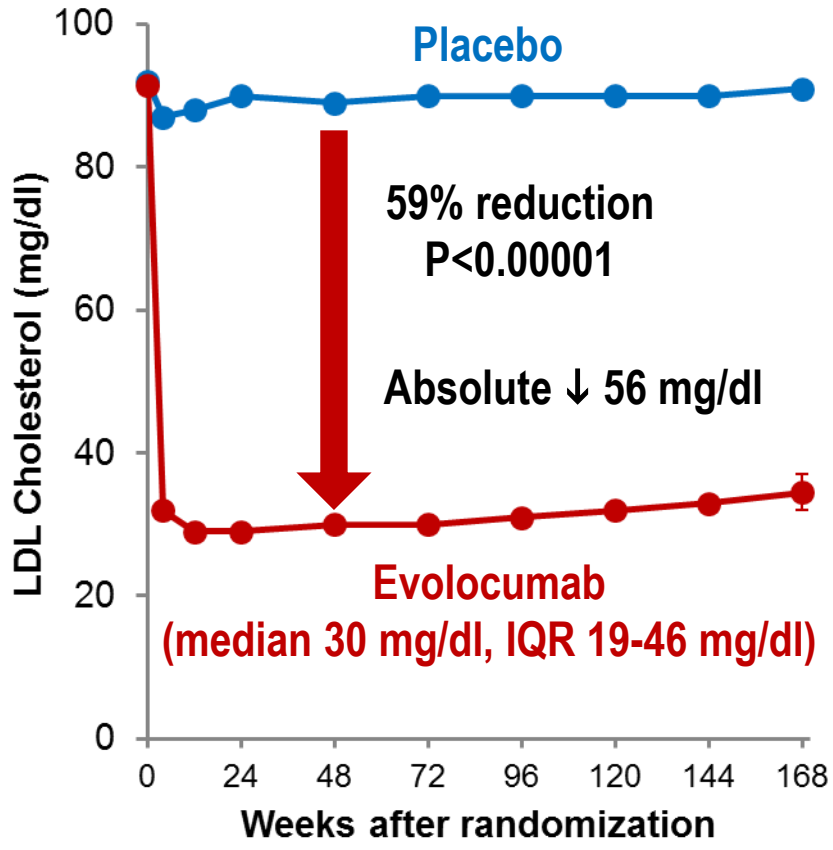
On-treatment LDL-C vs. Regression of Coronary Plaque

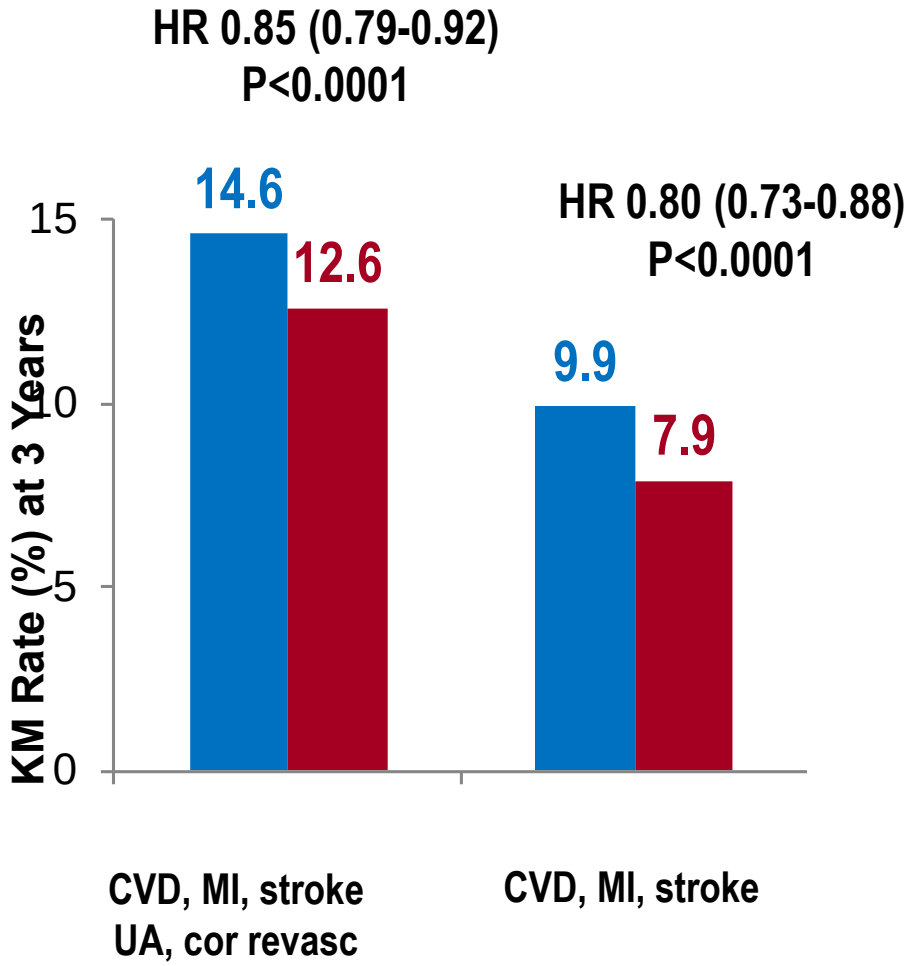


Nicholls SJ, et al. *JAMA.* 2016;316(22):2373-2384.

FOURIER: Effects of PCSK9i Evolocumab

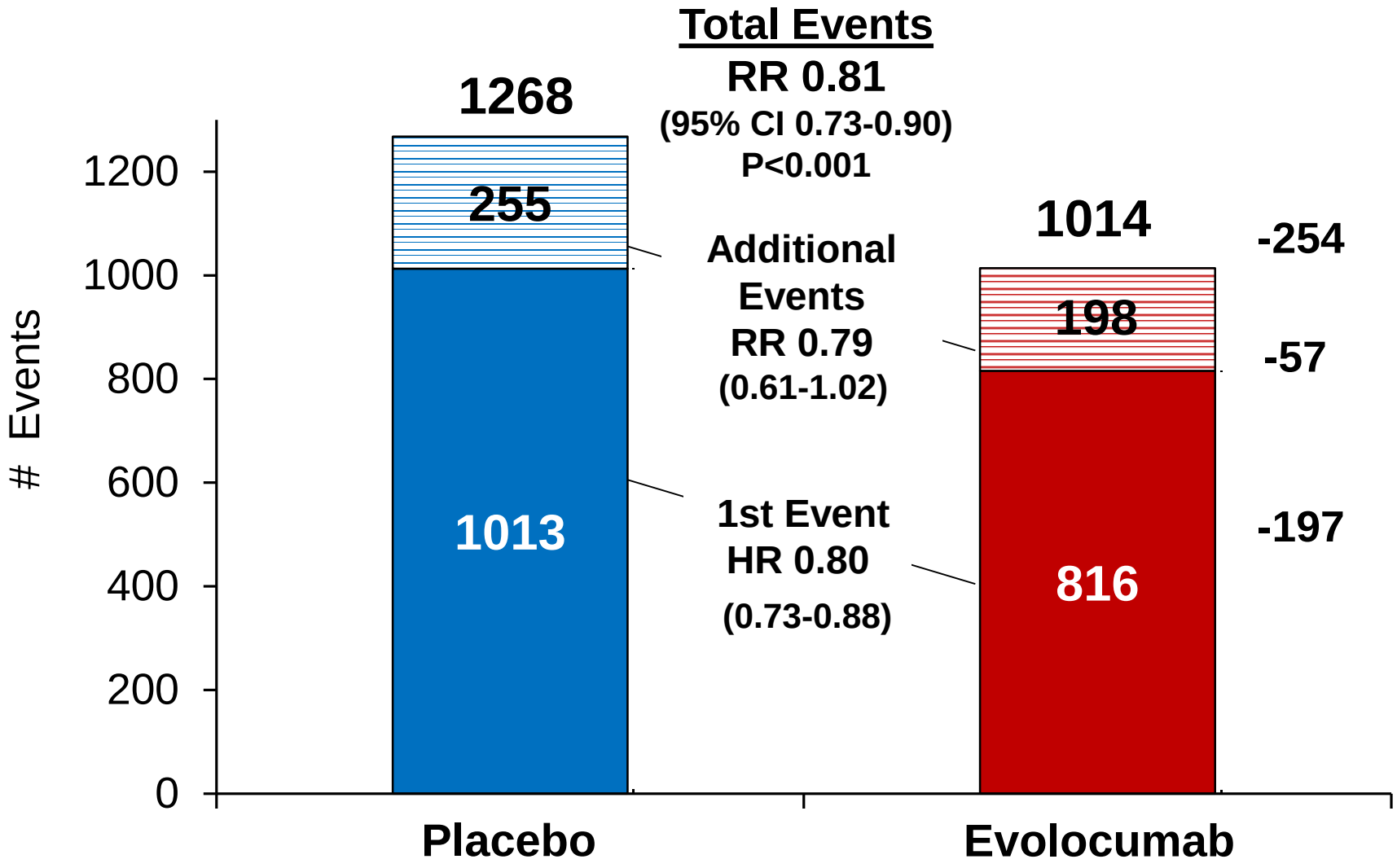
27,564 high-risk, stable patients with established CV disease



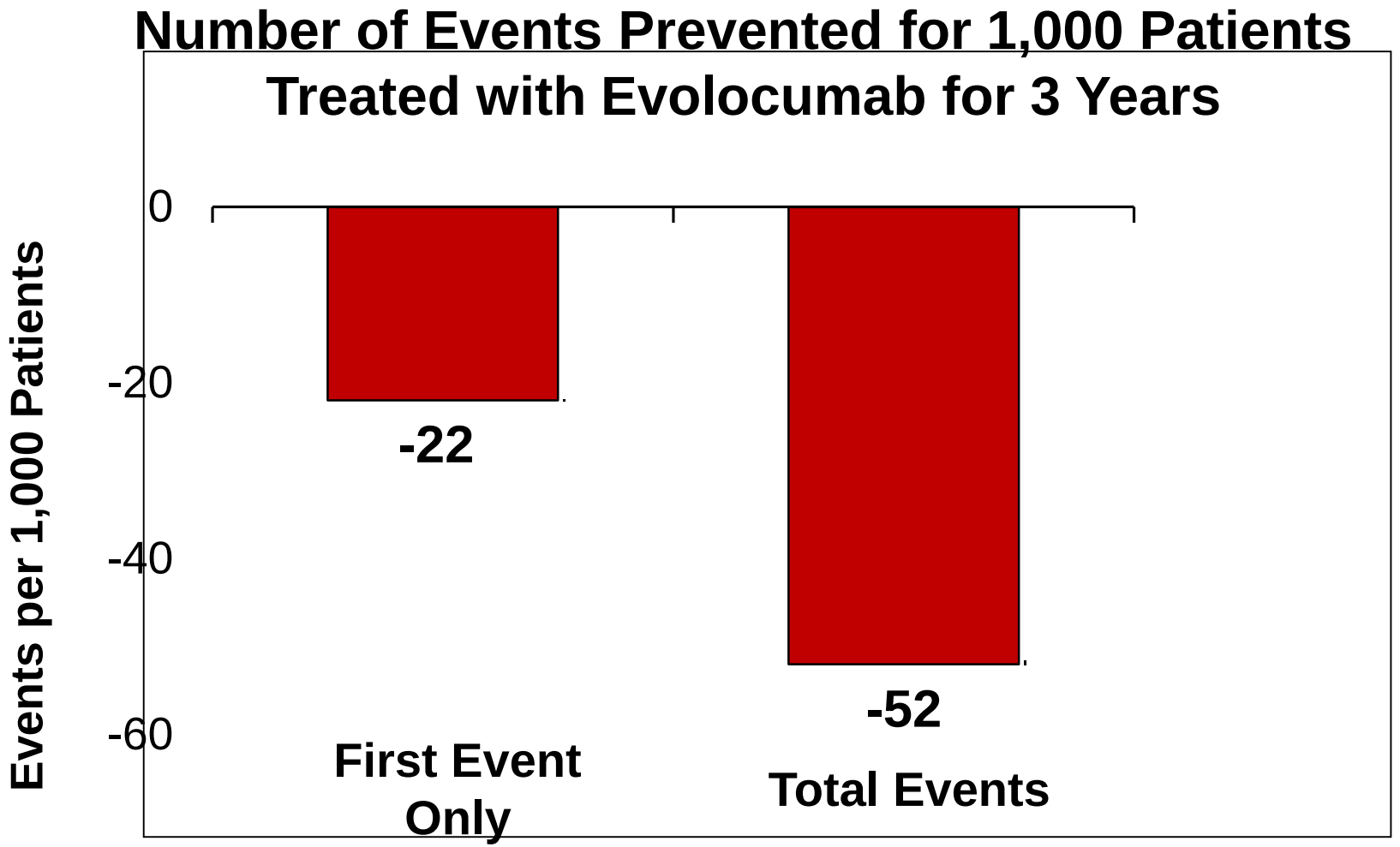


Sabatine MS et al. *NEJM.* 2017; 376: 1713-22.

