

PLACE



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria

**Auditorium
della Tecnica**

9ª Edizione

30 Settembre

1 Ottobre

2022

Sala Damato - 13.10 - 15.20

LUNCHEON PANEL PREVENZIONE CARDIOVASCOLARE

Moderatori:

Galiuto L (Roma) - Marcheselli A (Tivoli) - Sanguigni V (Roma)





IL RISCHIO CARDIOVASCOLARE RESIDUO: OLTRE IL COLESTEROLO LDL

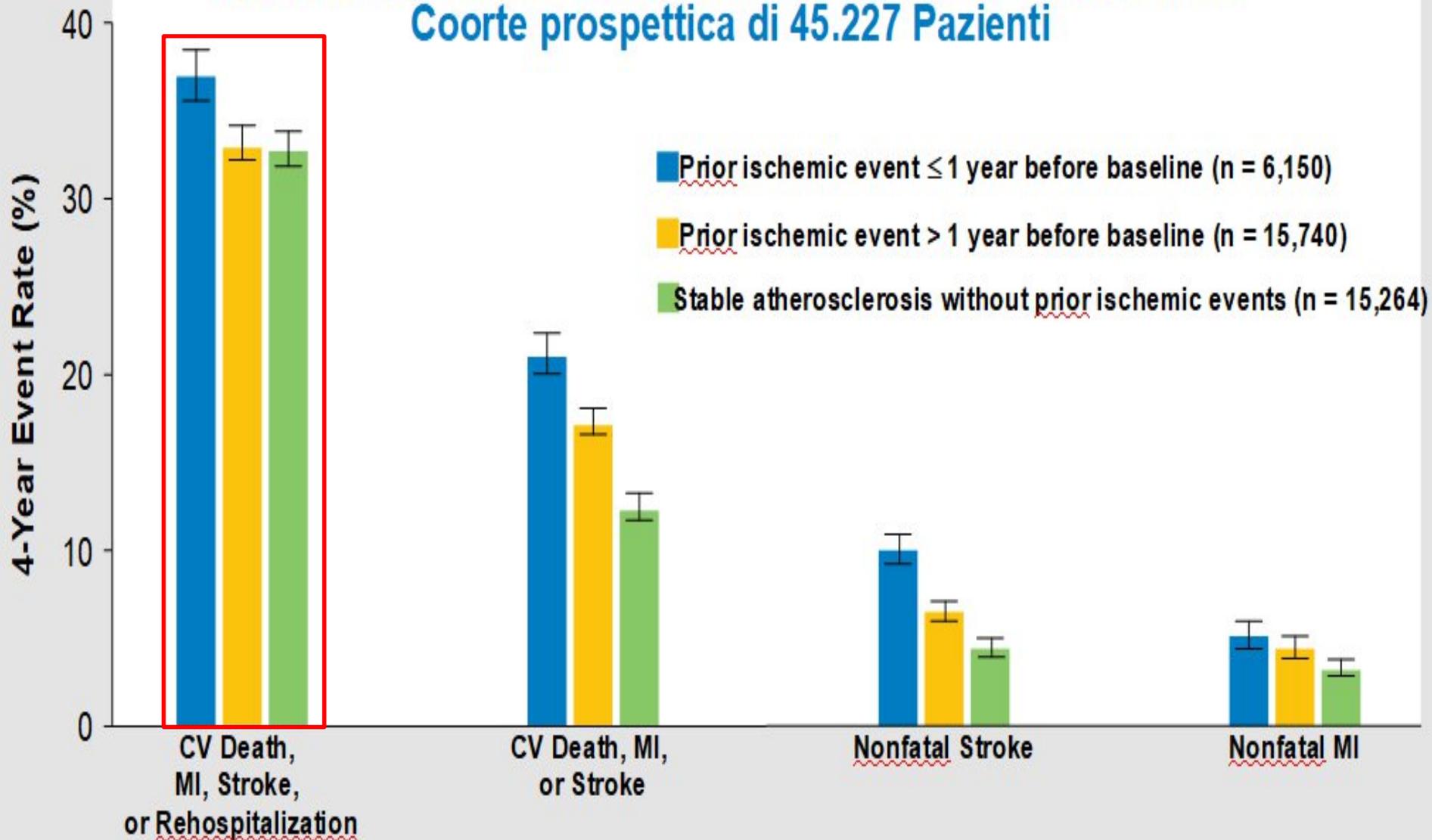
Salvatore Novo (Palermo)

**In Italia il numero di soggetti colpiti annualmente
da eventi coronarici supera i 135.000 casi**
(Rapporto OsMed 2020)

**Nel corso degli ultimi 10 anni, la mortalità dopo infarto
miocardico acuto è migliorata nei primi 30 giorni;
ma, non ha mostrato significativa riduzione ad un anno**
(AGENAS - PNE 2021)

**Questi dati denotano un parziale insuccesso
di quanto facciamo in prevenzione secondaria!**

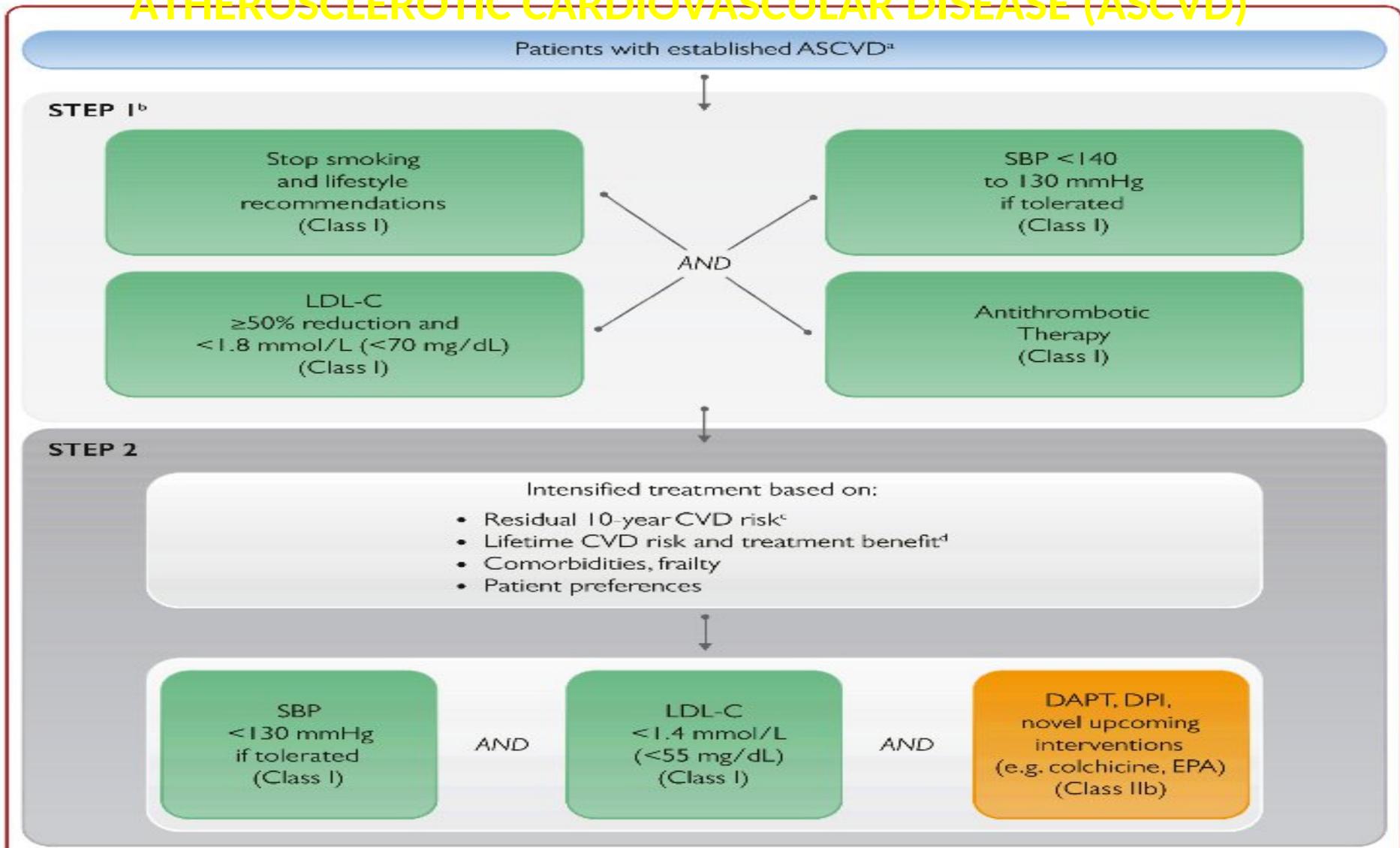
Registro REACH: Internazionale (29 Paesi), Osservazionale, Coorte prospettica di 45.227 Pazienti



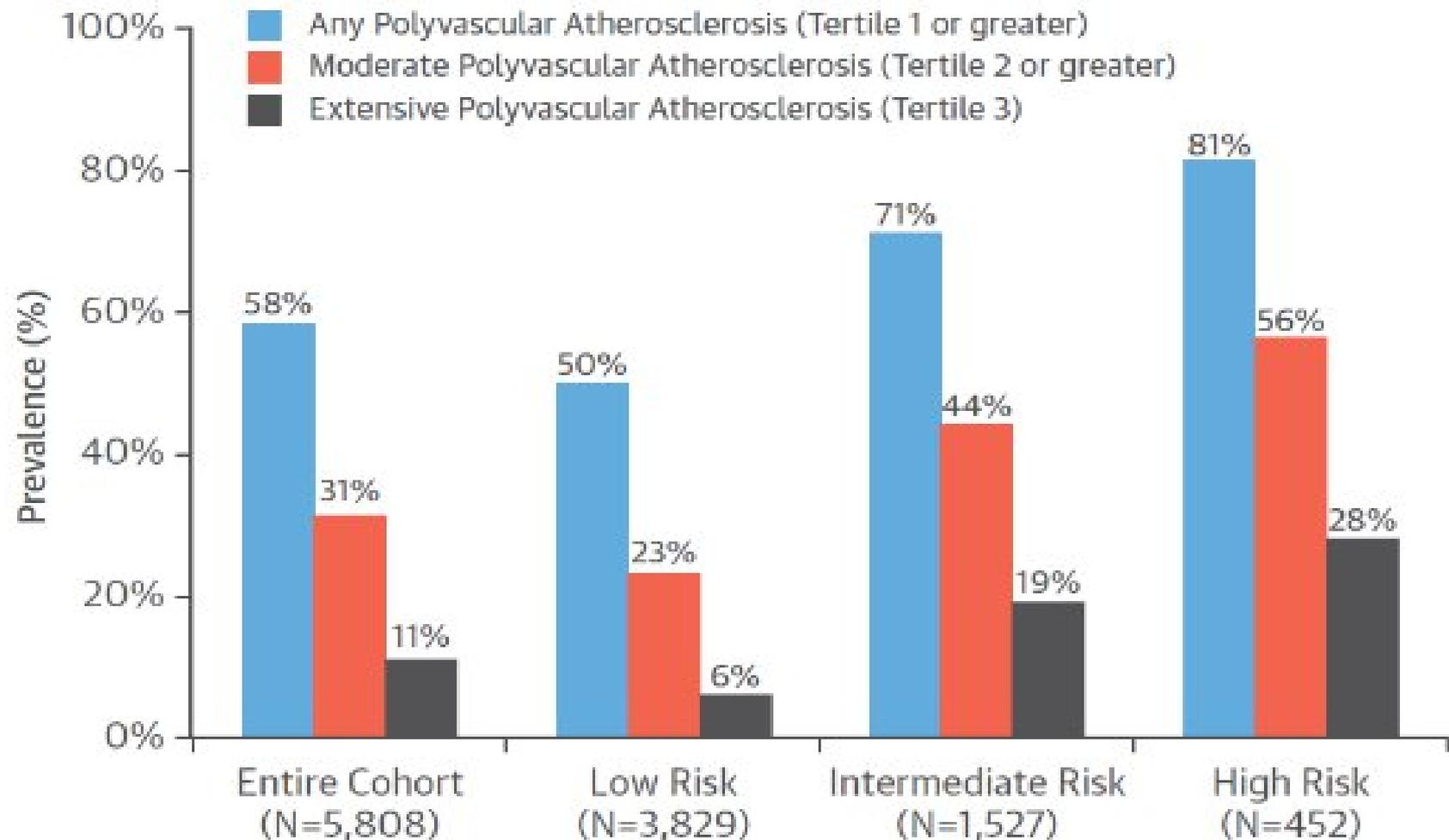
AGENDA

- * Quali sono i Target di LDL-C da raggiungere in Prevenzione Secondaria secondo le Linee Guida ESC 2021?
- * Abbiamo i farmaci per raggiungere tali target?
- * Li raggiungiamo?
- * Se non li raggiungiamo, ci sono nuove prospettive terapeutiche?
- * Cosa intendiamo per “Rischio Cardiovascolare Residuo”?
- * Quali prospettive in questo campo?

TARGET OF RISK FACTORS TREATMENT IN PATIENTS WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD)

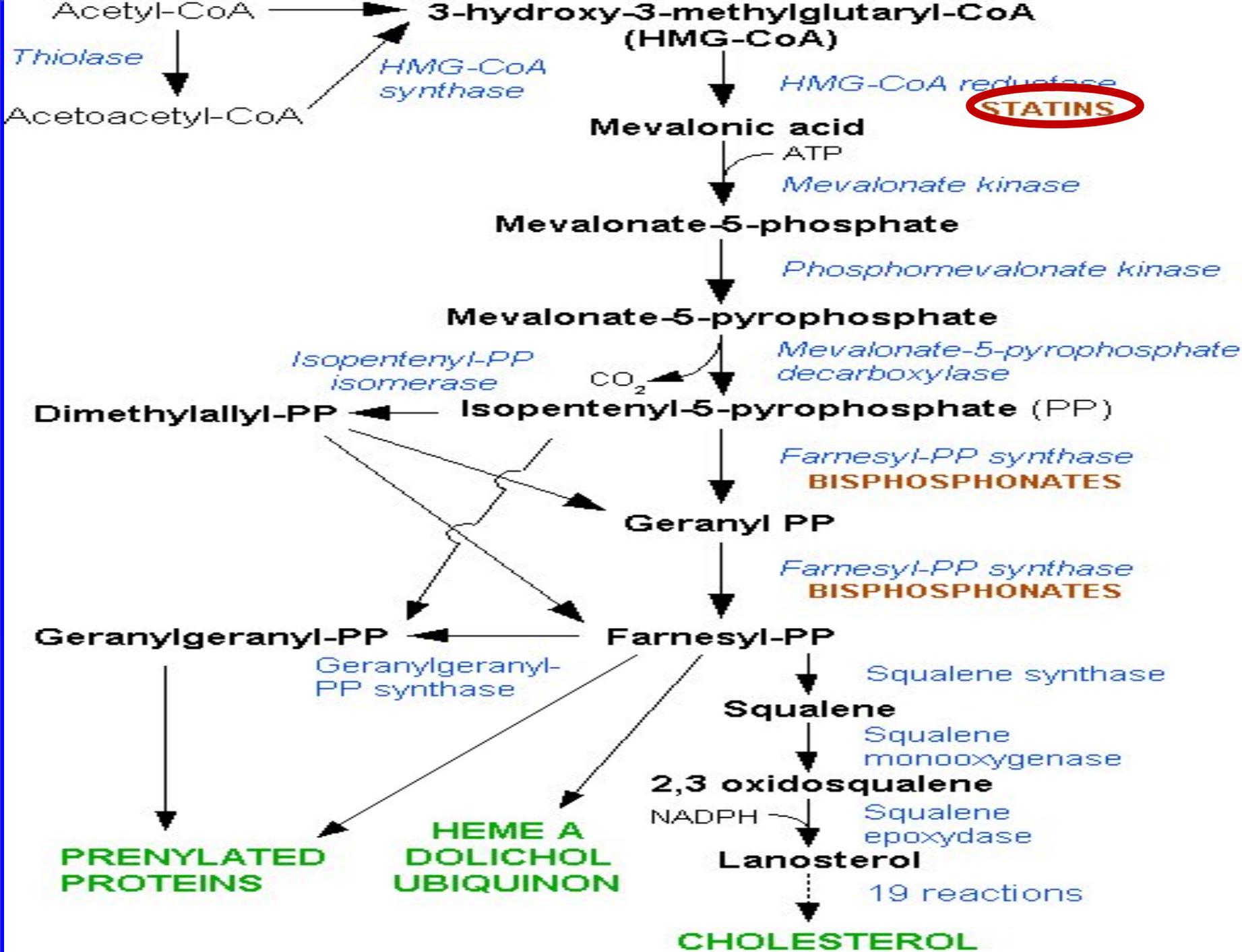


Prevalence of polyvascular atherosclerosis in the overall cohort and by Framingham risk groups



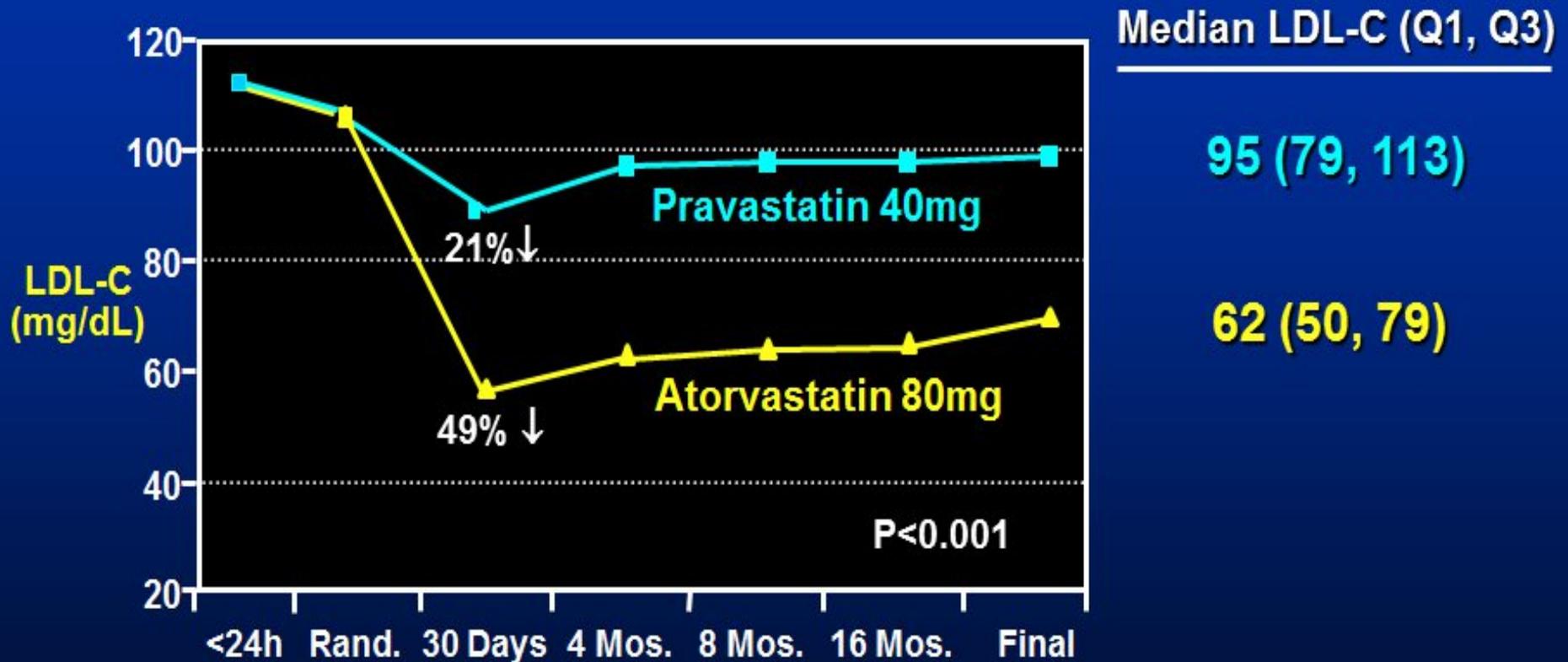
AGENDA

- * Quali sono i Target di LDL-C da raggiungere in Prevenzione Secondaria secondo le Linee Guida ESC 2021?
- * Abbiamo i farmaci per raggiungere tali target?
- * Se non li raggiungiamo, ci sono nuove prospettive terapeutiche?
- * Cosa intendiamo per “Rischio Cardiovascolare Residuo”?
- * Quali prospettive in questo campo?





Changes from (Post-ACS) Baseline in Median LDL-C



Note: Changes in LDL-C may differ from prior trials:

- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline

INCIDENCE OF PRIMARY END-POINT AND LDL-C “on trial” IN THE GROUP TREATED WITH ATORVASTATIN 80 mg IN PROVE-IT TRIAL

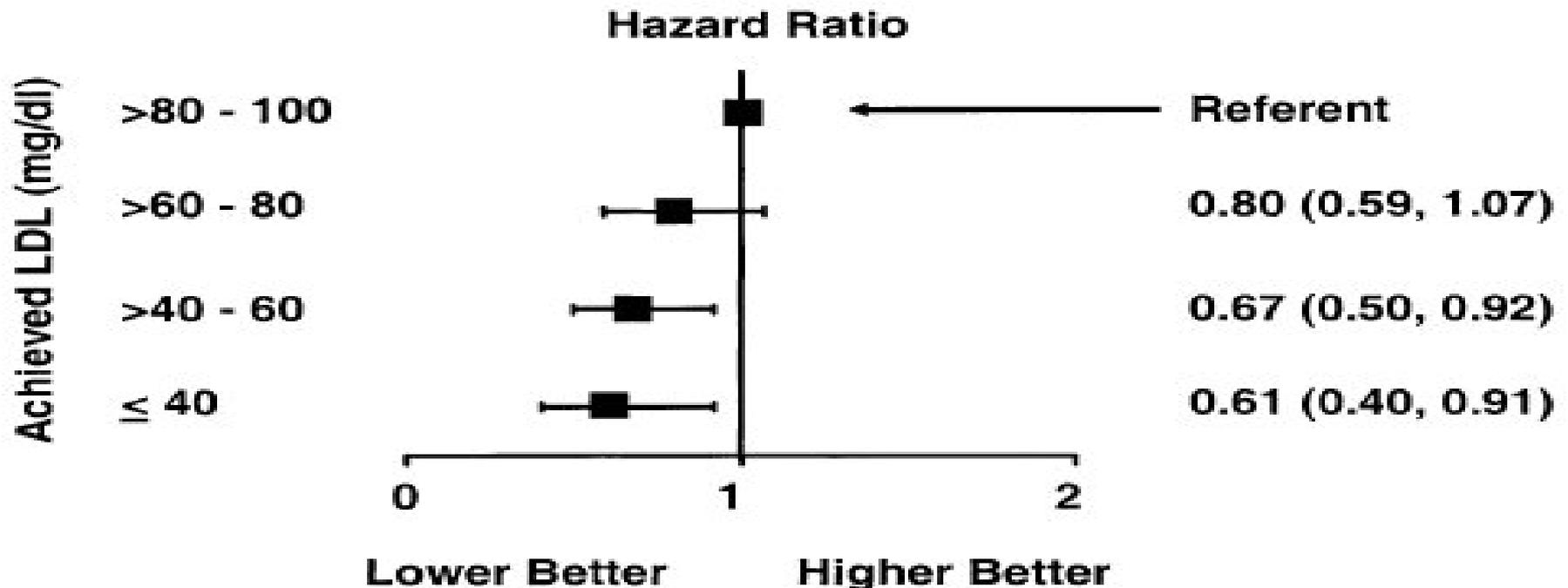
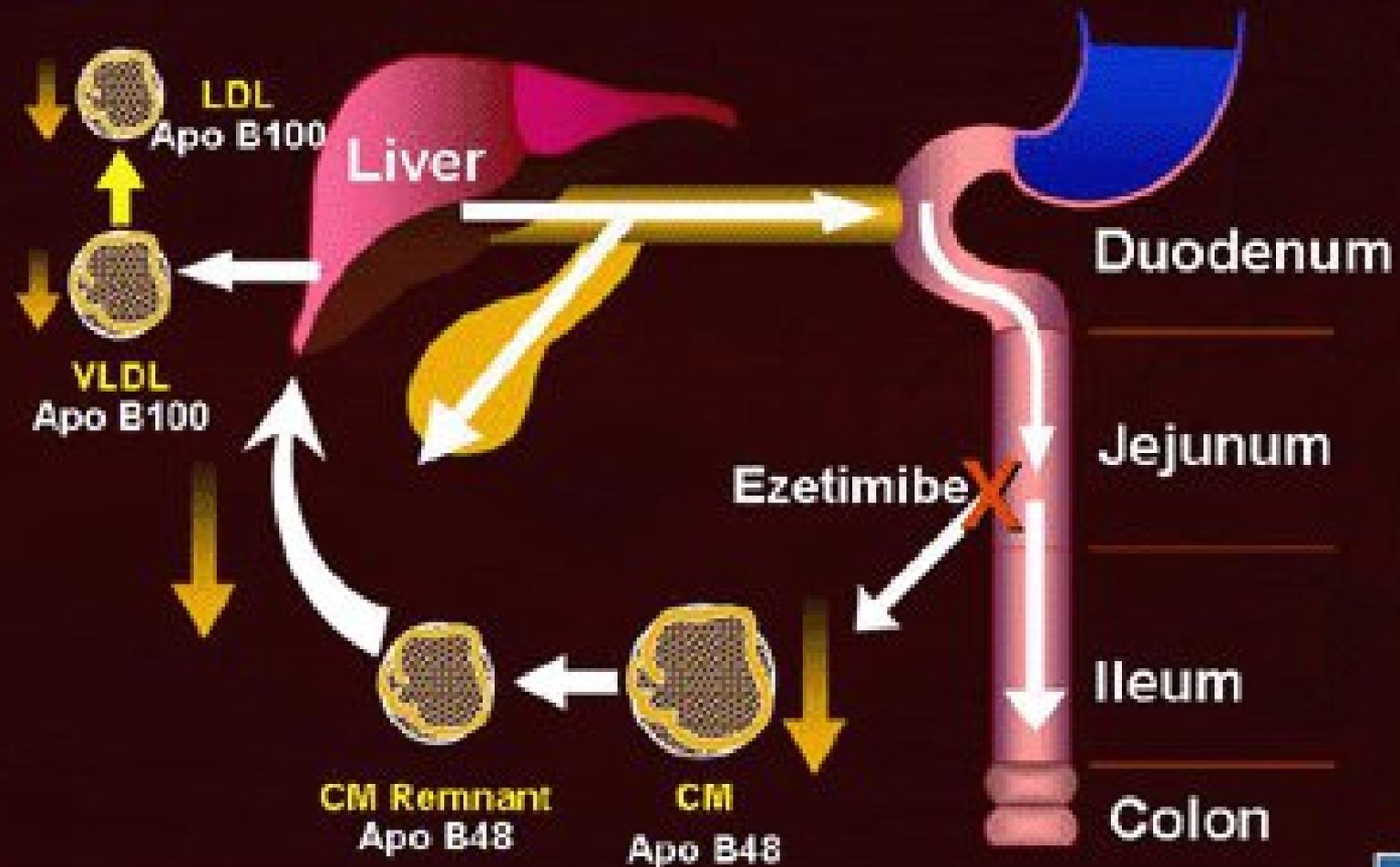


Figure 2. Hazard ratio of the primary end point compared with achieved calculated low-density lipoprotein (LDL) 80 to 100 mg/dl (adjusted for age, gender, baseline calculated low-density lipoprotein, diabetes mellitus, and prior myocardial infarction).