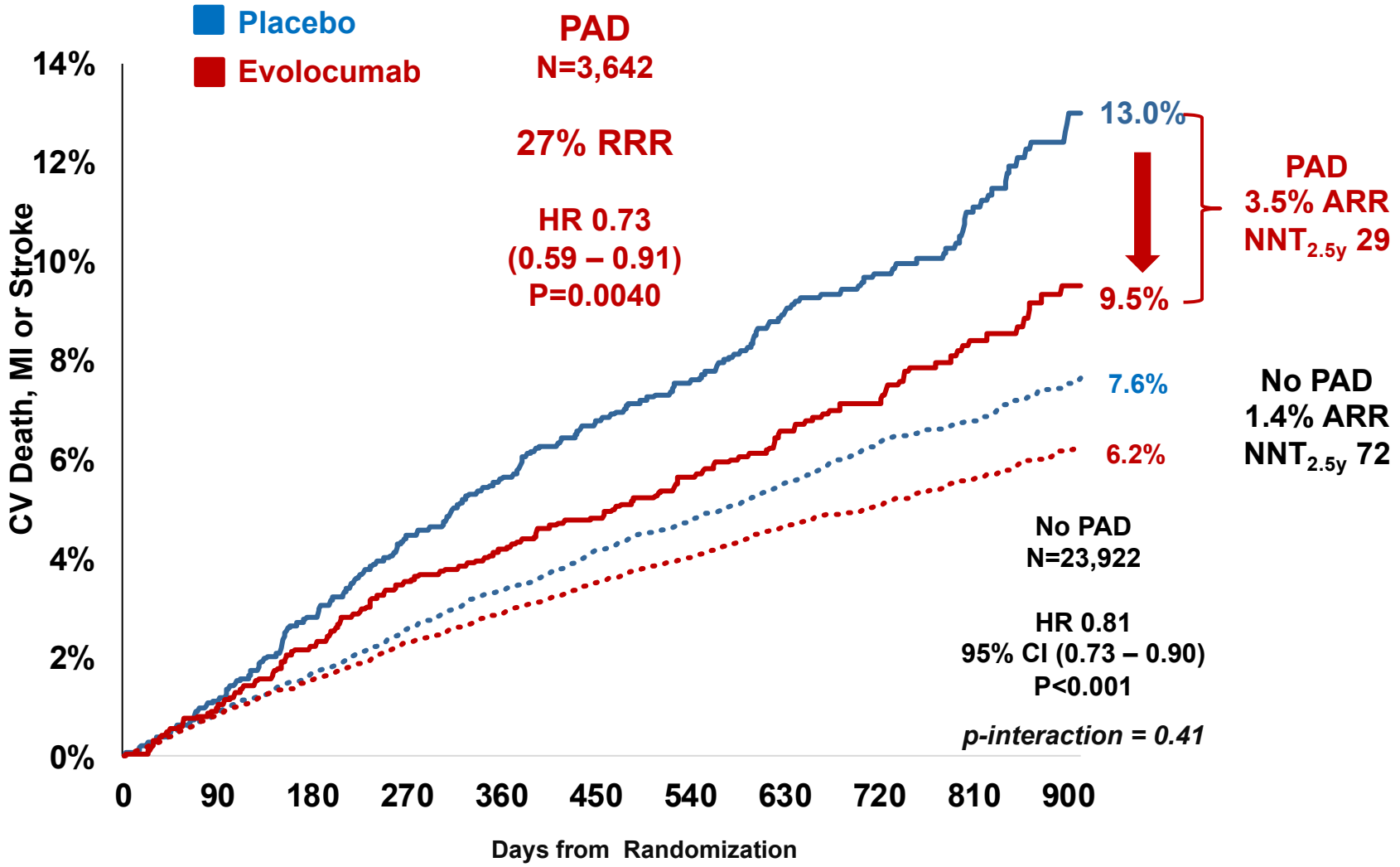
Total Key Secondary EP Events: CVD/MI/Stroke



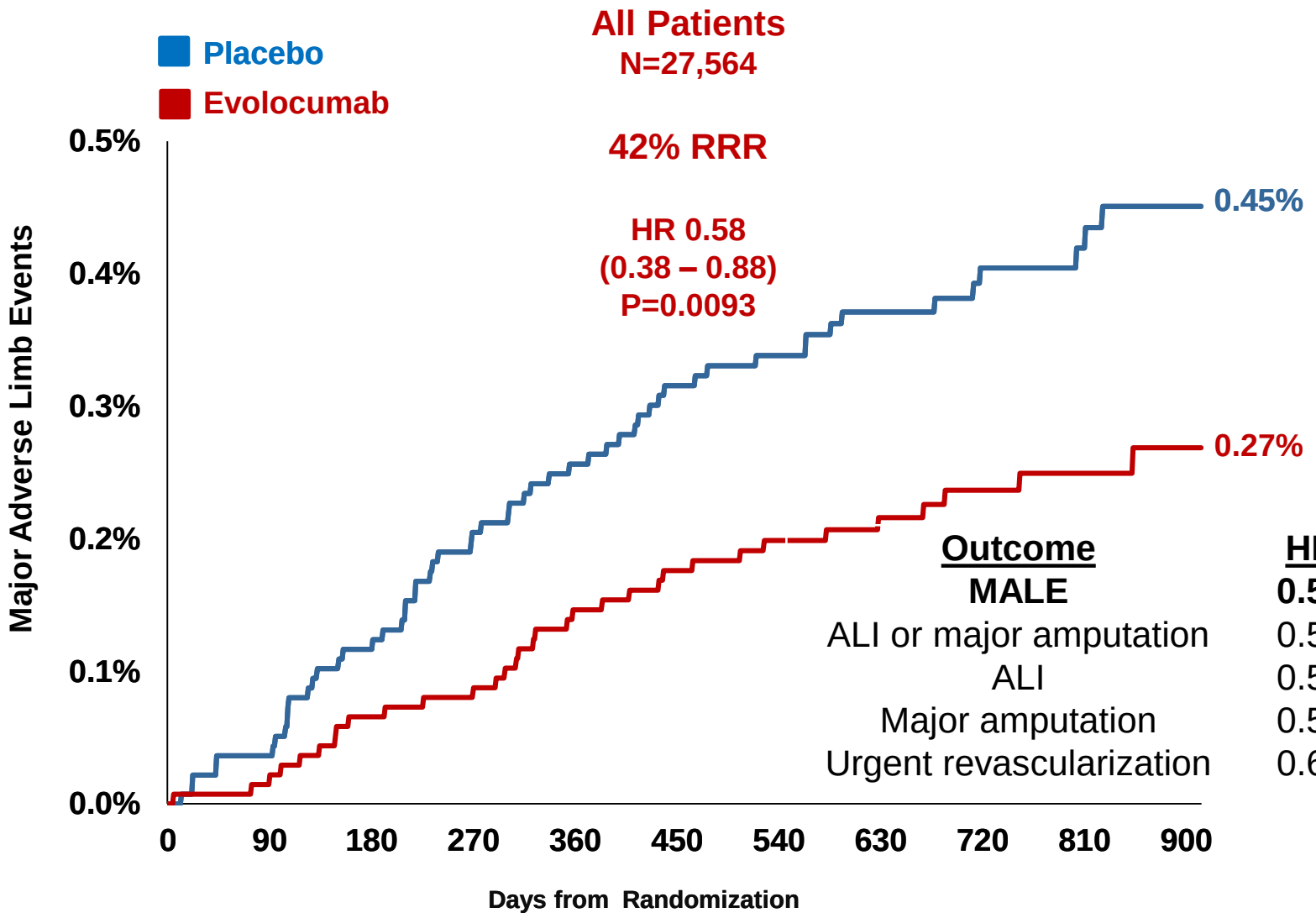
Total Primary Endpoint Events



CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease

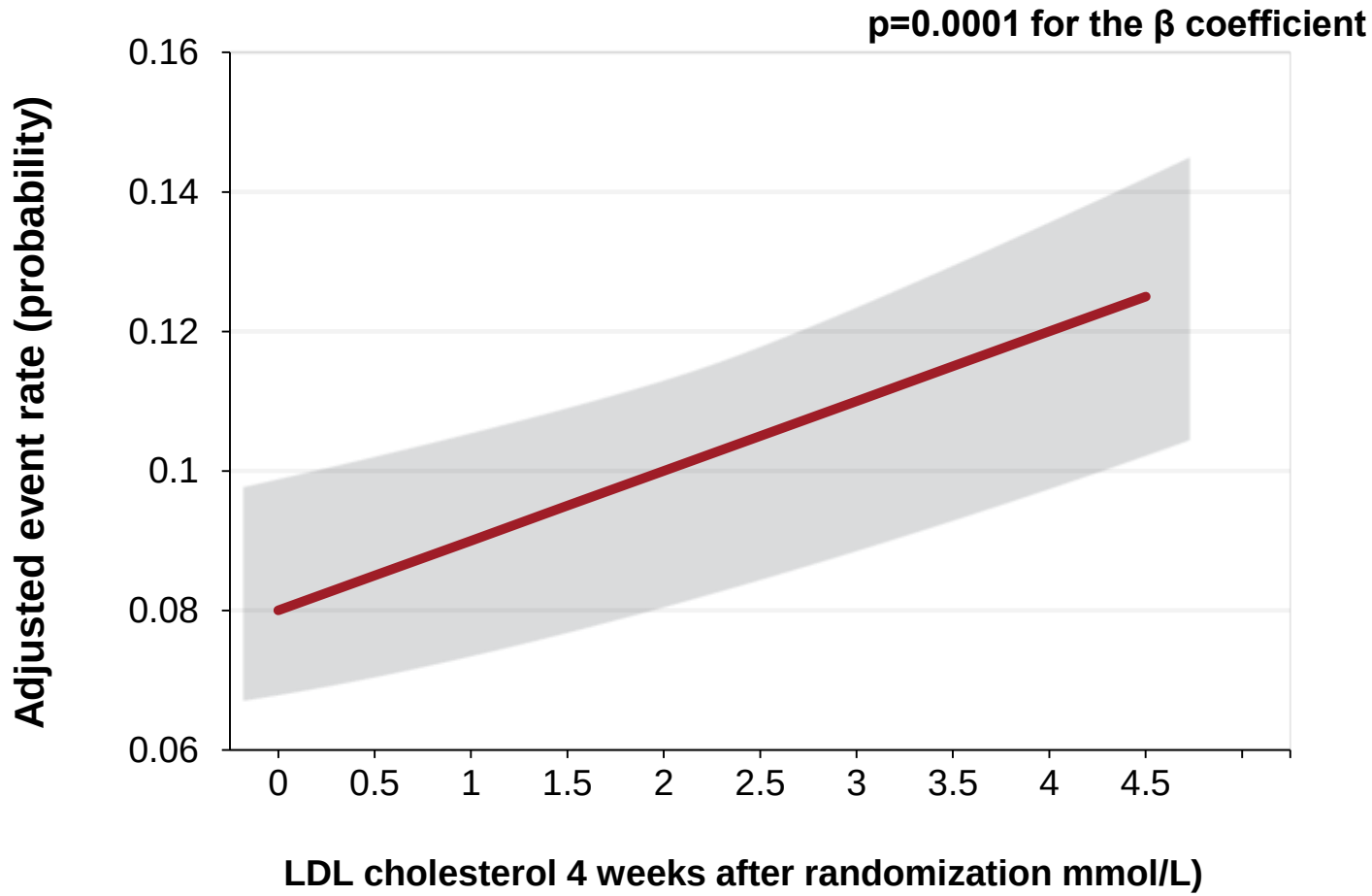


Major Adverse Limb Events



Outcome	HR	95% CI
MALE	**0.58**	**(0.38–0.88)**
ALI or major amputation	0.52	(0.31–0.89)
ALI	0.55	(0.31–0.97)
Major amputation	0.57	(0.17–1.95)
Urgent revascularization	0.69	(0.38–1.26)

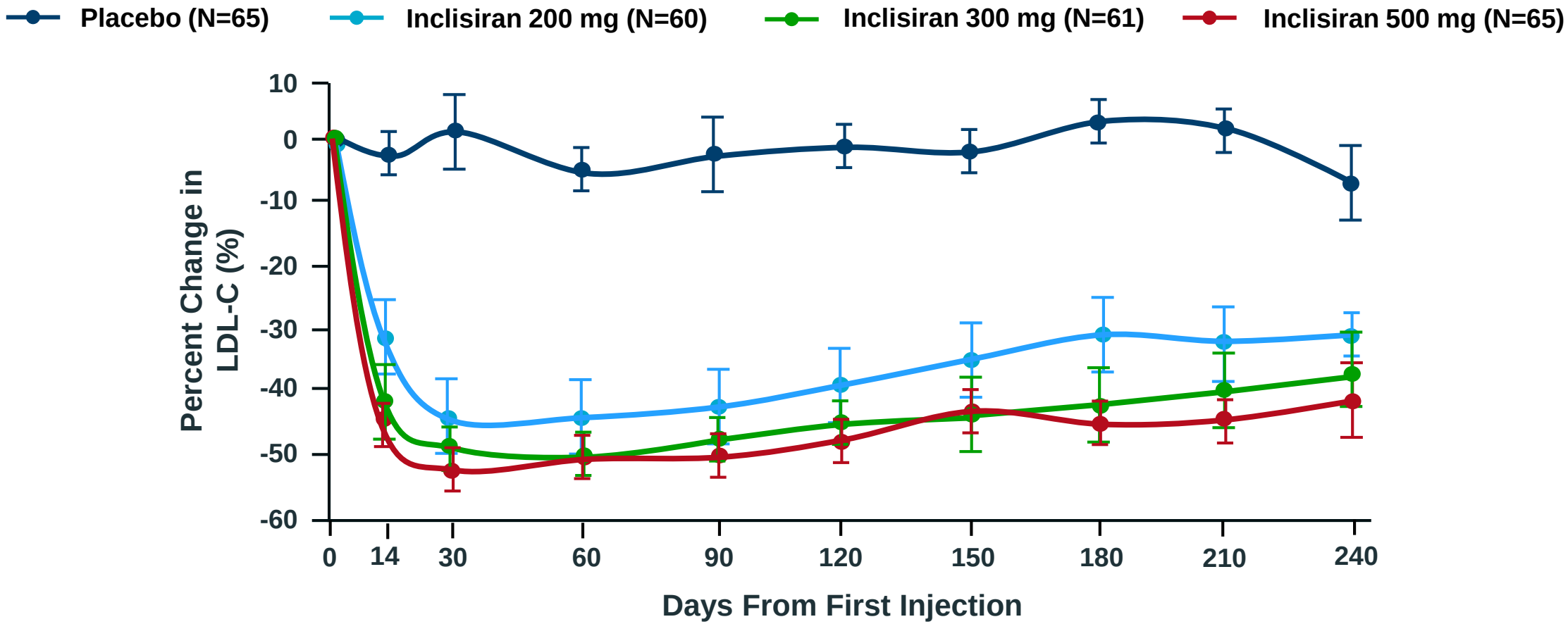
FOURIER – Lower CV Event Rates with Lower LDL-C Levels*, Even Down to 20 mg/dL



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

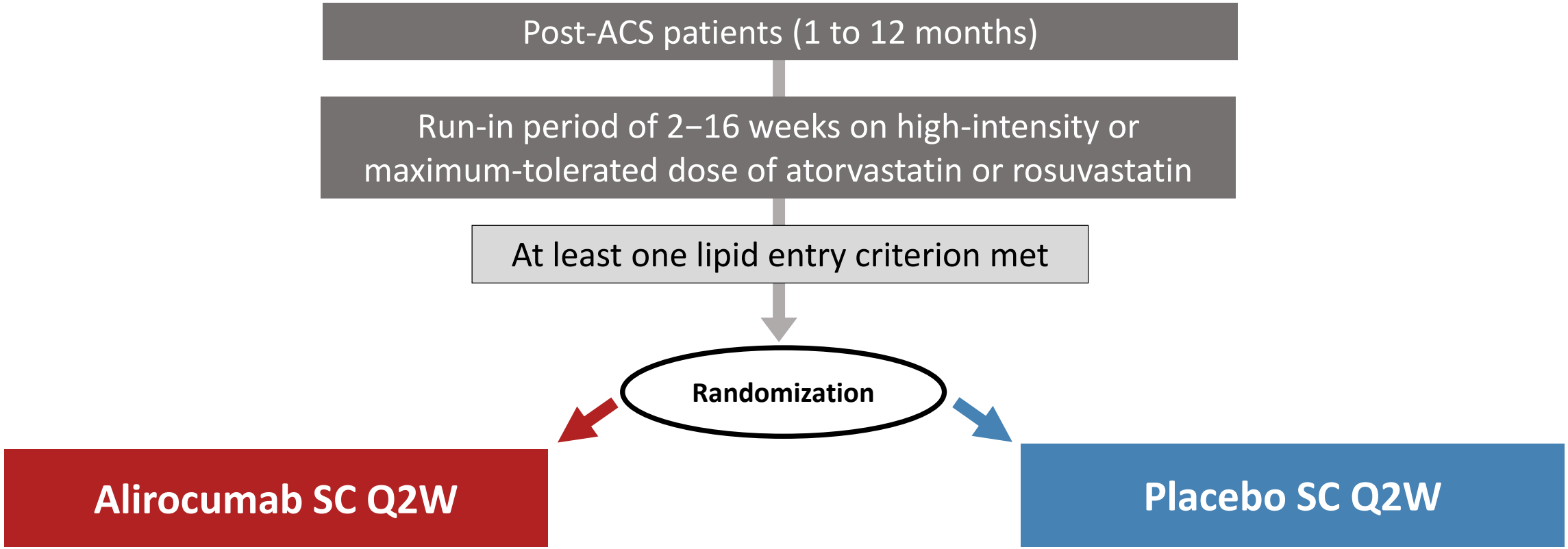
Giugliano RP, et al. *Lancet.* 2017 Aug 25. [Epub ahead of print]

ORION-1: Efficacy of Single-dose Inclisiran in Patients at High CV Risk with Elevated LDL-C



Ray KK, et al. *N Engl J Med.* 2017;376(15):1430-1440.