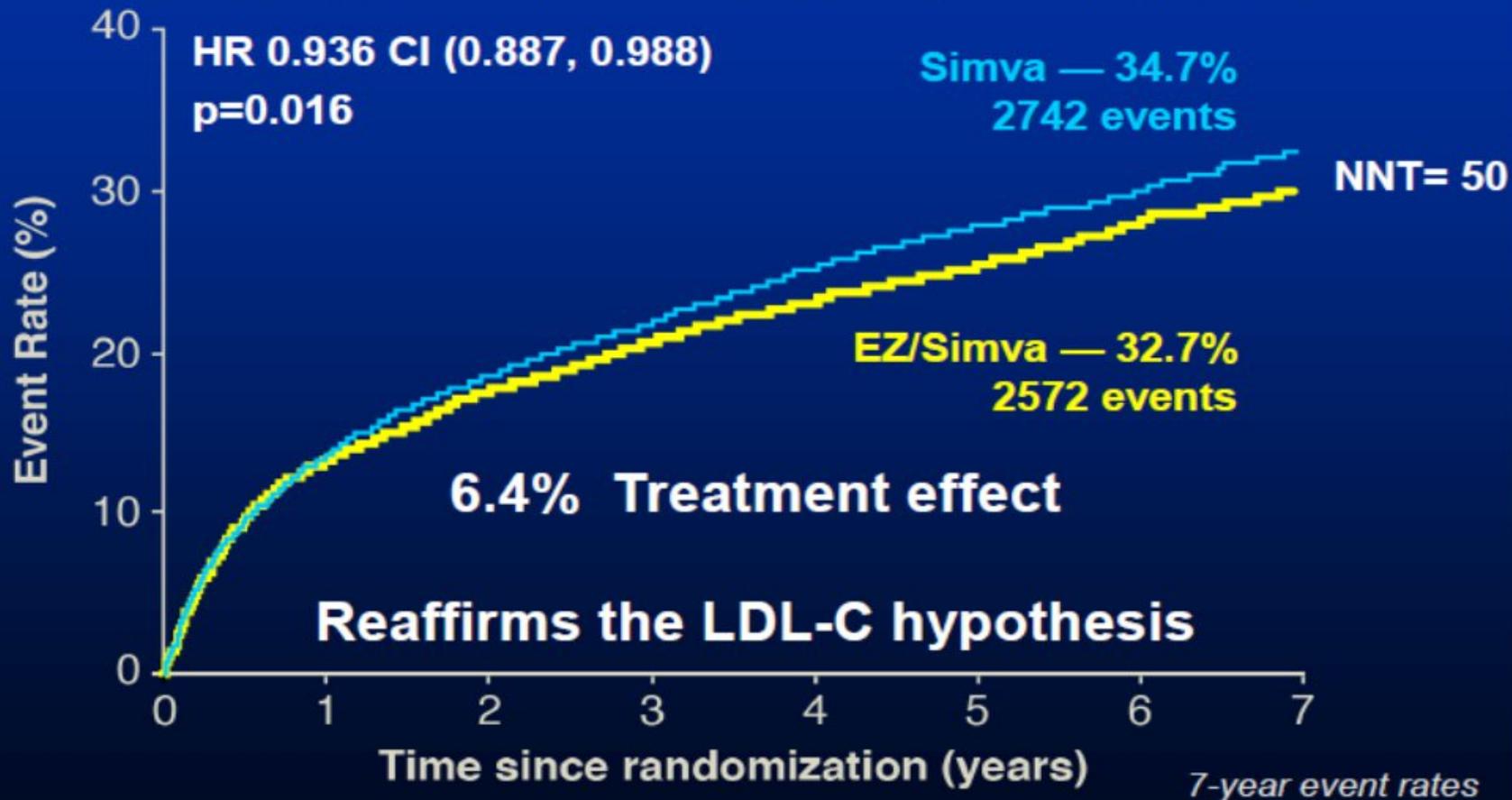
Ezetimibe: Mechanism of Action



Primary Endpoint — ITT

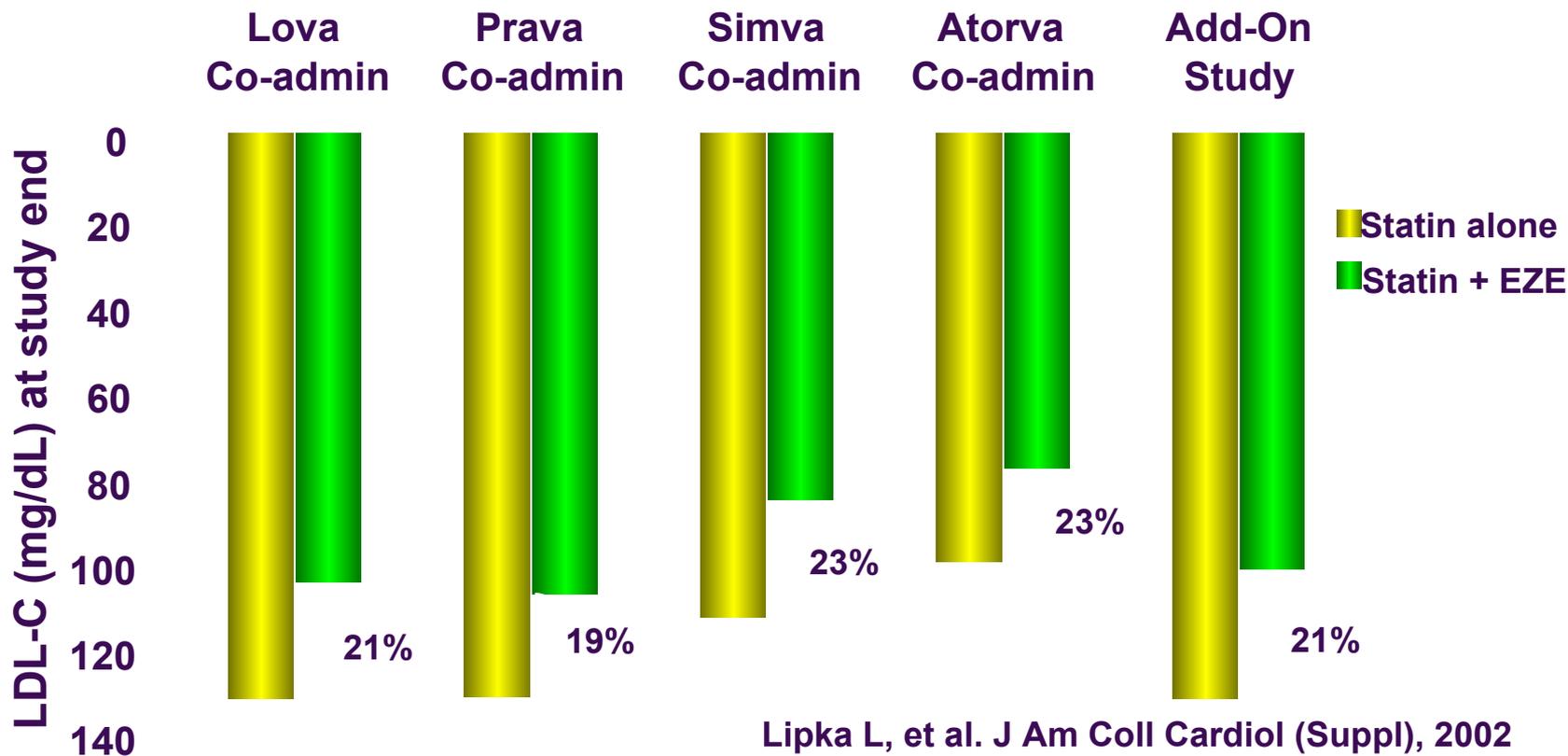


Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥ 30 days), or stroke



CONSISTENCY OF CO-ADMINISTRATION STUDIES

Ezetimibe lowers LDL-C an added 19%-23% vs statin alone



Lipka L, et al. J Am Coll Cardiol (Suppl), 2002
Melani L, et al. J Am Coll Cardiol (Suppl), 2002
Davidson M, et al. J Am Coll Cardiol (Suppl), 2002
Ballantyne C, et al. J Am Coll Cardiol (Suppl), 2002
Bays H, et al. J Am Coll Cardiol (Suppl), 2002

176 studies
4,143,517 patients

Asian race
↑25.4%

Age
↑33.1%

Black race
↑29.3%

Age ≥ 65 years
↑31.2%

Obesity
↑30.6%

Female
↑47.9%

Hypothyroidism
↑37.6%

Depression
↓12.2%

Diabetes mellitus
↑26.6%

Chronic liver disease
↑24.3%

Antiarrhythmics
↑31.2%

Chronic renal failure
↑25.2%

Alcohol consumption
↑22%

Calcium channel blockers
↑35.5%

Exercise
↑23.2%

High statin dose
↑37.5%

Overall prevalence
9.1% (8.1-10%)



Smoking

Arterial hypertension

Duration of statin therapy

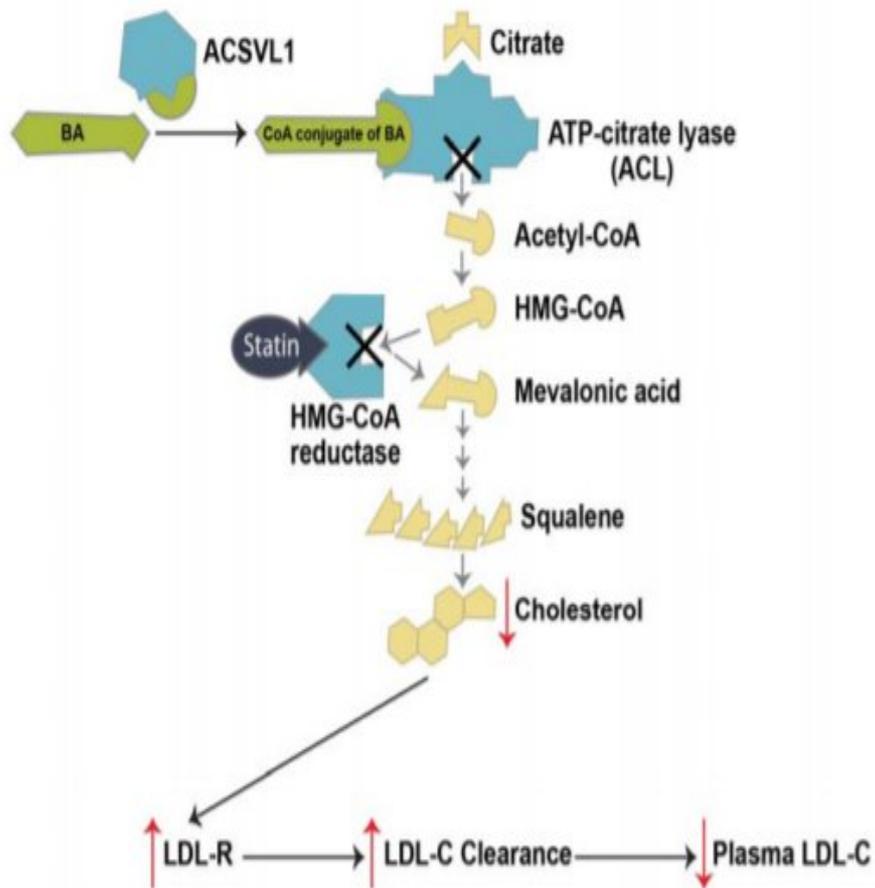
White race

Caucasian race

Hispanic race

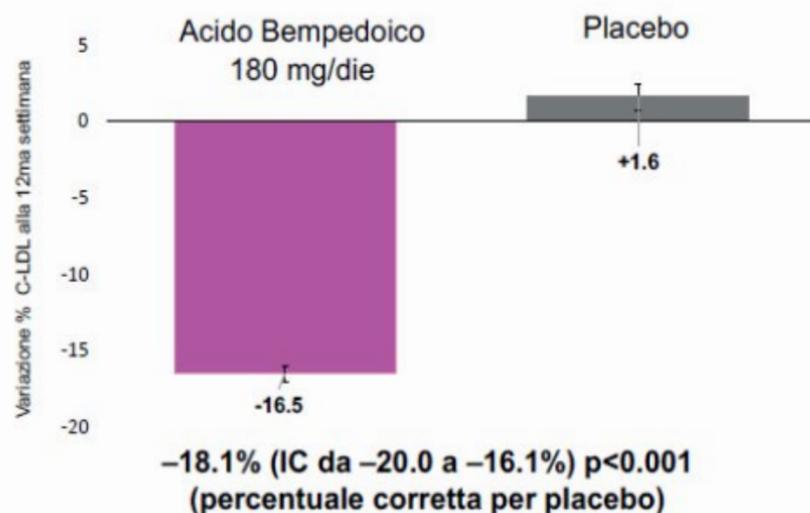
Warfarin

Bempedoic Acid Mechanism of Action

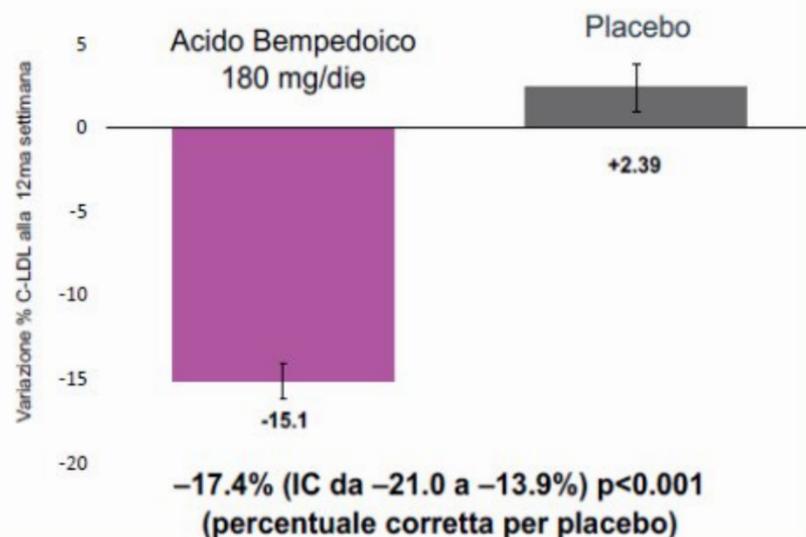


- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Bempedoic acid inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Bempedoic acid upregulates LDL receptors and lowers LDL-C
- Activated bempedoic acid is not present in skeletal muscle

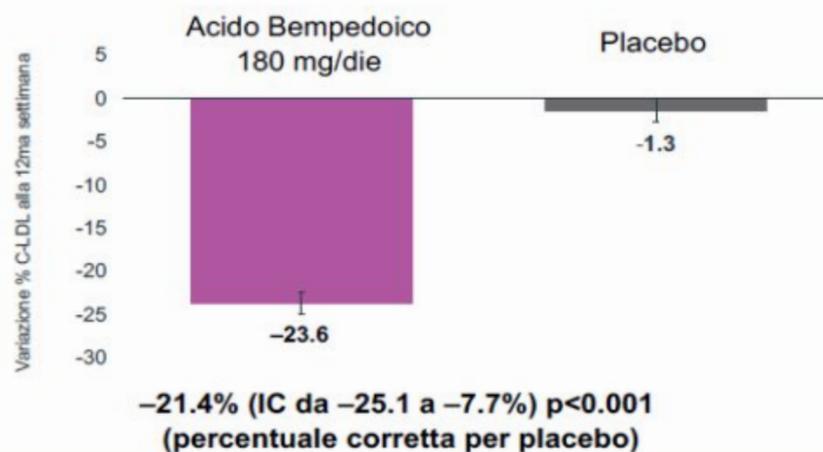
CLEAR Harmony¹⁰ 99.8% trattati con statine



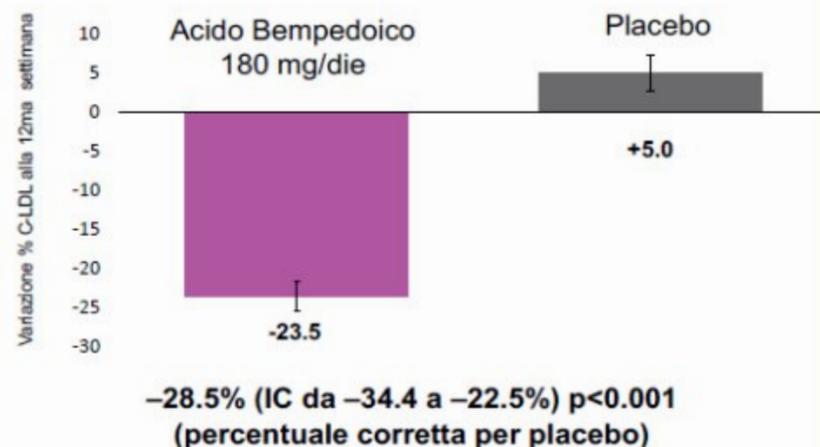
CLEAR Wisdom¹² 89.6% trattati con statine



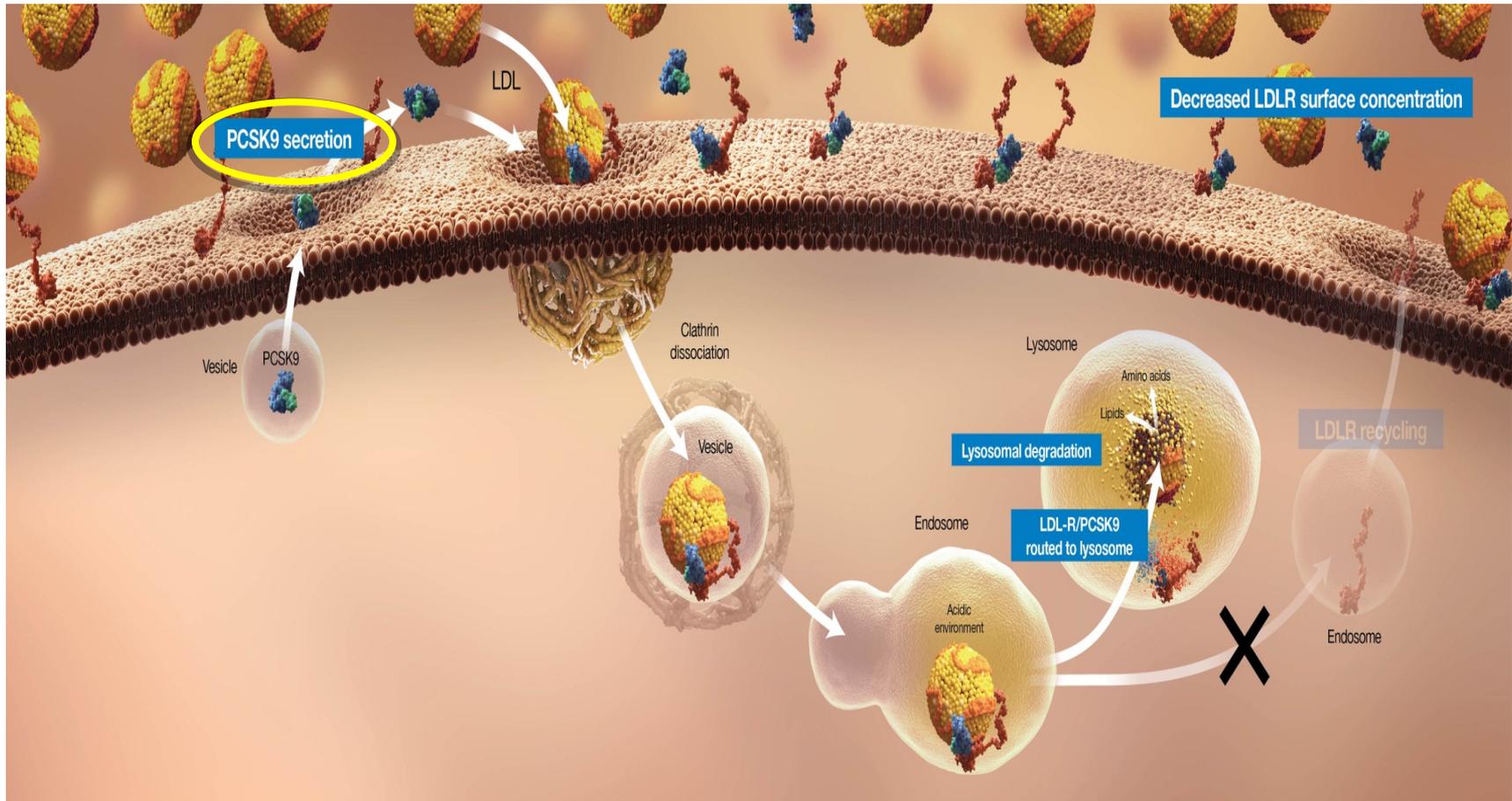
CLEAR Serenity¹³ 8% trattati con statine



CLEAR Tranquility¹⁴ 100% trattati con EZE; 31% con statine

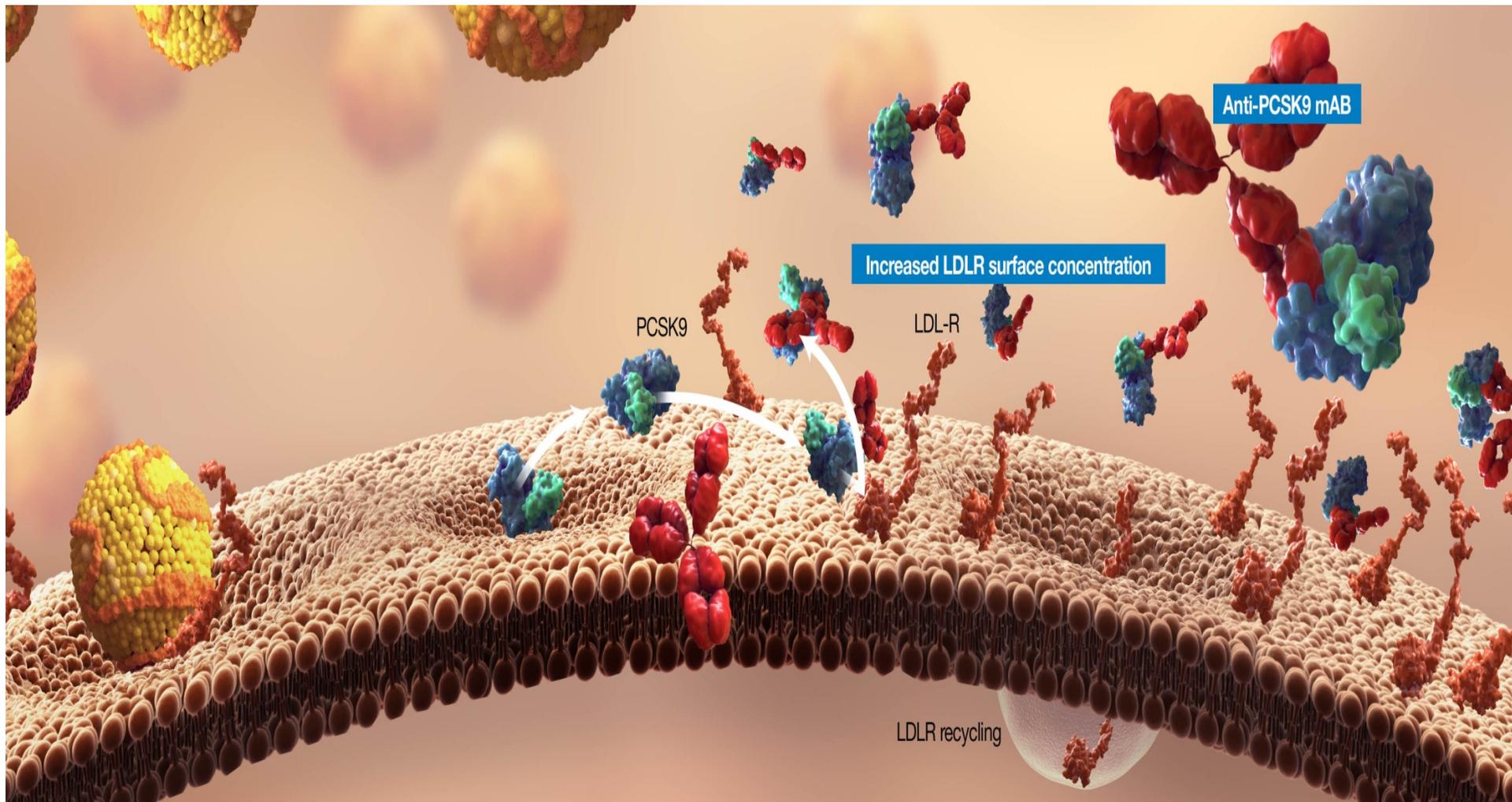


PCSK9 REGULATES THE SURFACE EXPRESSION OF LDL-Rs BY TARGETING FOR LYSOSOMAL DEGRADATION



1. Qian YW, et al. *J Lipid Res.* 2007; 48: 1488-98
2. Horton JD, et al. *J Lipid Res.* 2009; 50: S172-S177
3. Zhang DW, et al. *J Biol Chem.* 2007; 282: 18602-12