ODYSSEY OUTCOMES

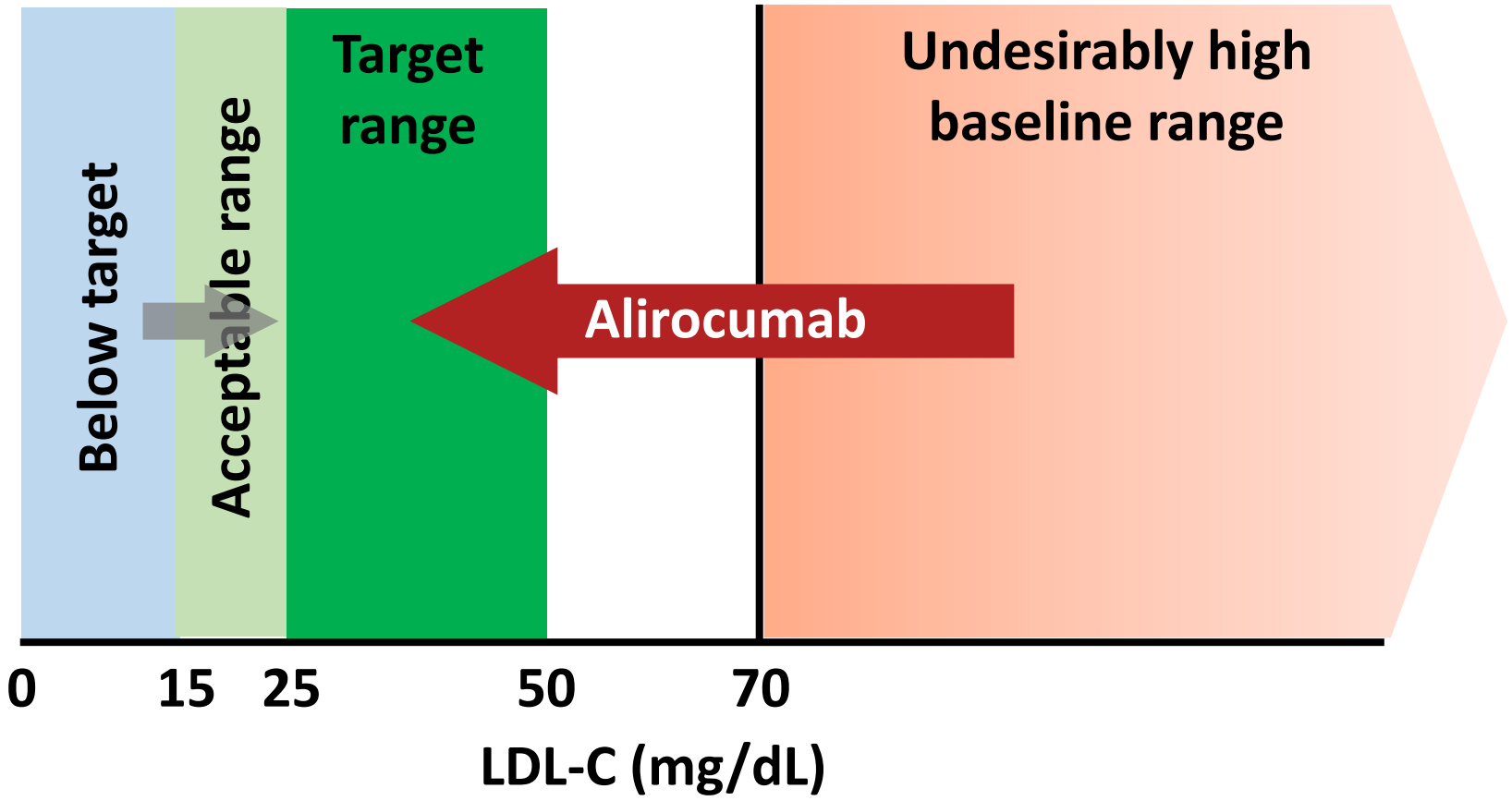


Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

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

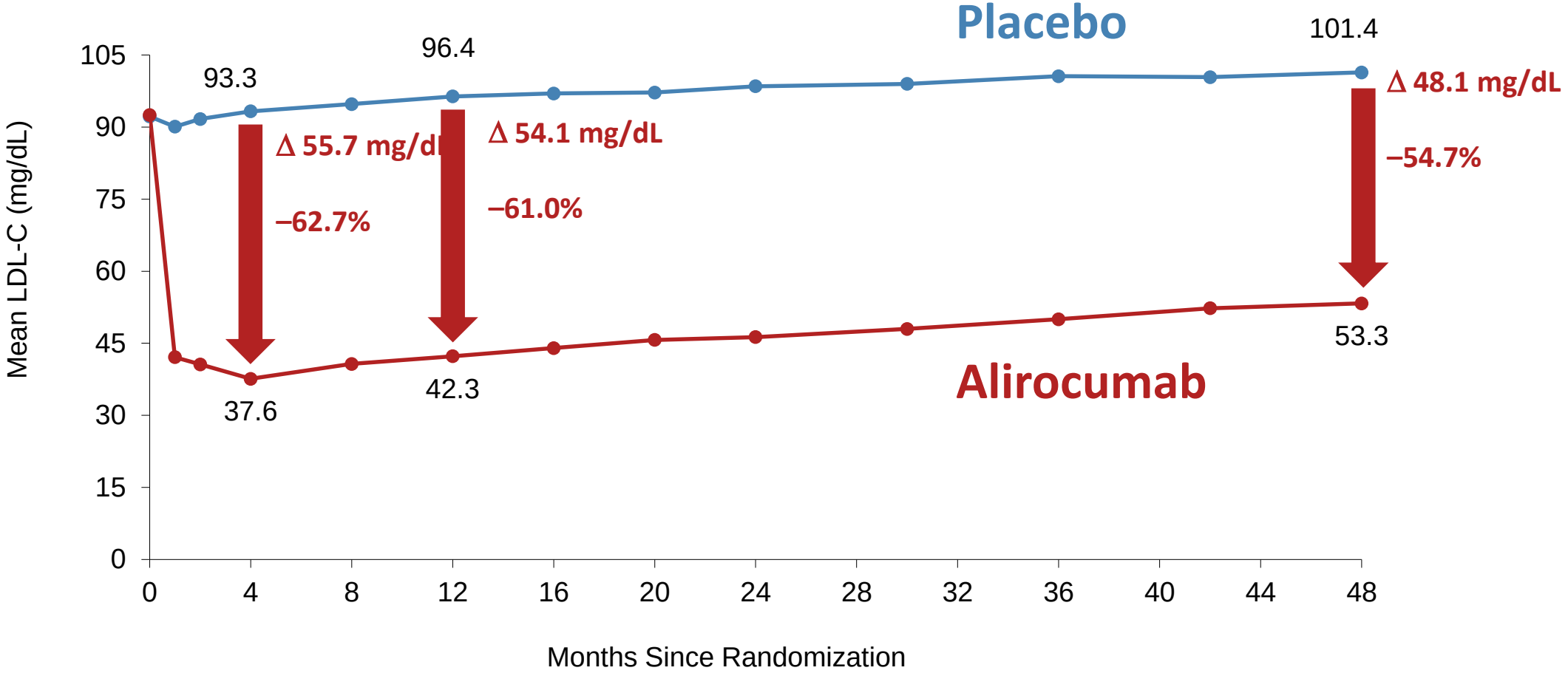
A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



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

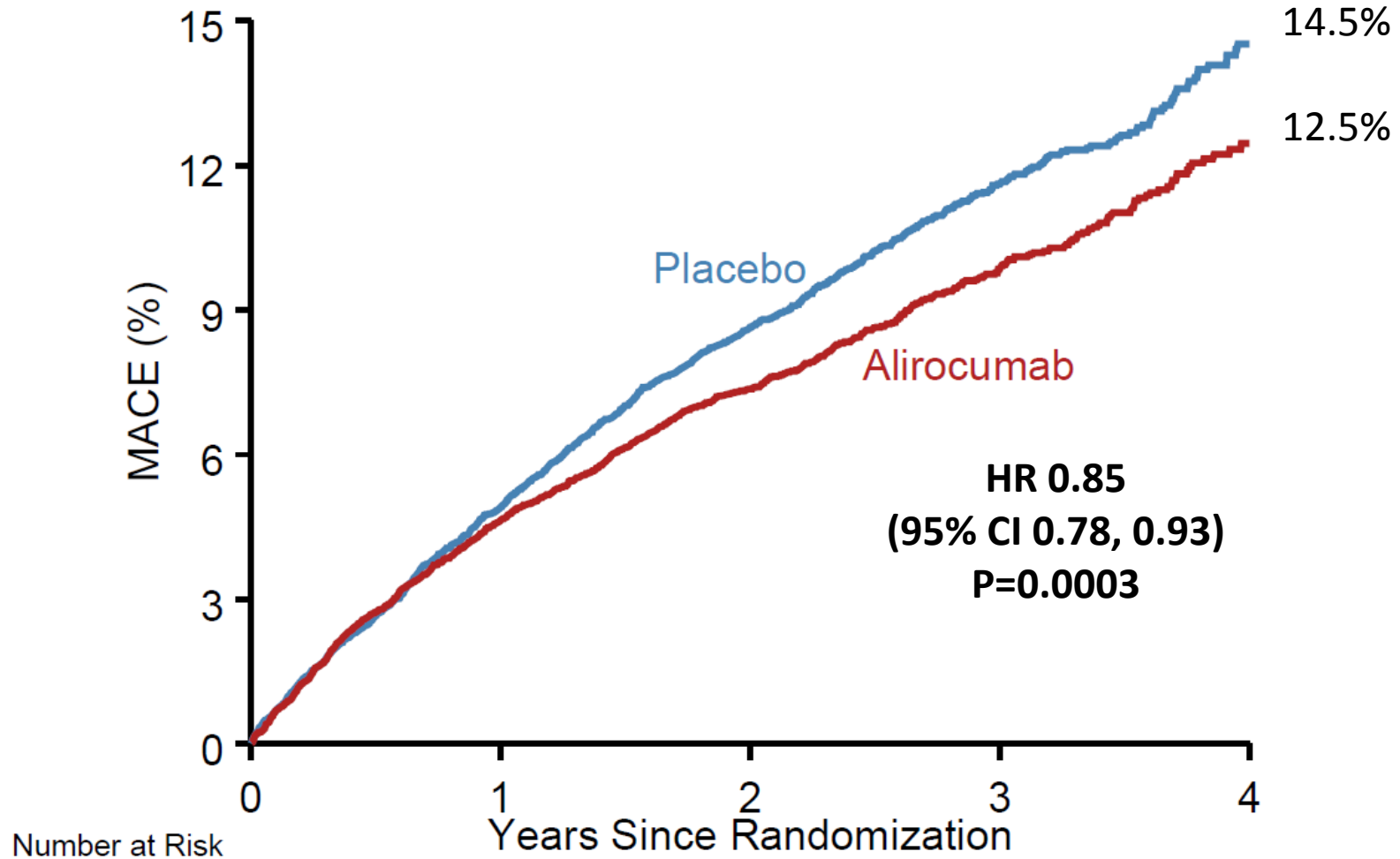
LDL-C: On-Treatment Analysis



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

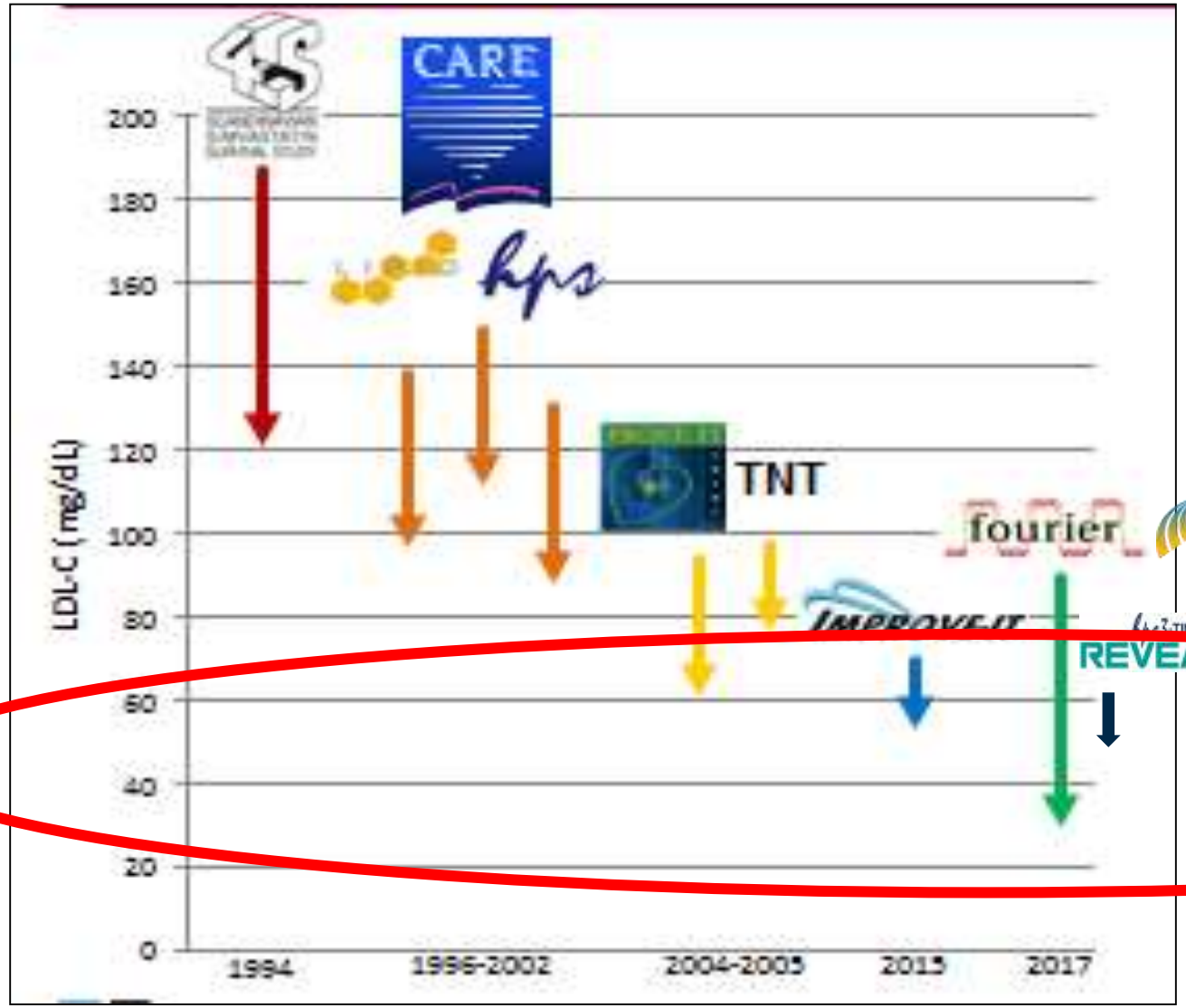
ODYSSEY OUTCOMES

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
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***