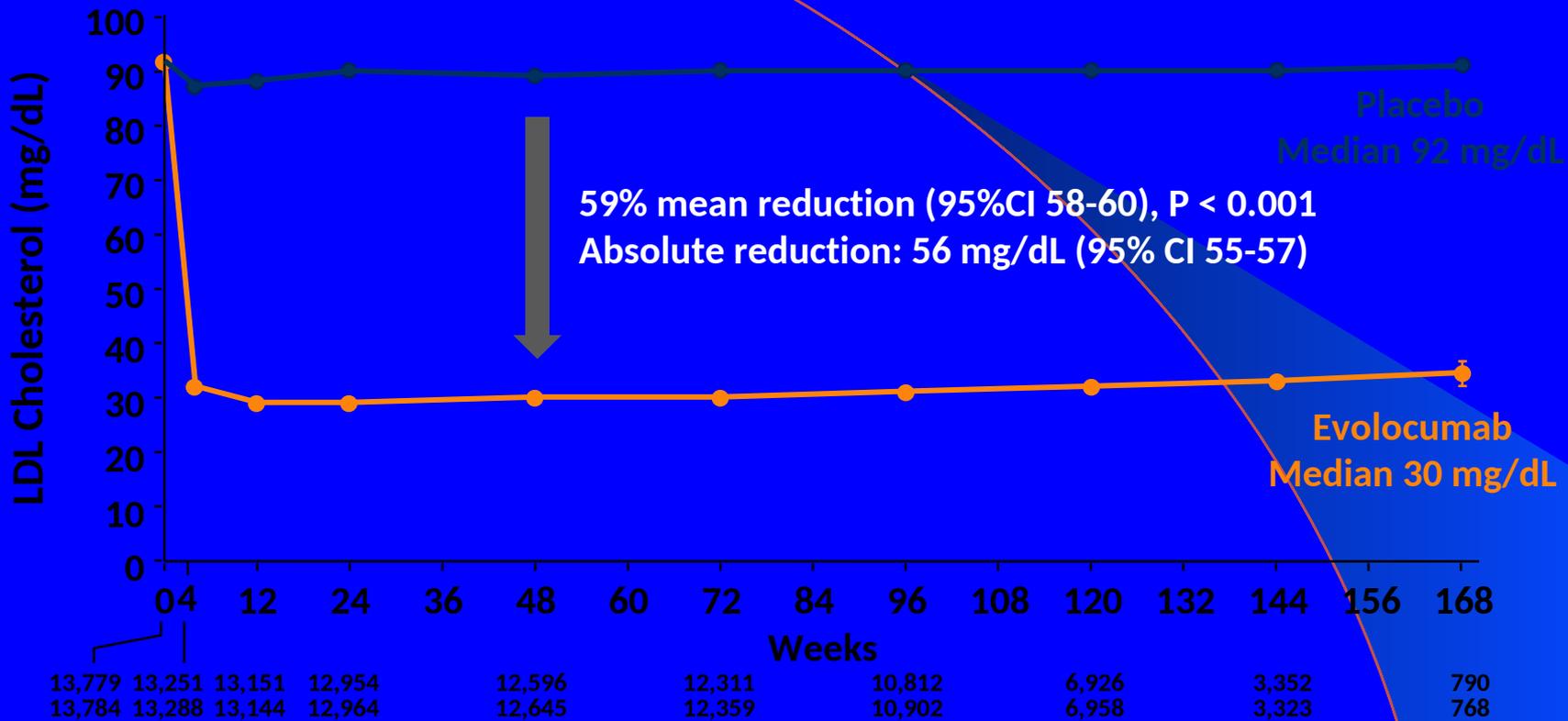
BLOCKADE OF PCSK9/LDL-Rs INTERACTION MAY LOWER LDL LEVELS



Chan JC, et al. Proc Natl Acad Sci – USA 2009; 106: 9820-25

Cardiovascular

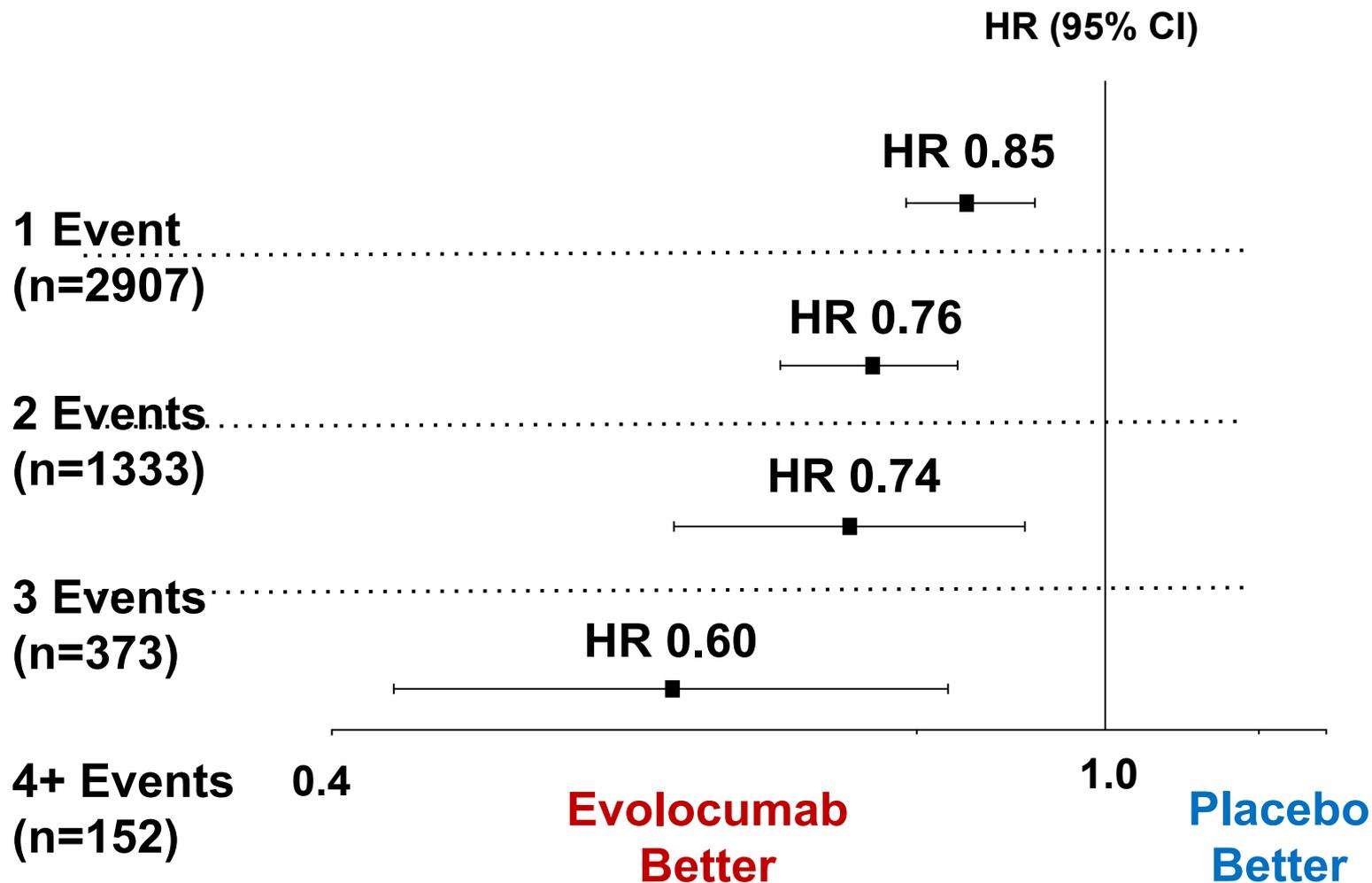
Median LDL-C Levels Over Time: All Patients – FOURIER Study



LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs $< 0.1\%$ in the placebo group



Primary Endpoint Events: Wei, Lin, Weissfeld Model

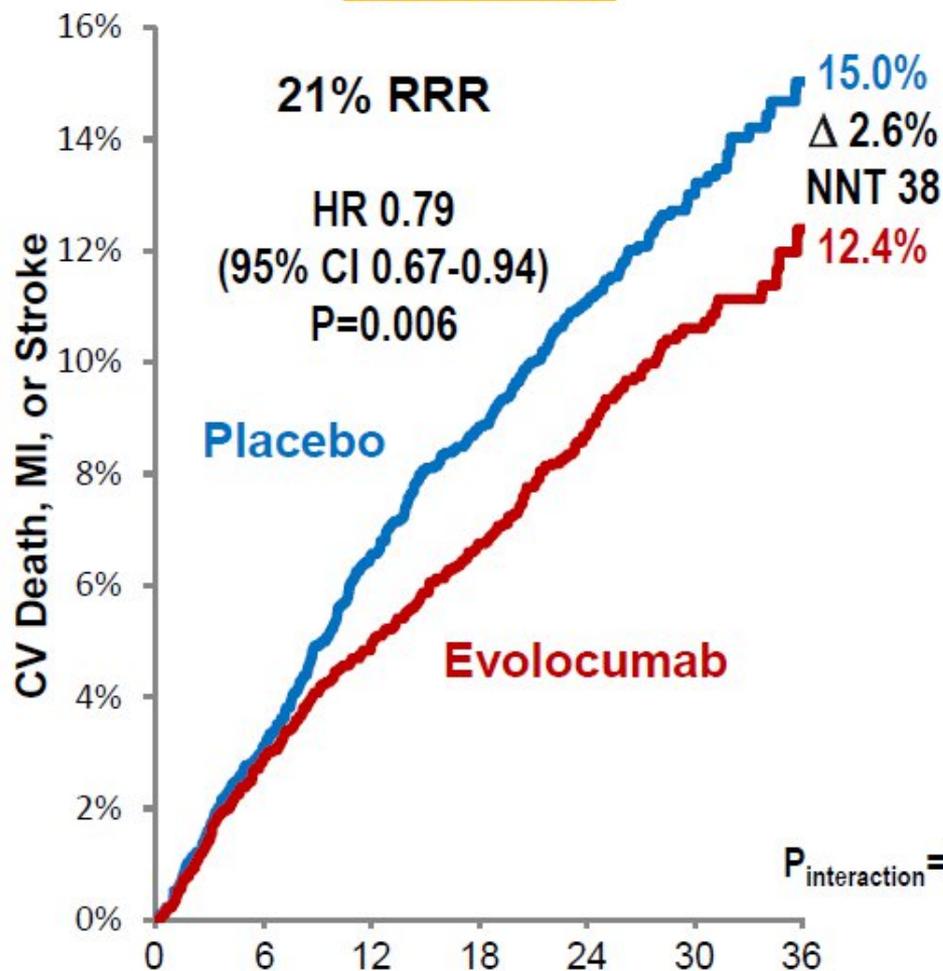




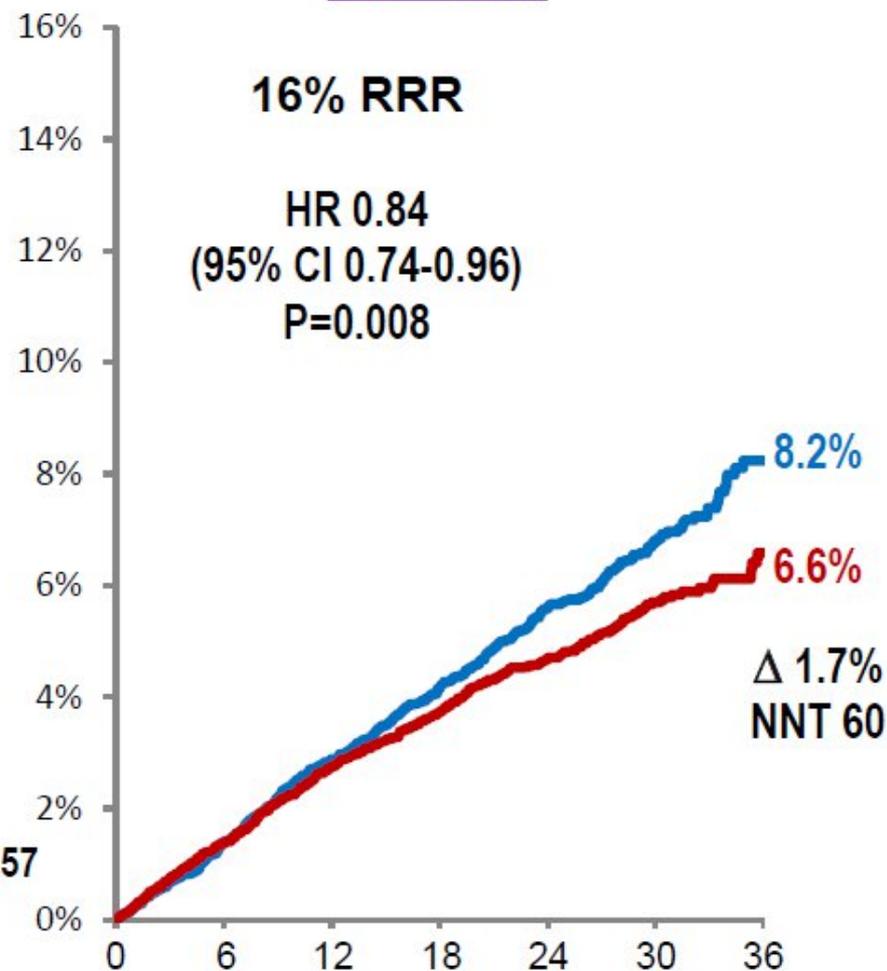
Benefit of EvoMab Based on # of Prior MIs



≥2 Prior MIs



1 Prior MI

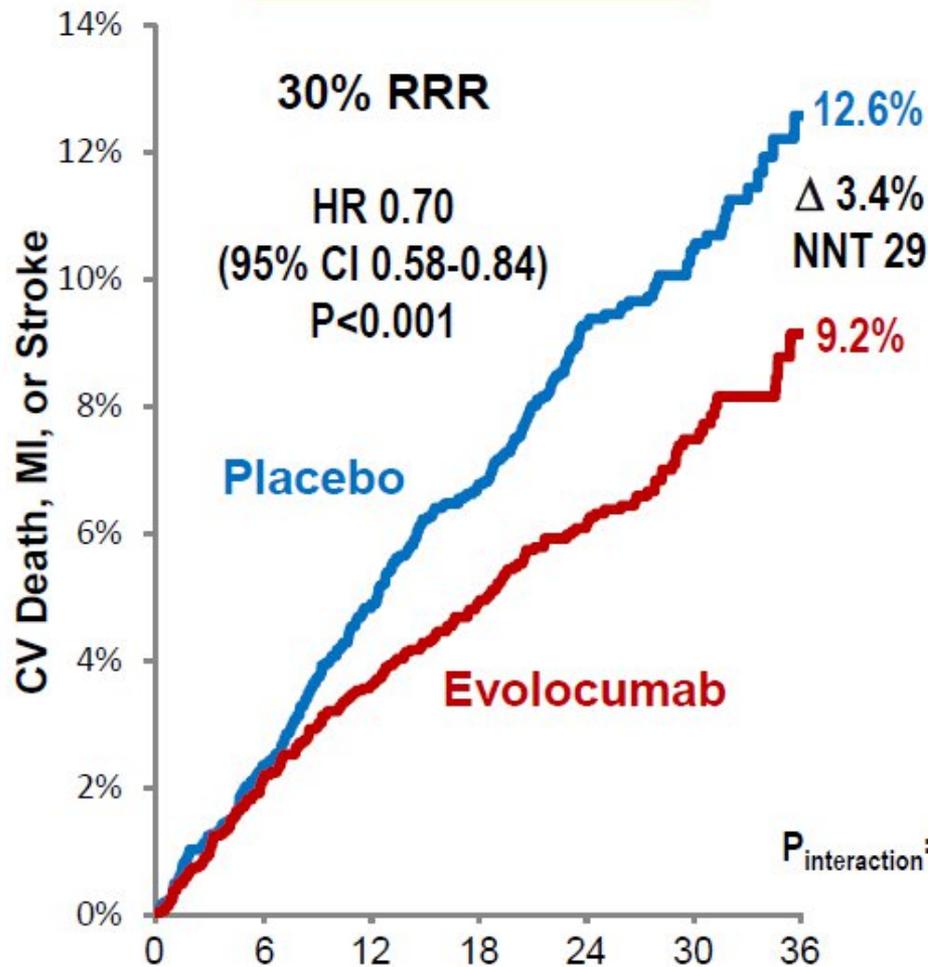




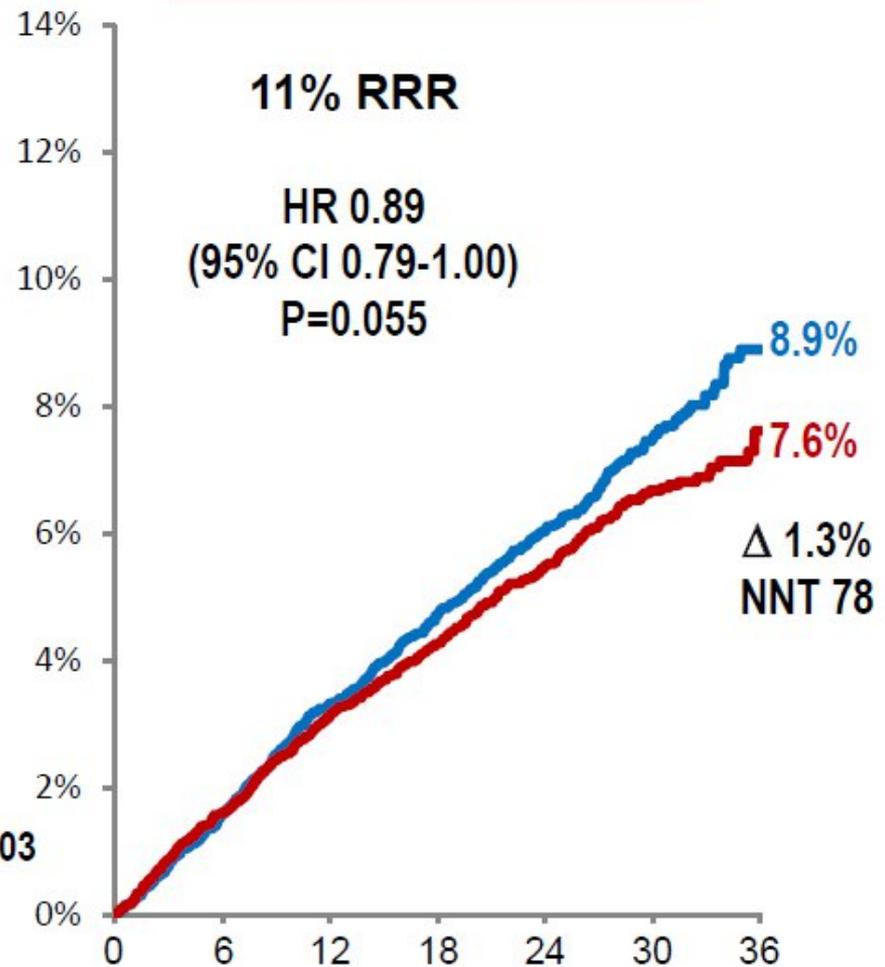
Benefit of EvoMab Based on Multivessel Disease