ODYSSEY OUTCOMES

LDL-C Levels for Optimal CV Risk Reduction: What We Know Now



High is bad

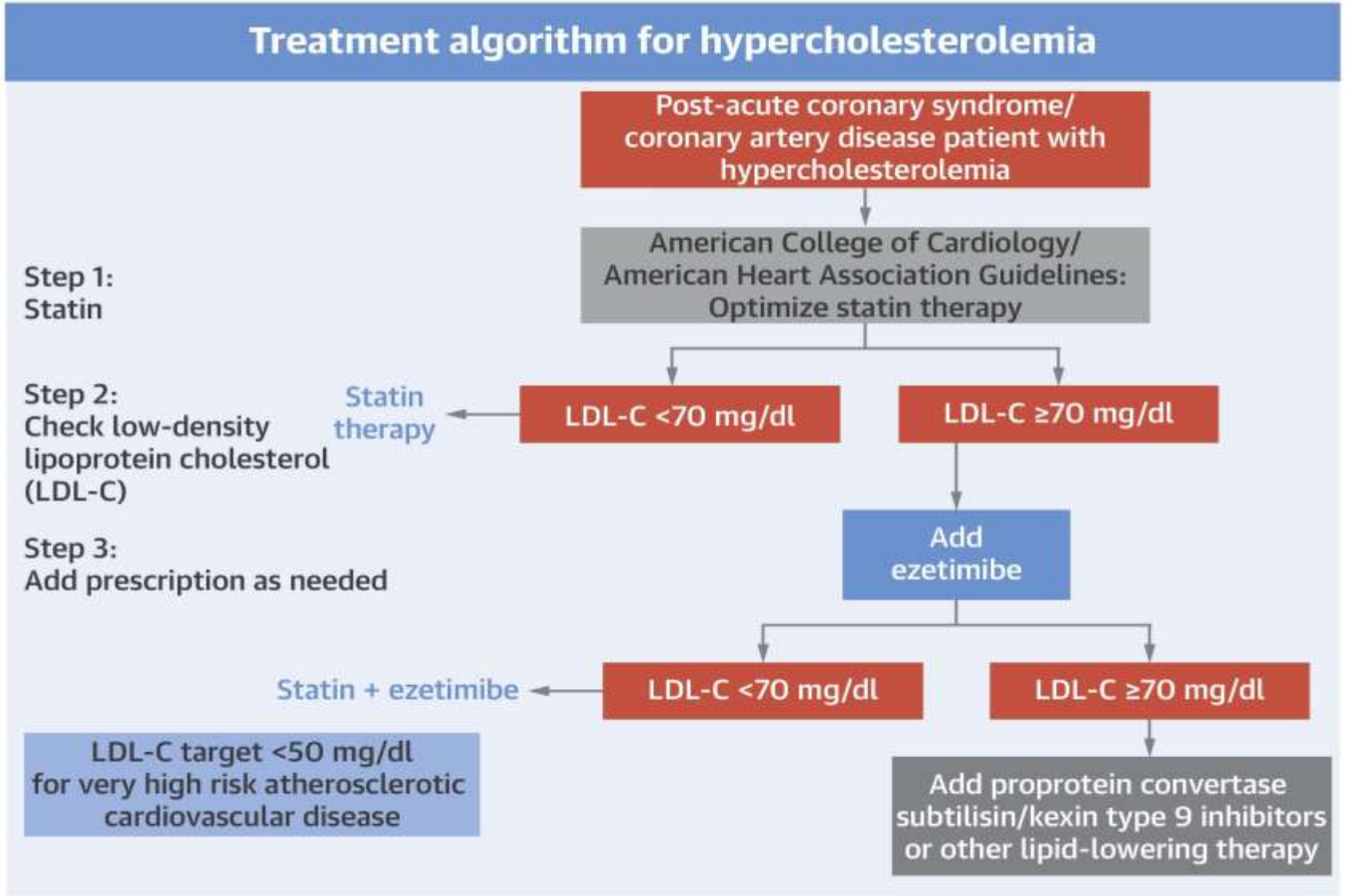
Average is not good

Lower is better

Even lower is even better

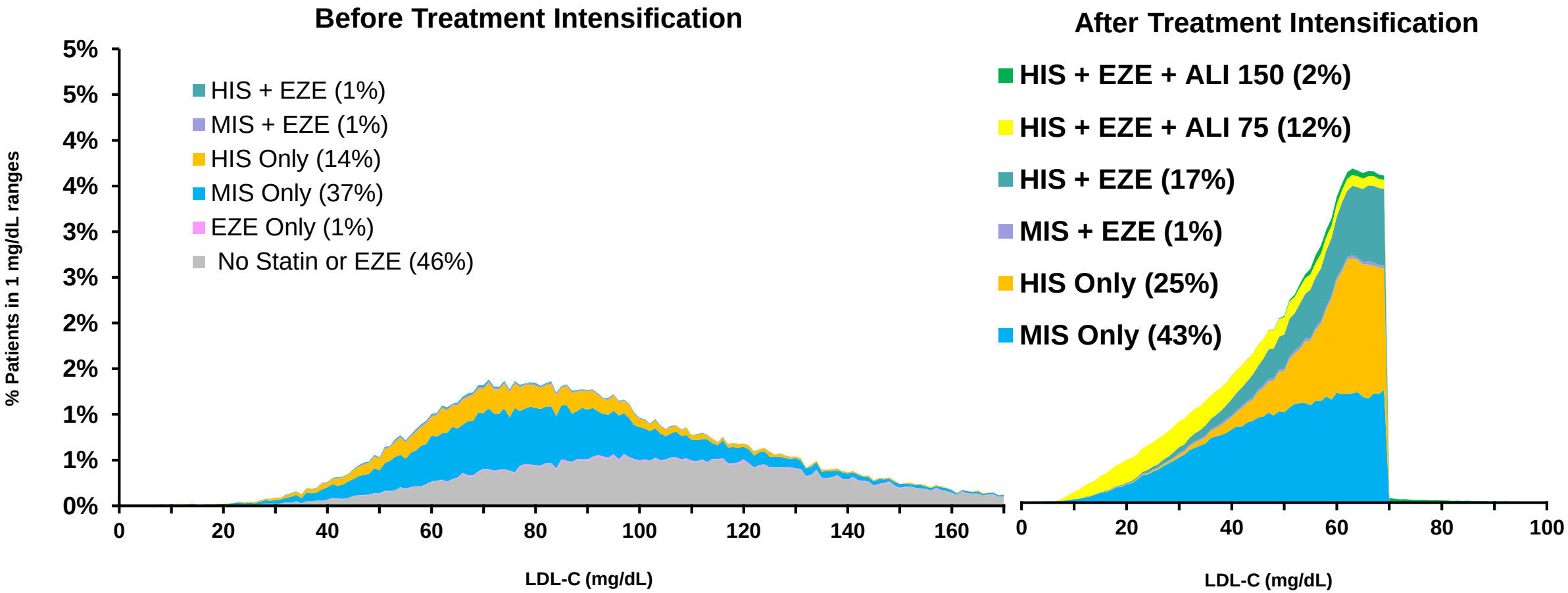
Lowest is best

CENTRAL ILLUSTRATION: Clinical Algorithm for Managing Low-Density Lipoprotein Cholesterol



Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314–29.

Results: LDL-C Distribution and LLT Utilization at Baseline and after Full Treatment Intensification



ALI 75 = alirocumab 75 mg; ALI 150 = alirocumab 150 mg; EZE = ezetimibe; HIS = high-intensity statin; MIS = moderate- to low-intensity statin.

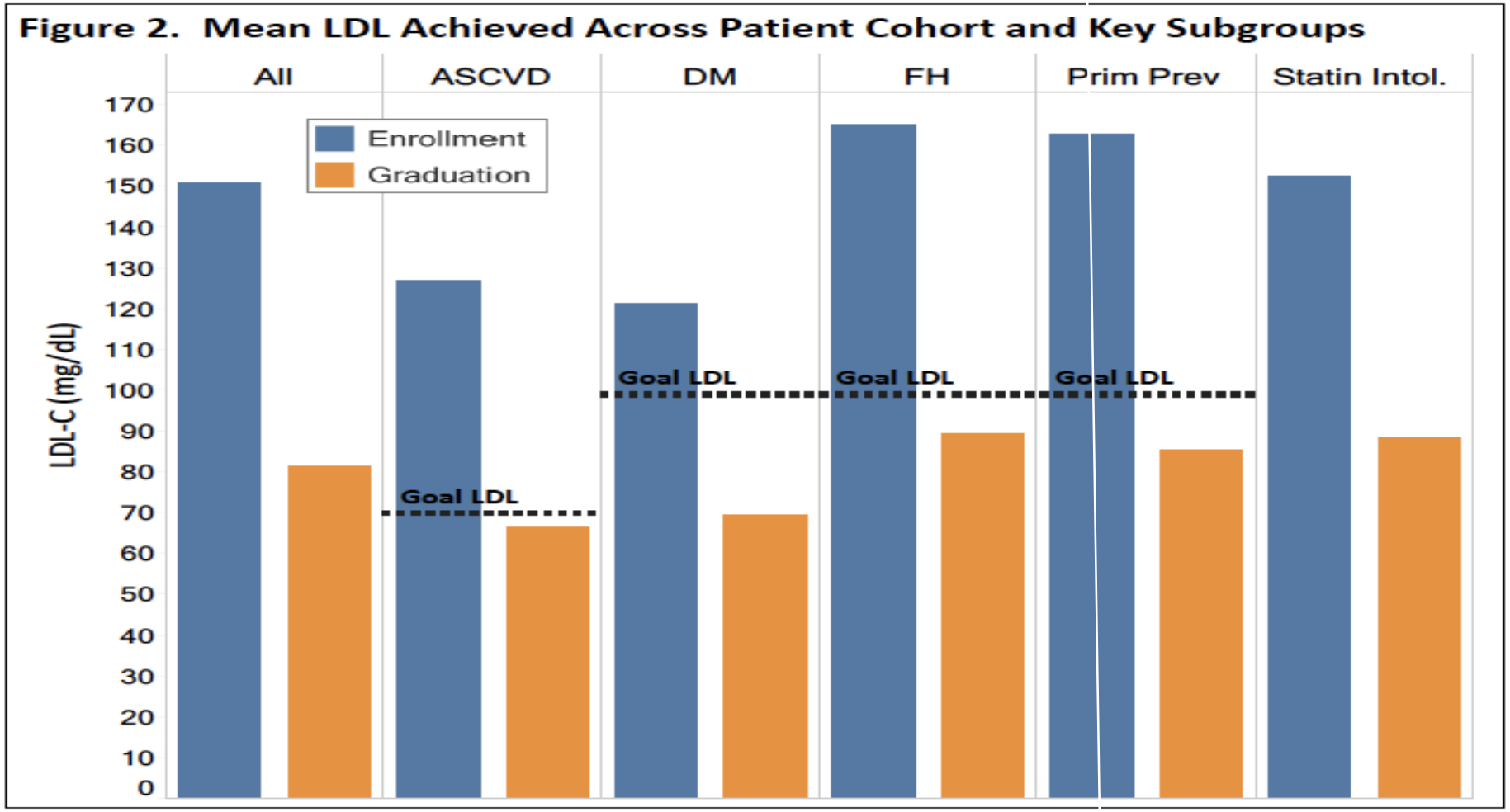
Cannon CP, Khan I, et al. *JAMA Cardiol.* 2017 Aug 2. [Epub ahead of print]

Implementation

Recommendations for Implementation		
COR	**LOE**	**Recommendations**
I	A	Interventions focused on improving adherence to prescribed therapy are recommended for management of adults with elevated cholesterol levels, including telephone reminders, calendar reminders, integrated multidisciplinary educational activities, and pharmacist-led interventions, such as simplification of the drug regimen to once-daily dosing.
I	B-NR	Clinicians, health systems, and health plans should identify patients who are not receiving guideline-directed medical therapy and should facilitate the initiation of appropriate guideline-directed medical therapy, using multifaceted strategies to improve guideline implementation.
I	B-NR	Before therapy is prescribed, a patient-clinician discussion should take place to promote shared decision-making and should include the potential for ASCVD risk-reduction benefit, adverse effects, drug-drug interactions, and patient preferences.

Brigham Lipid Optimization (B-LO) Program

- **1012 pts with high ASCVD risk**
- **Remote management program executed by non-physician navigators with physician oversight and decision- support software utilizing**



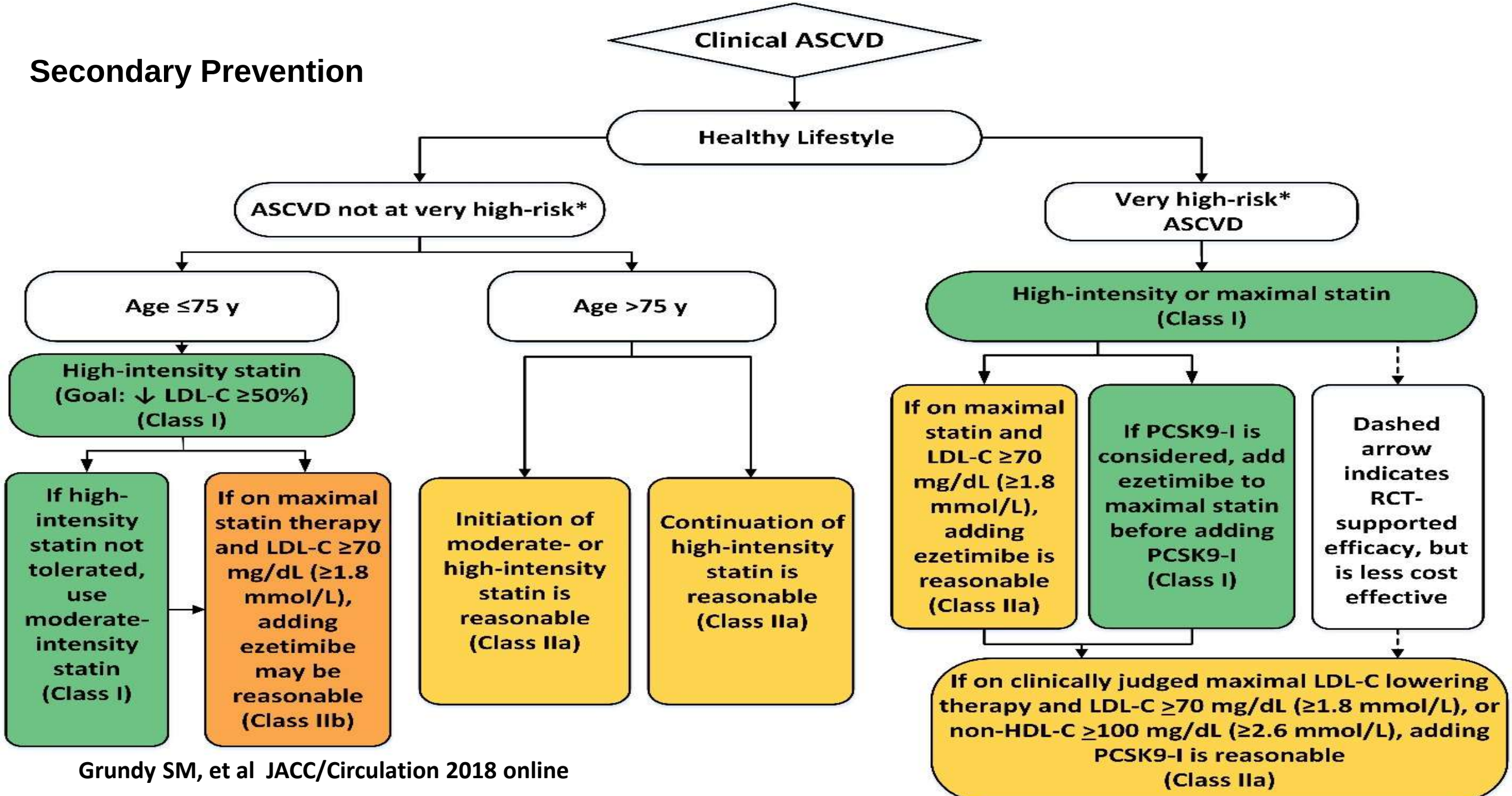
Patient satisfaction with program (scale 0-10):

- *10 - 77%*
- *9 – 8%*
- *8 – 8 %*

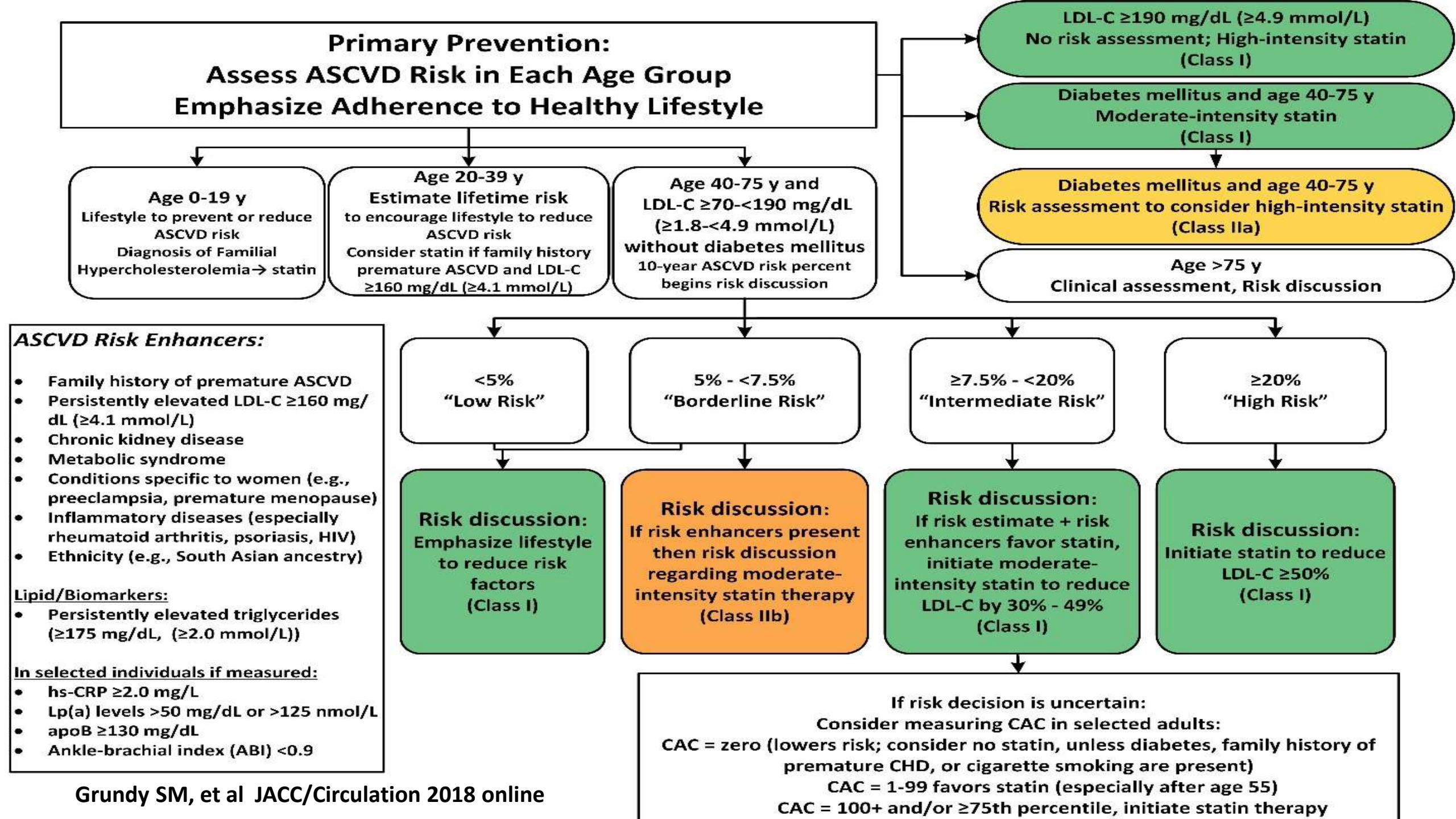
Benson M, Plutzky J, et al. ACC.18

2018 ACC/AHA Cholesterol Guidelines

Secondary Prevention

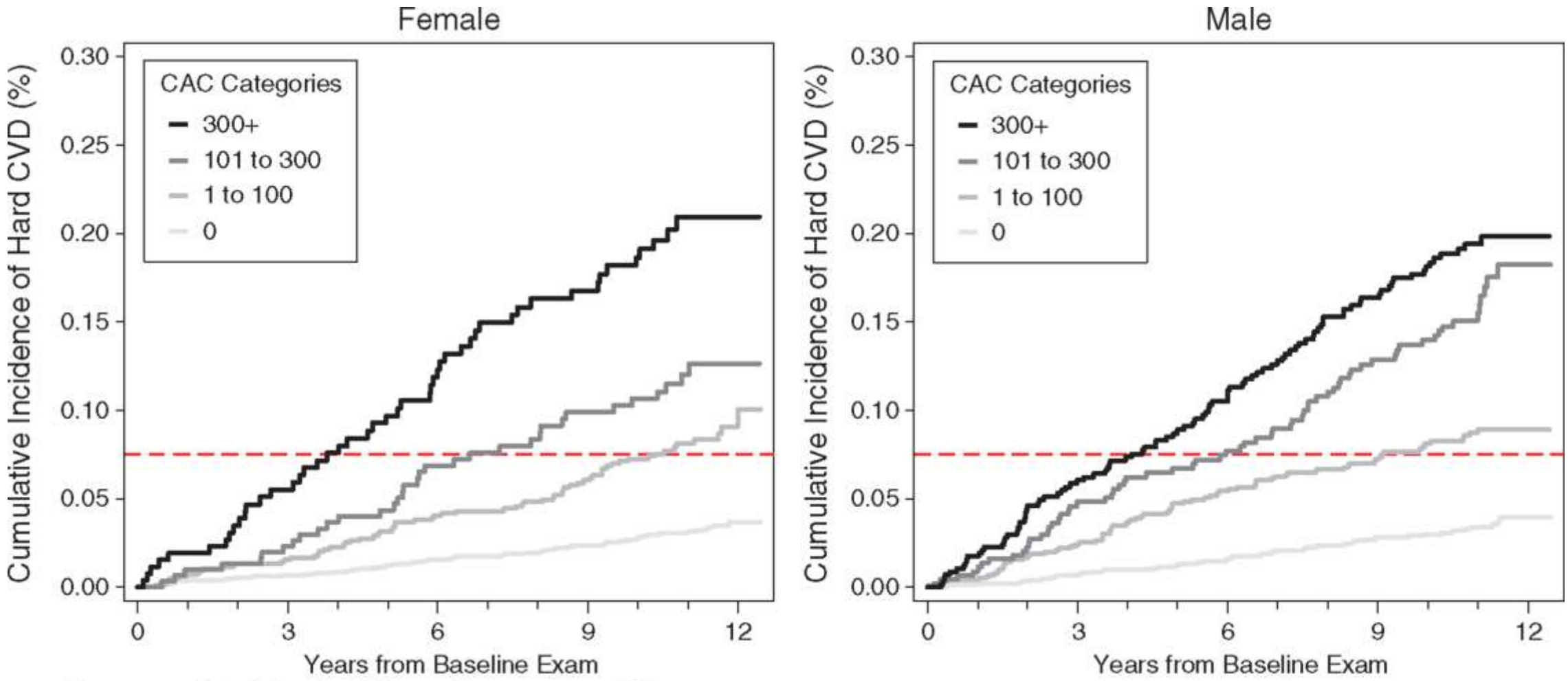


Grundy SM, et al JACC/Circulation 2018 online



Grundy SM, et al JACC/Circulation 2018 online

Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: (MESA)



N=6,783. Red dashed line shows 7.5% risk.