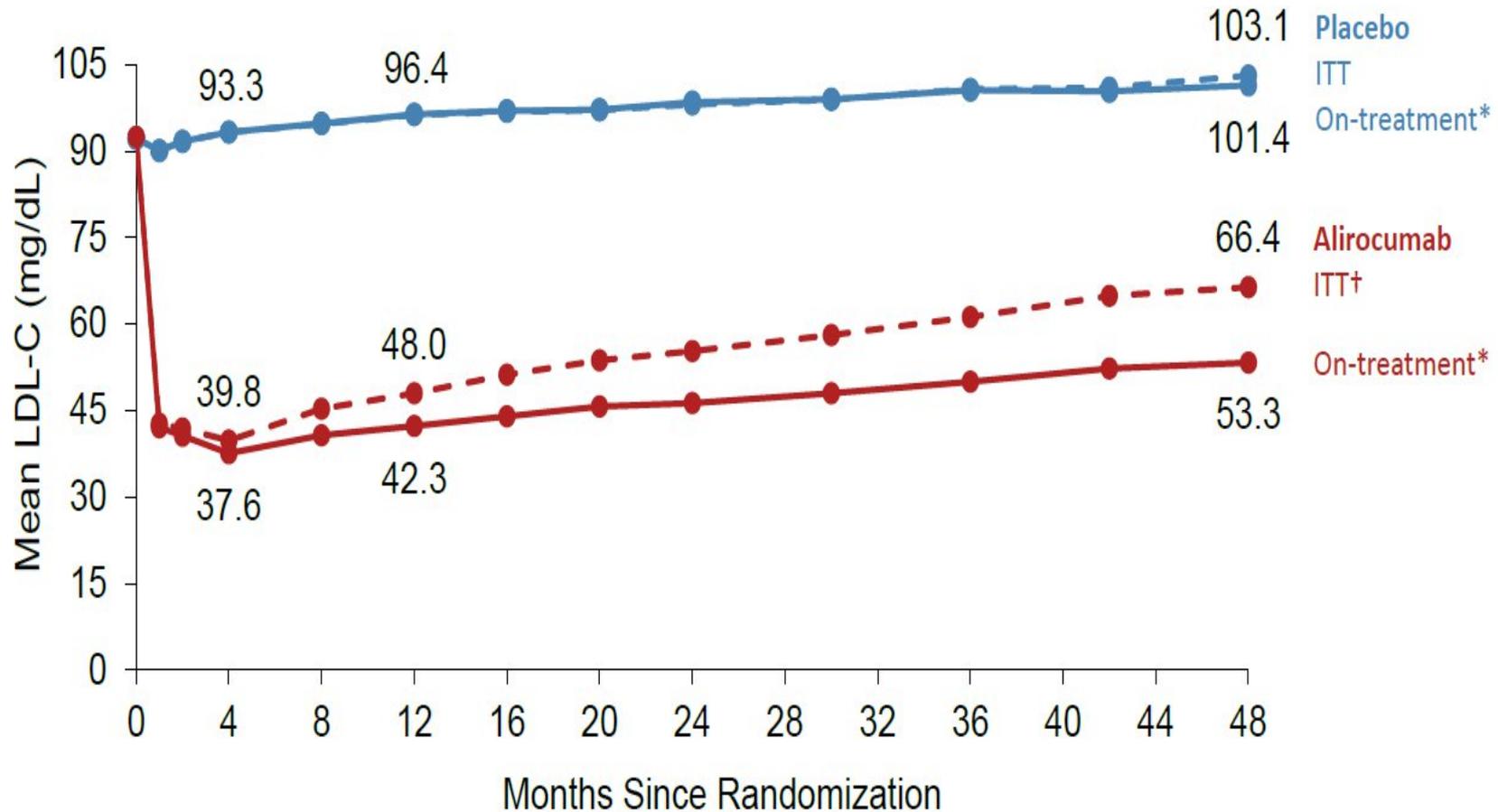
Multivessel Disease



No Multivessel Disease



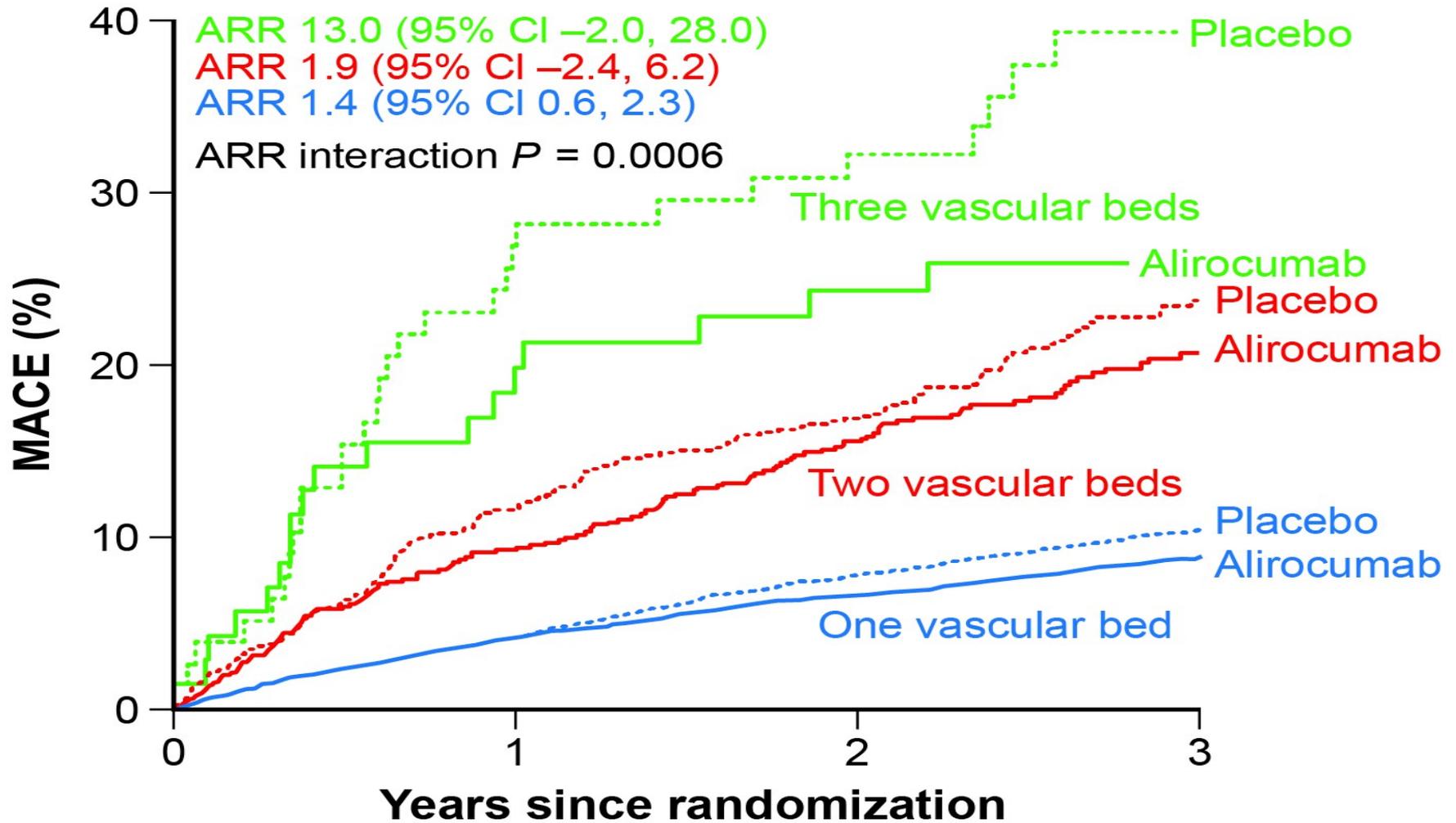
LDL-C: ITT and On-Treatment Analyses



*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

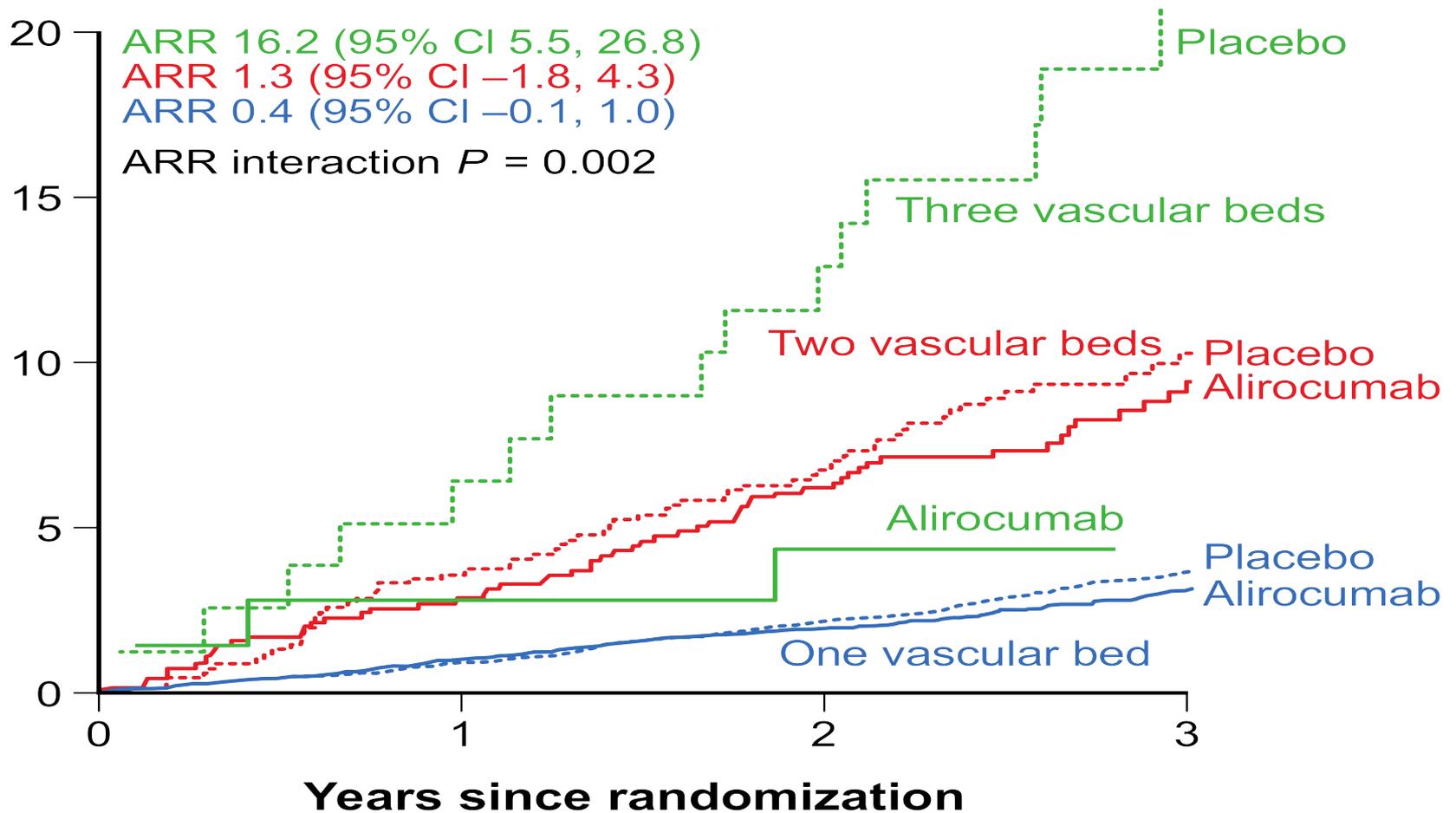
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

MACE: one, two or three vascular beds



Goodman SG, Jukema JW et al, JACC 2019; 74: 1177-86

Death: one, two or three vascular beds



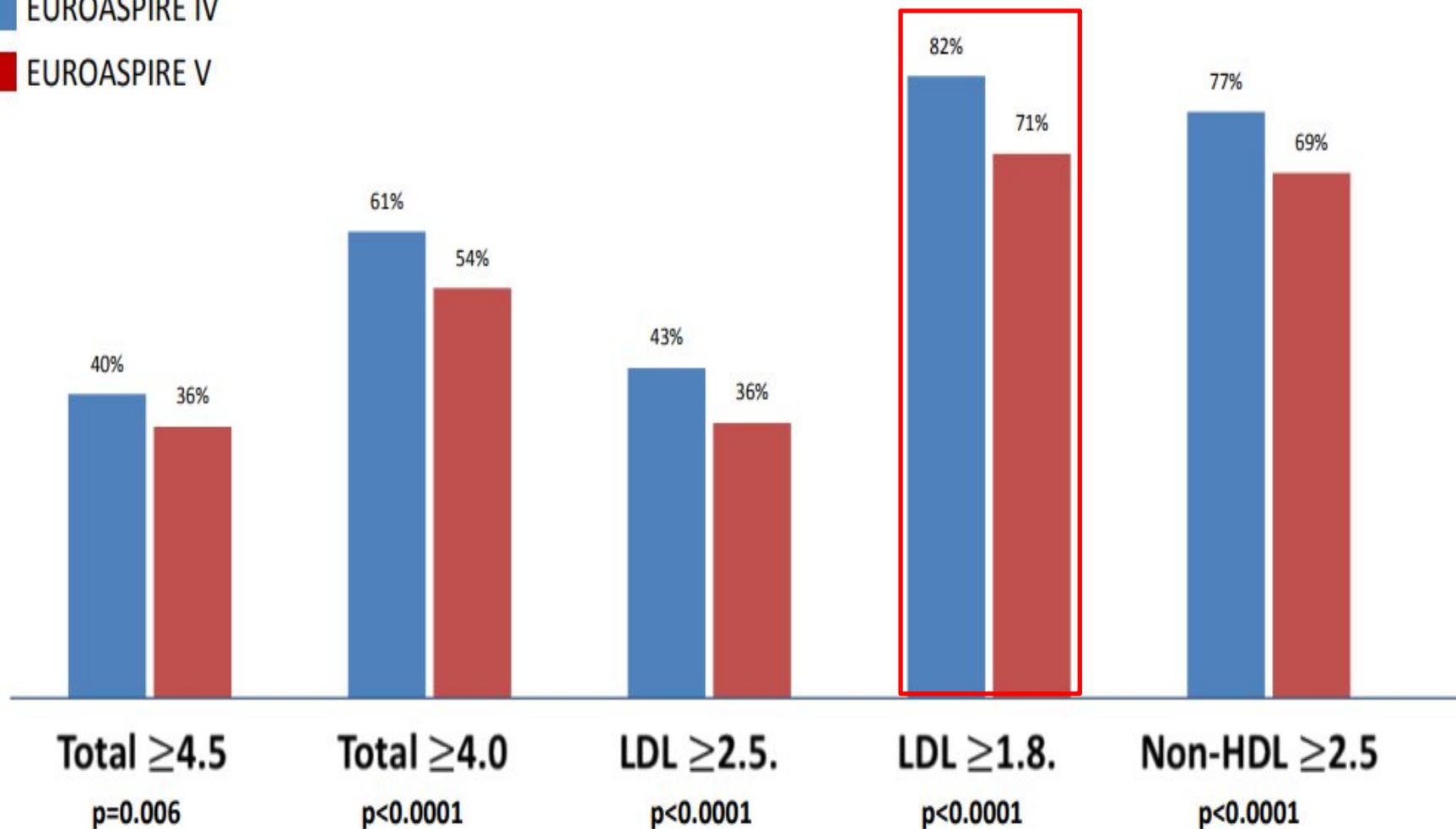
Goodman SG, Jukema JW et al, JACC 2019; 74: 1177-86



EUROASPIRE IV and V

Cholesterol mmol/L; Total, LDL and HDL

EUROASPIRE IV
EUROASPIRE V

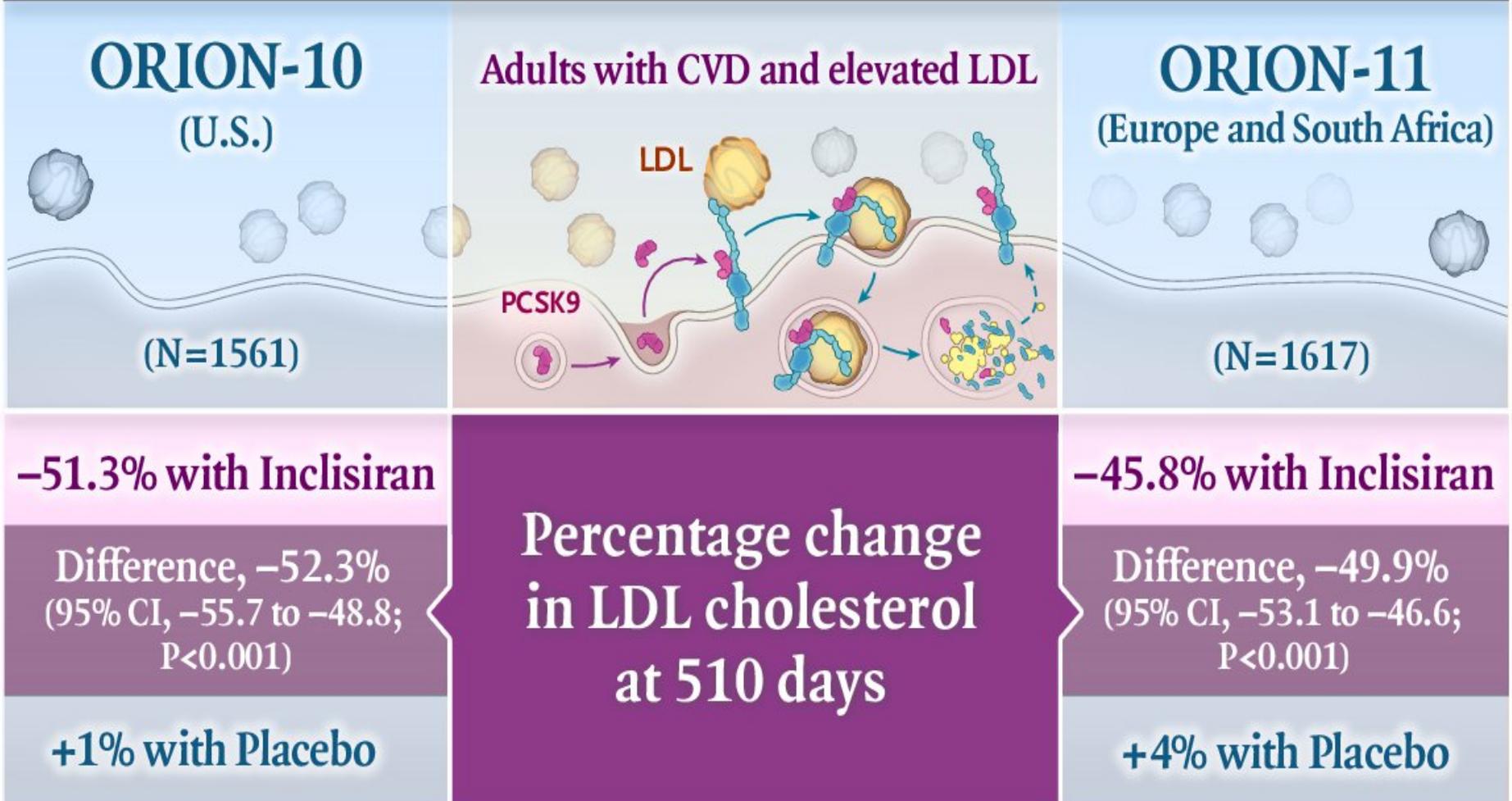


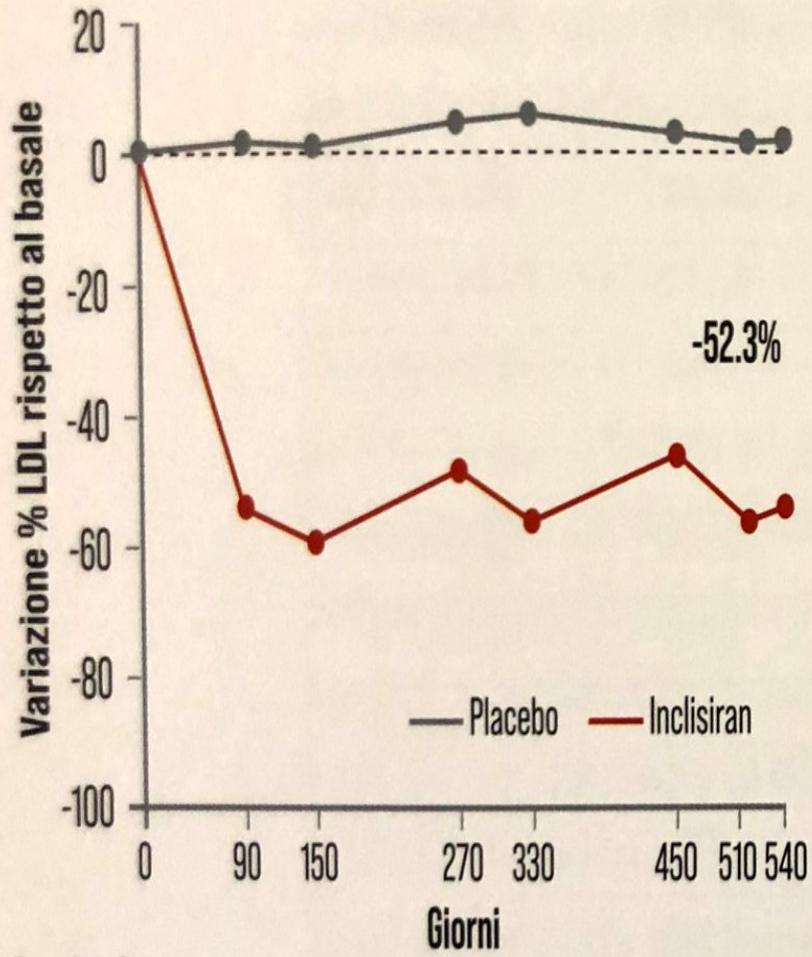
AGENDA

- * Quali sono i Target di LDL-C da raggiungere in Prevenzione Secondaria secondo le ultime Linee Guida ESC sulla Prevenzione Cardiovascolare nella Pratica Clinica 2021?
- * Abbiamo i farmaci per raggiungere tali target e li raggiungiamo?
- * Se non li raggiungiamo, ci sono nuove prospettive terapeutiche?
- * Cosa intendiamo per “Rischio Cardiovascolare Residuo”?
- * Quali prospettive in questo campo?

Inclisiran in Patients with Elevated LDL Cholesterol

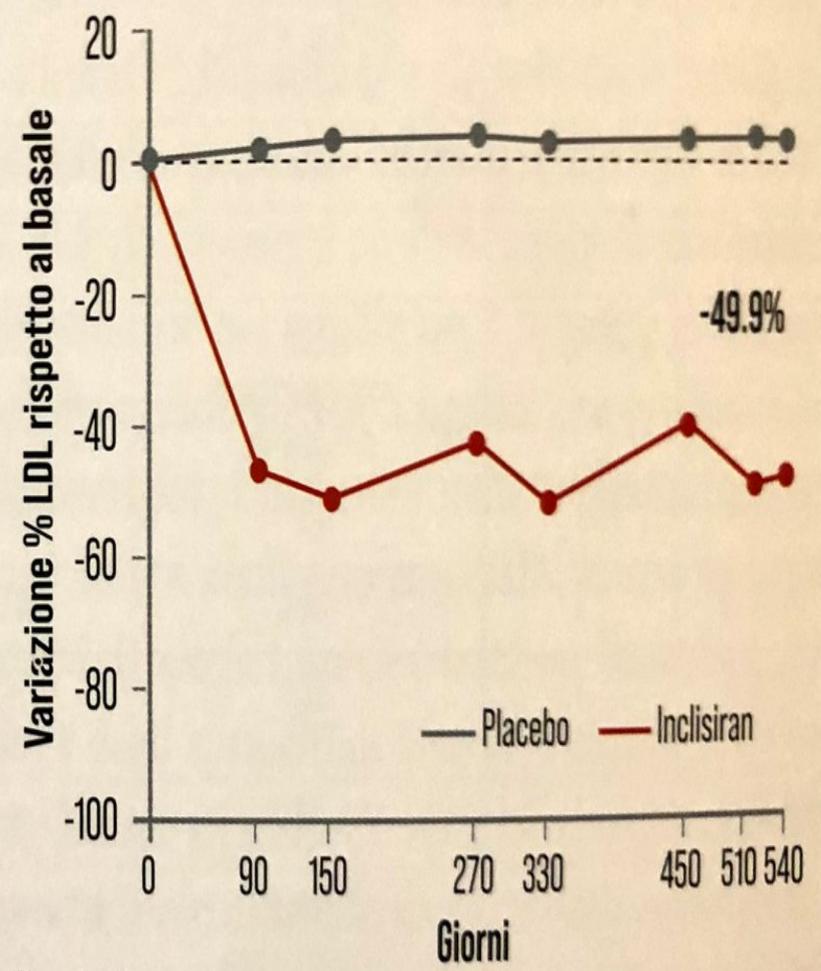
TWO PHASE 3, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS





N.ro di pazienti

Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705



N.ro di pazienti

Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

AGENDA

- * Quali sono i Target di LDL-C da raggiungere in Prevenzione Secondaria secondo le ultime Linee Guida ESC sulla Prevenzione Cardiovascolare nella Pratica Clinica 2021?
- * Abbiamo i farmaci per raggiungere tali target e li raggiungiamo?
- * Se non li raggiungiamo, ci sono nuove prospettive terapeutiche?
- * Cosa intendiamo per “Rischio Cardiovascolare Residuo”? e Quali prospettive in questo campo?

**Prioritizing Health:
Residual Cardiovascular Risk:
Beyond Traditional Risk Factors
ACC Feb 25, 2022 -
Cardiology Magazine**

Residual metabolic risk

Inflammation

Residual thrombotic risk

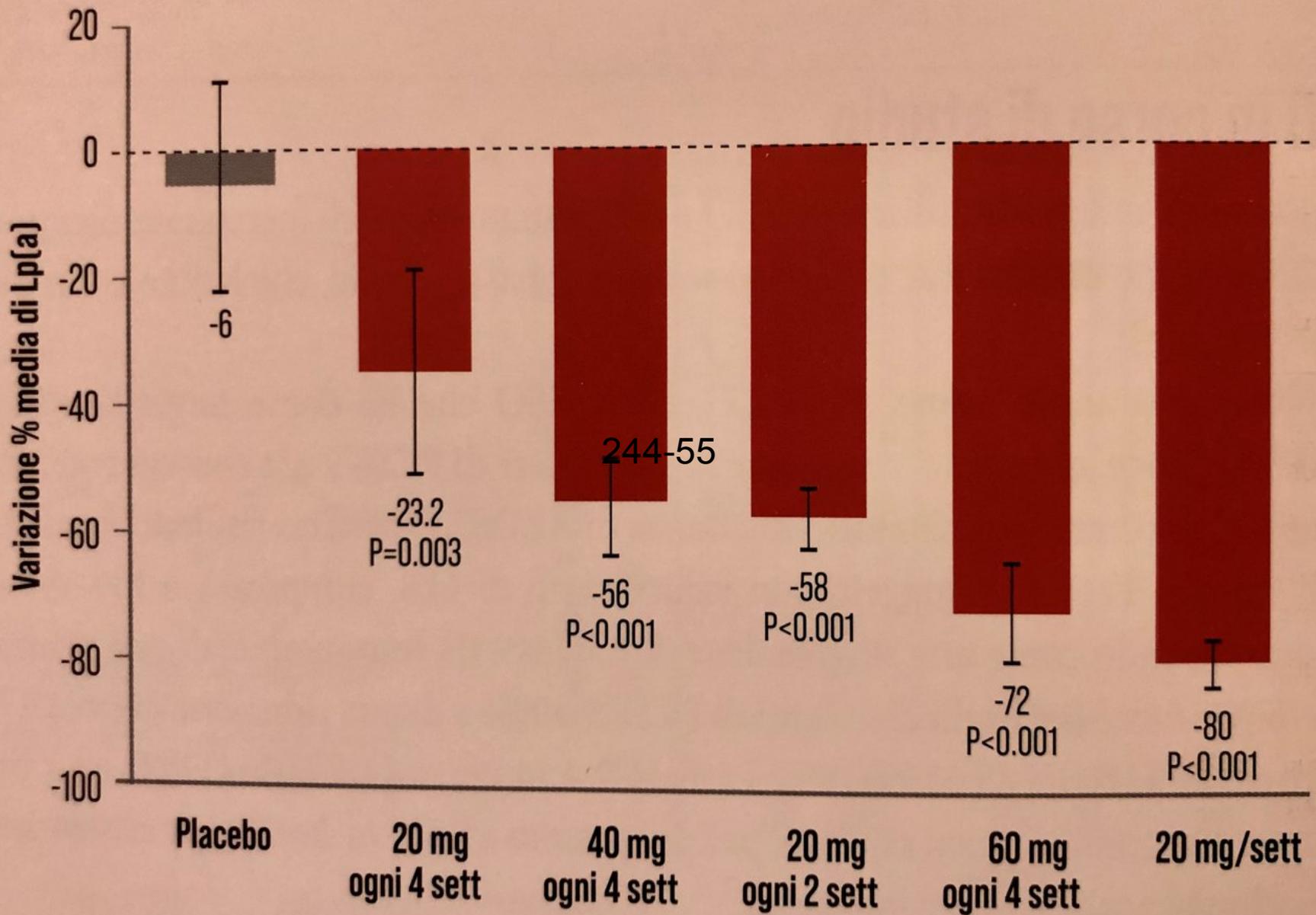


Colchicine- COLCOT
Canakinumab- CANTOS
Statins- JUPITER

Icosapent ethyl- REDUCE-IT
SGLT2 inhibitors
GLP1 receptor agonists
Lp(a) lowering therapies