Budoff MJ et al. EHJ 2018;39, 2401–2408,

European Atherosclerosis Society Consensus Panel: Adverse effects of statin therapy: perception vs. the evidence

ESC European Society of Cardiology

Highly favourable Benefit / Risk Ratio for statin therapy

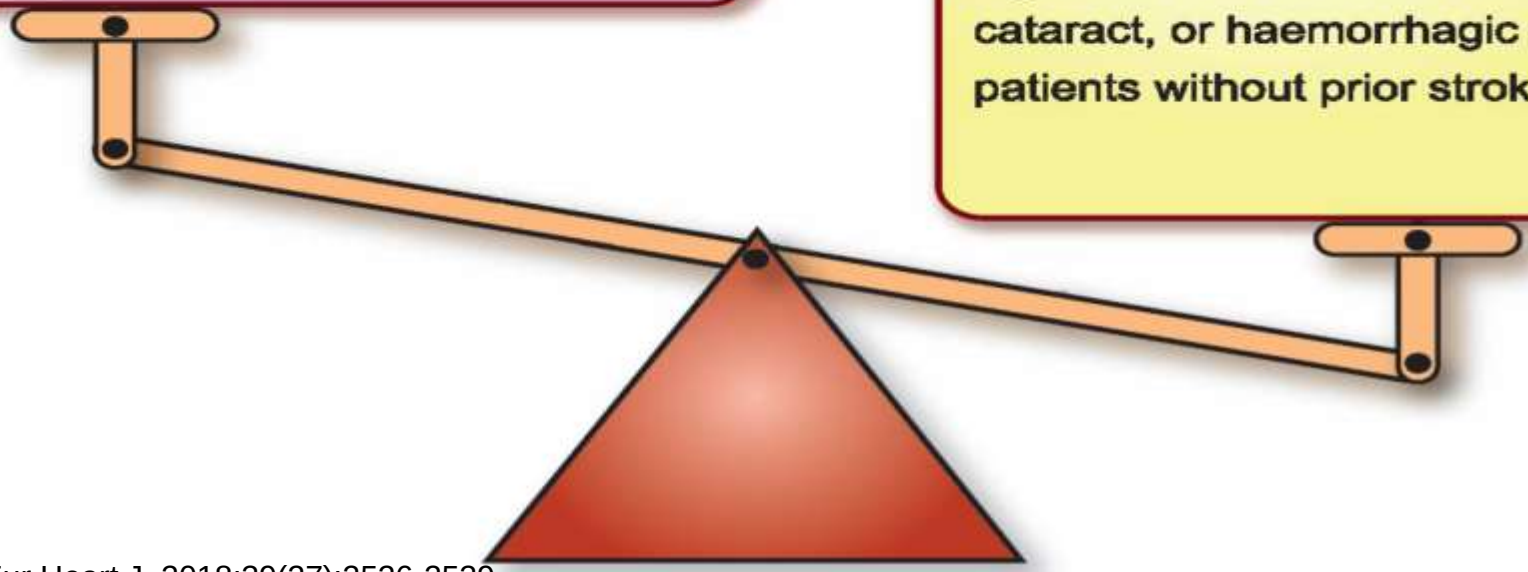
POTENTIAL RISKS

- Modest risk of new-onset diabetes (~0.1% annually), higher in those with the metabolic syndrome cluster
- Muscle symptoms, but be aware of the nocebo effect
- Very rarely, clinically relevant liver injury
- Possible increase in risk of haemorrhagic stroke in patients with a prior stroke suggested by SPARCL; not confirmed in the substantive evidence base of RCTs, cohort and case-control studies

BENEFITS

- **Reduction in LDL-C levels**
- **Regression of coronary atheroma**
- **Reduction in ASCVD events**

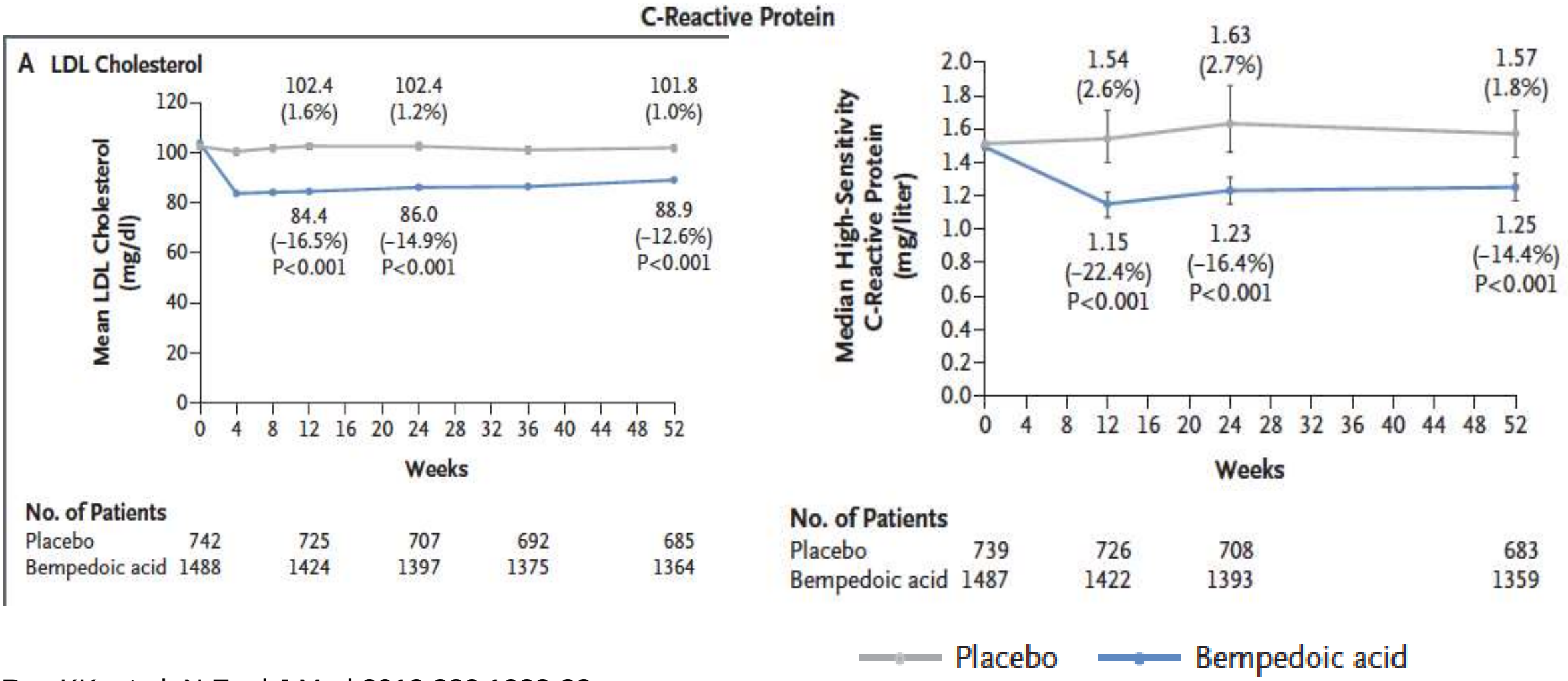
No evidence to support adverse effects of statins on cognitive function, clinically significant renal deterioration, or risk for cataract, or haemorrhagic stroke in patients without prior stroke



Mach F, et al. Eur Heart J. 2018;39(27):2526-2539.

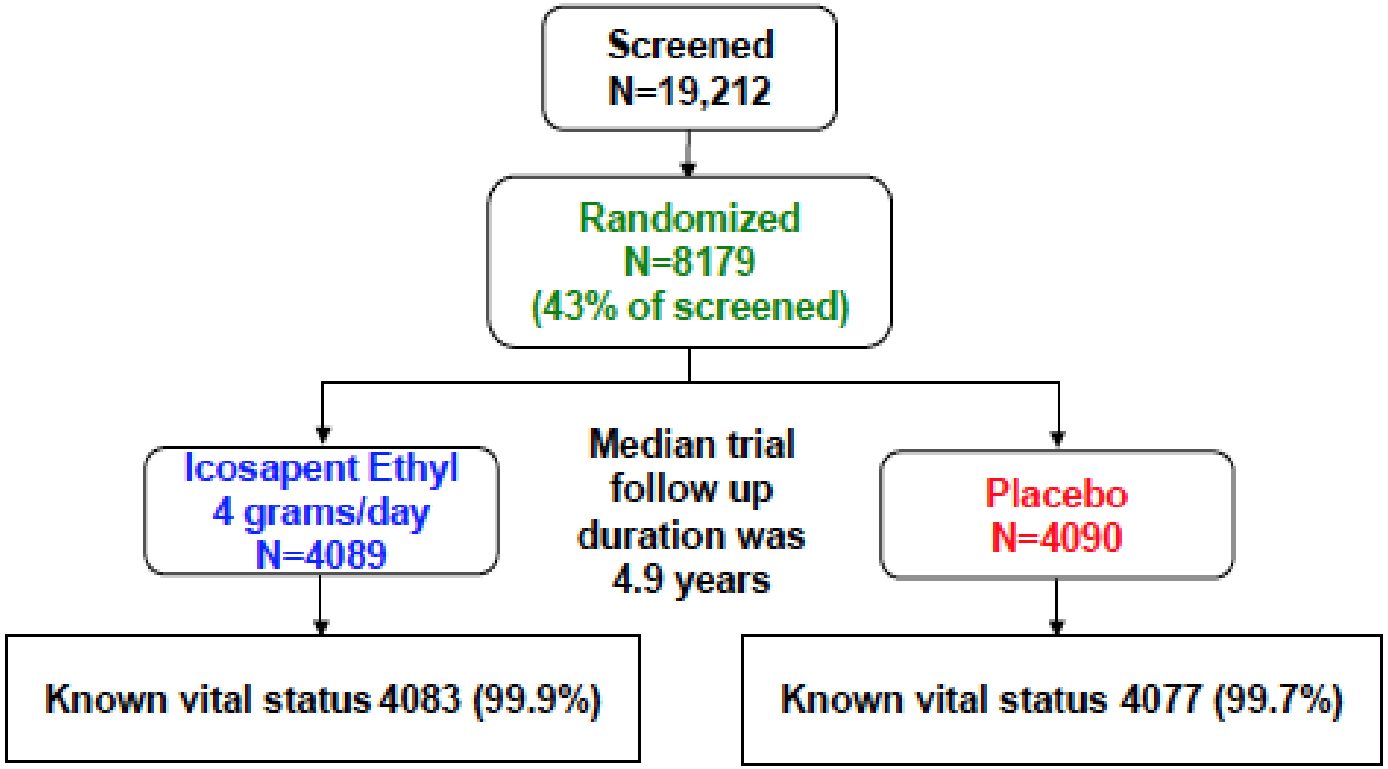
The NEW ENGLAND JOURNAL of MEDICINE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol



Ray KK, et al. N Engl J Med 2019;380:1022-32.

REDUCE-IT Design



1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥135 mg/dL and <500 mg/dL
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

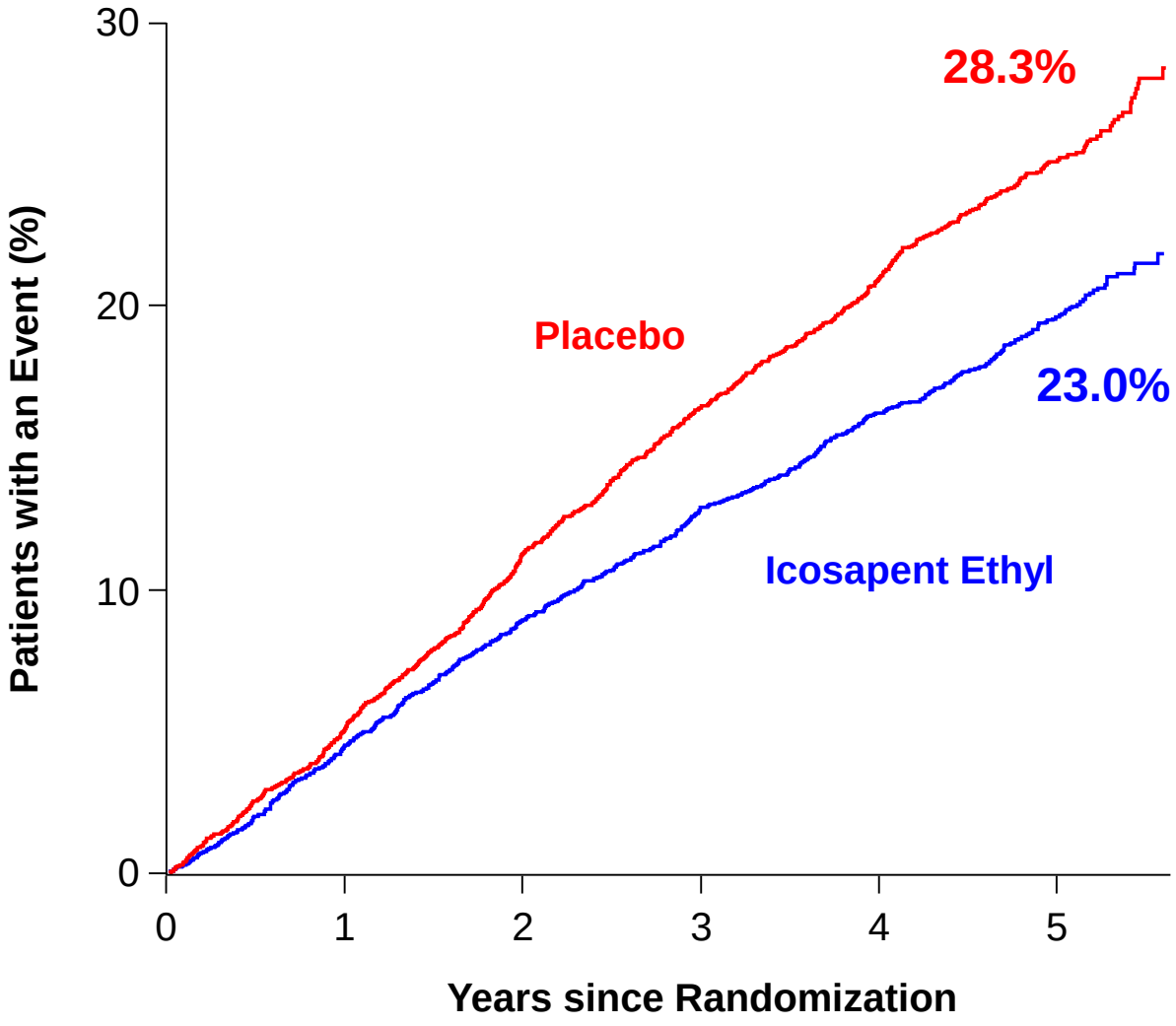
Key Secondary Endpoint Events: CV death, nonfatal MI, nonfatal stroke

Double-blind study; Events adjudicated by CEC that was blinded to treatment during adjudication

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019; 380:11-22.

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

ARR = 4.8%

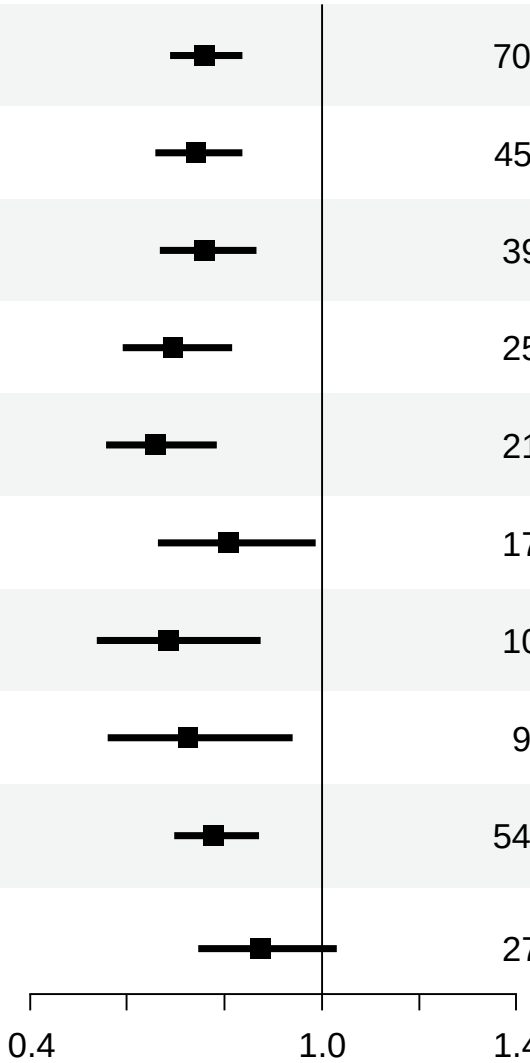
NNT = 21 (95% CI, 15–33)

P=0.00000001

!!

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing



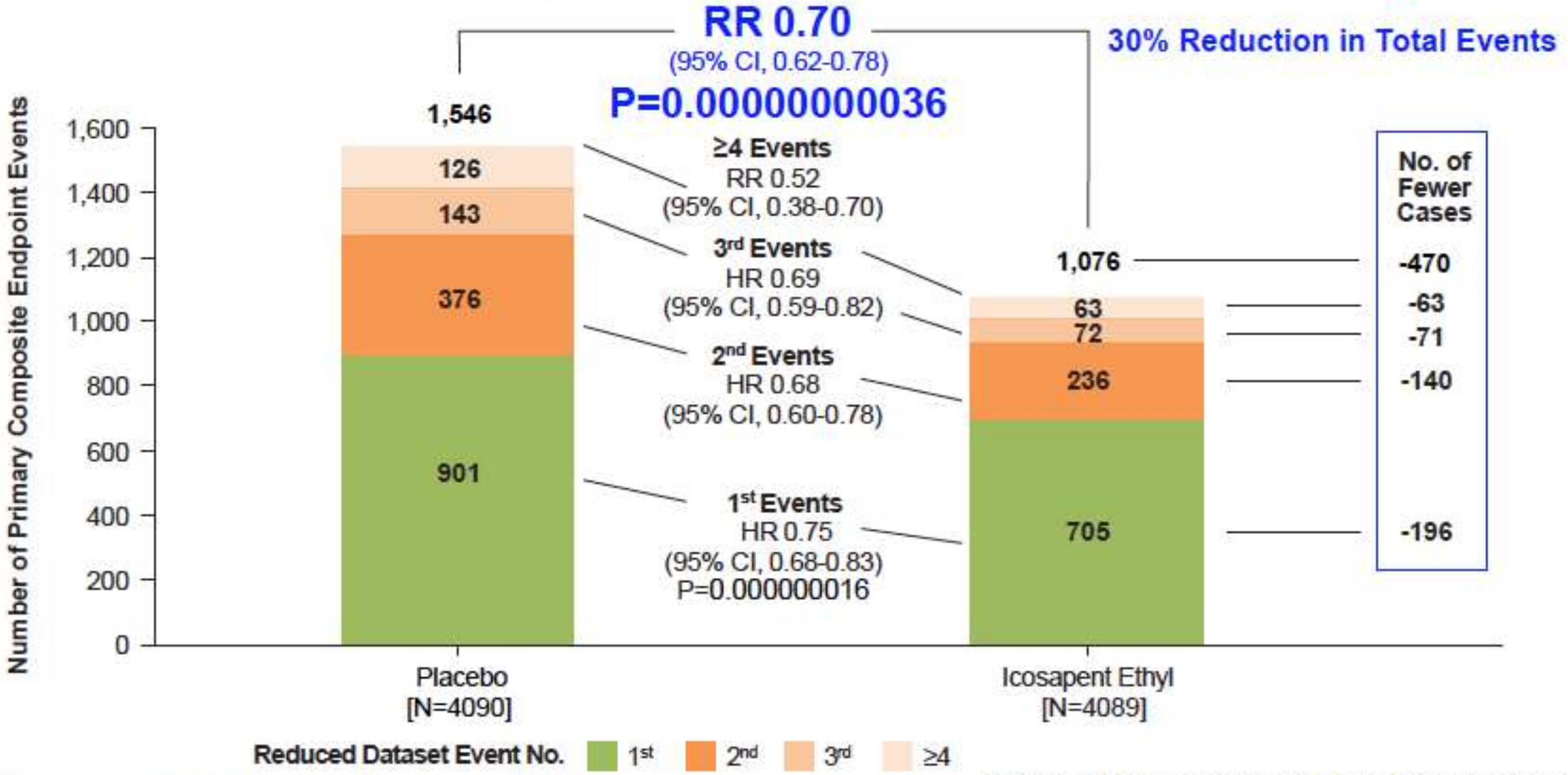
Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

First and Subsequent Events



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019.

Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

Omega-3 fatty acids for Cardiovascular Prevention

→ **Diet: Apparent benefit of fish consumption (observational studies)**

→ **Low-dose Supplementation**

- Initial trials suggested benefit (JELIS - with medium dose EPA)
- Meta-analysis (trials to 2018), ASCEND and VITAL trials: No overall CV benefit

→ **High-dose omega-3 FA: Positive CV Benefit**

→ REDUCE-IT trial (4 gm EPA) shows 25% ↓ in CV events, 30%↓ in total CV events

→ STRENGTH trial with Epanova (4 gm mixed EPA/DHA agent) – due in late 2019

Conclusions

- New 2018 ACC/AHA guidelines
  - Recommend statins for 4 benefit groups
  - Then add non-statins if LDL > 70 mg/dl for secondary prev. and >100 mg/dl for FH
- IMPROVE IT, REVEAL, FOURIER, and ODYSSEY OUTCOMES have shown
  - *Non-statin* agents (ezetimibe and PSCK9 inhibitors) lowering LDL-C and CV events
  - Achieving lower LDL levels (< 50 mg/dL) shown to be safe and significantly reduces the risk of cardiovascular events in very high risk ASCVD
- PCSK9 inhibitors: FH or Clinical ASCVD on max tolerated statin with LDL> goal
- High-dose eicosapent ethyl (EPA) – CV benefit in Pts. with elevated Triglycerides
- BUT: We need to use the therapies we have proven to have benefit!