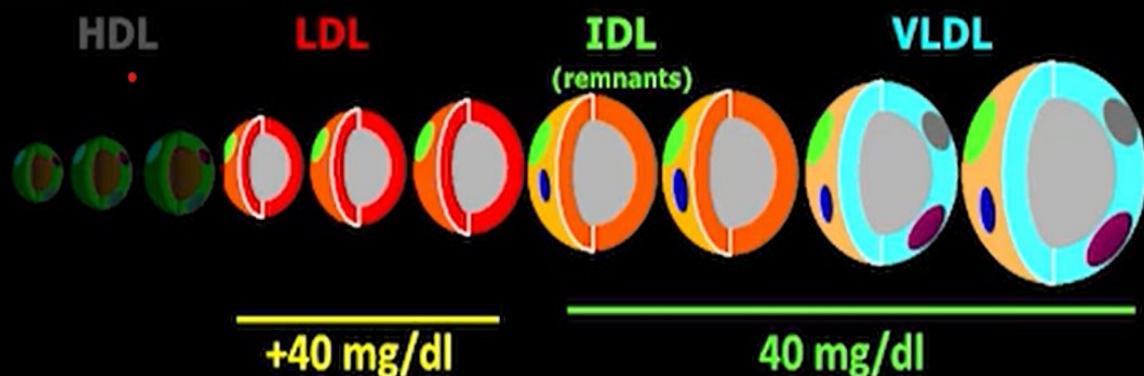
Low-dose rivaroxaban- COMPASS
Dual anti-platelets- PEGASUS
TIMI 54, THEMIS-PCI

“Residual
Cardiovascular
Risk”



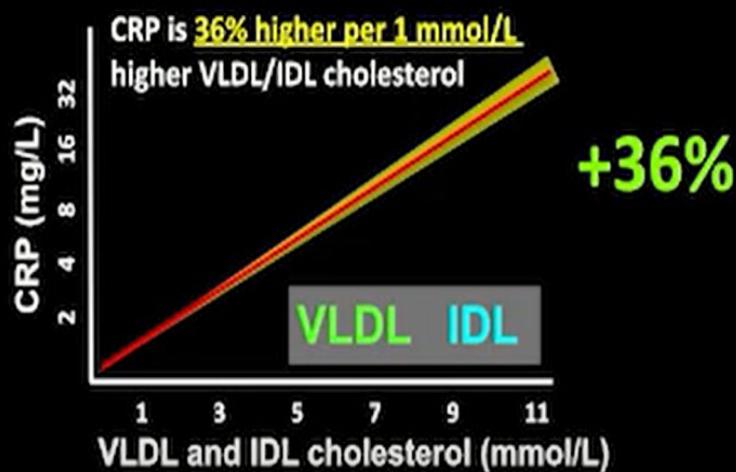
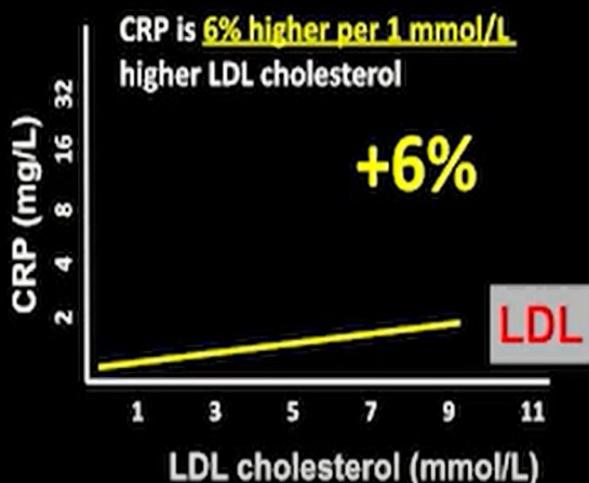
Patients received an hepatocyte-directed antisense oligonucleotide AKCEA-APO(a)-Lrx reducing Lp(a) - Tsimikas S et al. NEJM 2020; 382: 244-55

Association of nonfasting IDL and VLDL cholesterol (**right**) and LDL-C (**left**) with C-reactive protein (CRP) in 48 250 participants from the Copenhagen General Population Study.



Multivariable adjusted association CRP and LDL-C and IDL/VLDL-C

Age, sex, lipid-lowering therapy, smoking, hypertension, diabetes, menopause, and HRT



Association of Hypertriglyceridemia with All-Cause Mortality and Atherosclerotic Cardiovascular Events in a Low-Risk Italian Population: The TG-REAL Retrospective Cohort Analysis

Outcome measures included incident ASCVD events and all-cause mortality. Individuals with normal TG levels (<150 mg/dL) were compared with those with high (150-500 mg/dL) and very high TG (>500 mg/dL).

158,042 individuals (142,289 with normal, 15,558 with high, and 195 with very high TG) were considered.

In the whole cohort, the overall incidence rates of ASCVD and all-cause mortality were 7.2 and 17.1 per 1000 person-years, respectively.

After multivariate adjustment for potential confounders, individuals with high and very high TG showed a significantly increased risk of all-cause mortality ([HR=1.49, $p < 0.001$ and HR=3.08, $p < 0.01$, respectively) and incident ASCVD events (HR=1.61, $p < 0.001$, and HR=2.30, $p < 0.05$, respectively) as compared to those with normal TG.

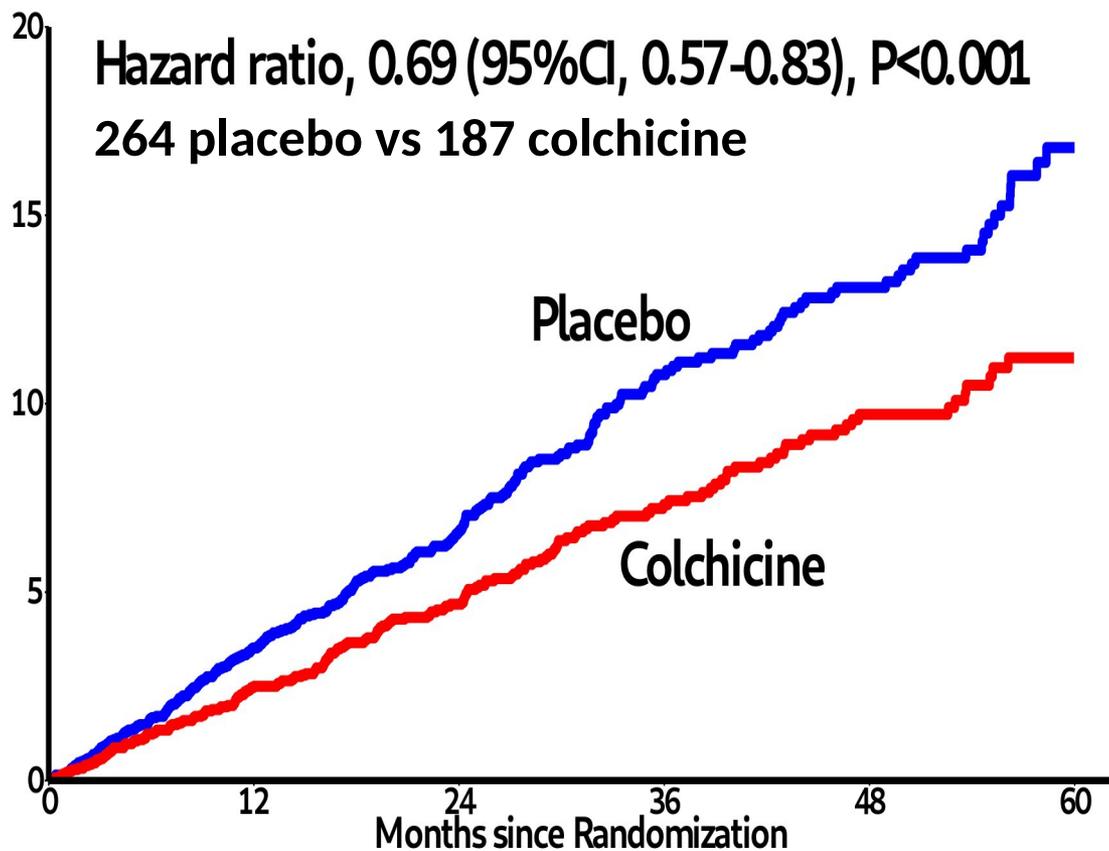
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. The REDUCE-IT Trial

A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years.

A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (HR=0.75, $p < 0.001$); the corresponding rates of the key secondary end point were 11.2% and 14.8% (HR 0.74, $p < 0.001$); cardiovascular death (4.3% vs. 5.2%; HR=0.80, $p=0.03$). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, $p=0.004$). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group ($P=0.06$).

LODOCO 2 - Primary end point

Cardiovascular death, Myocardial infarction, Ischemic stroke or Ischemia-driven coronary revascularization



No. at Risk

2760
2762

2655
2685

1703
1761

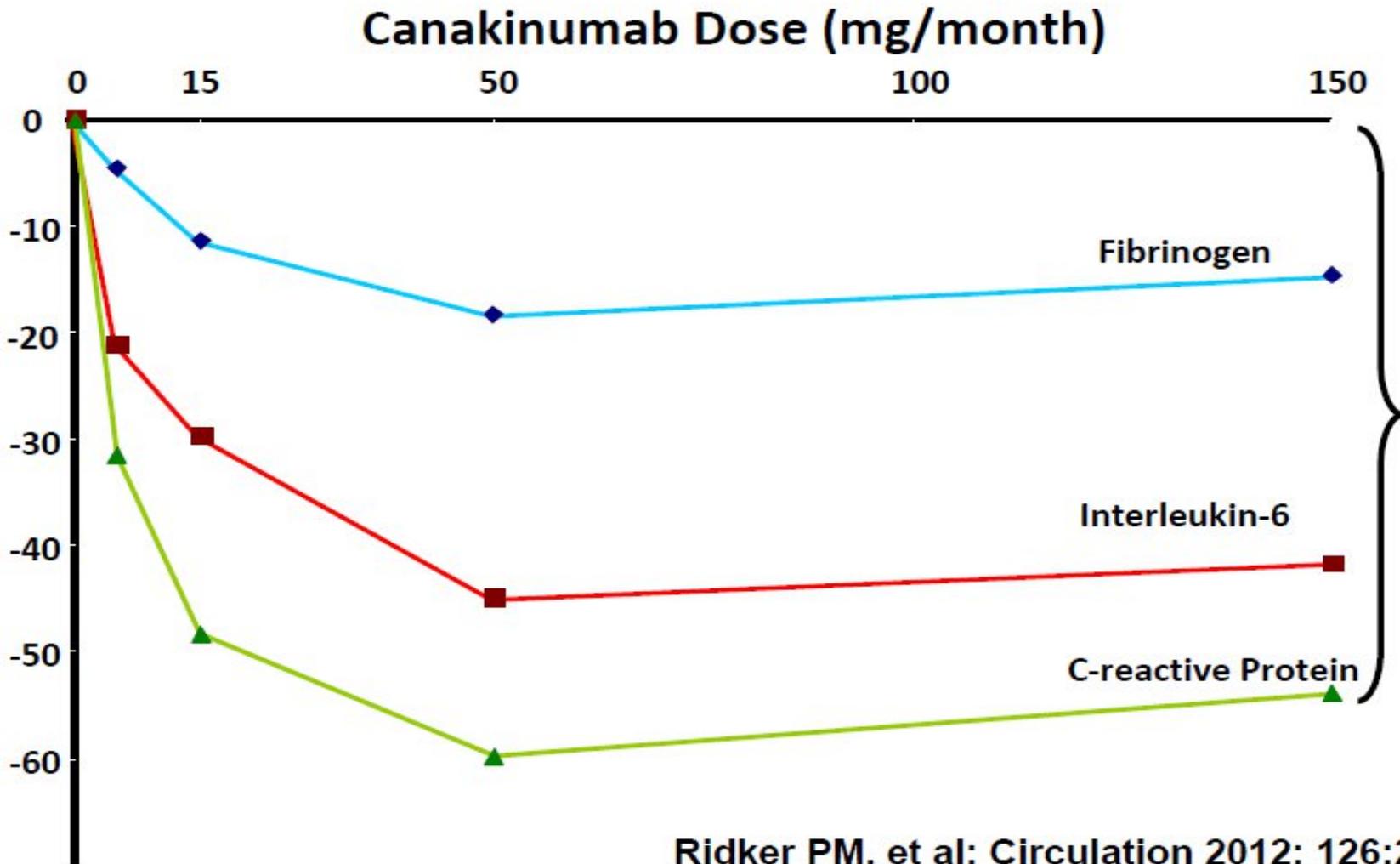
821
890

590
629

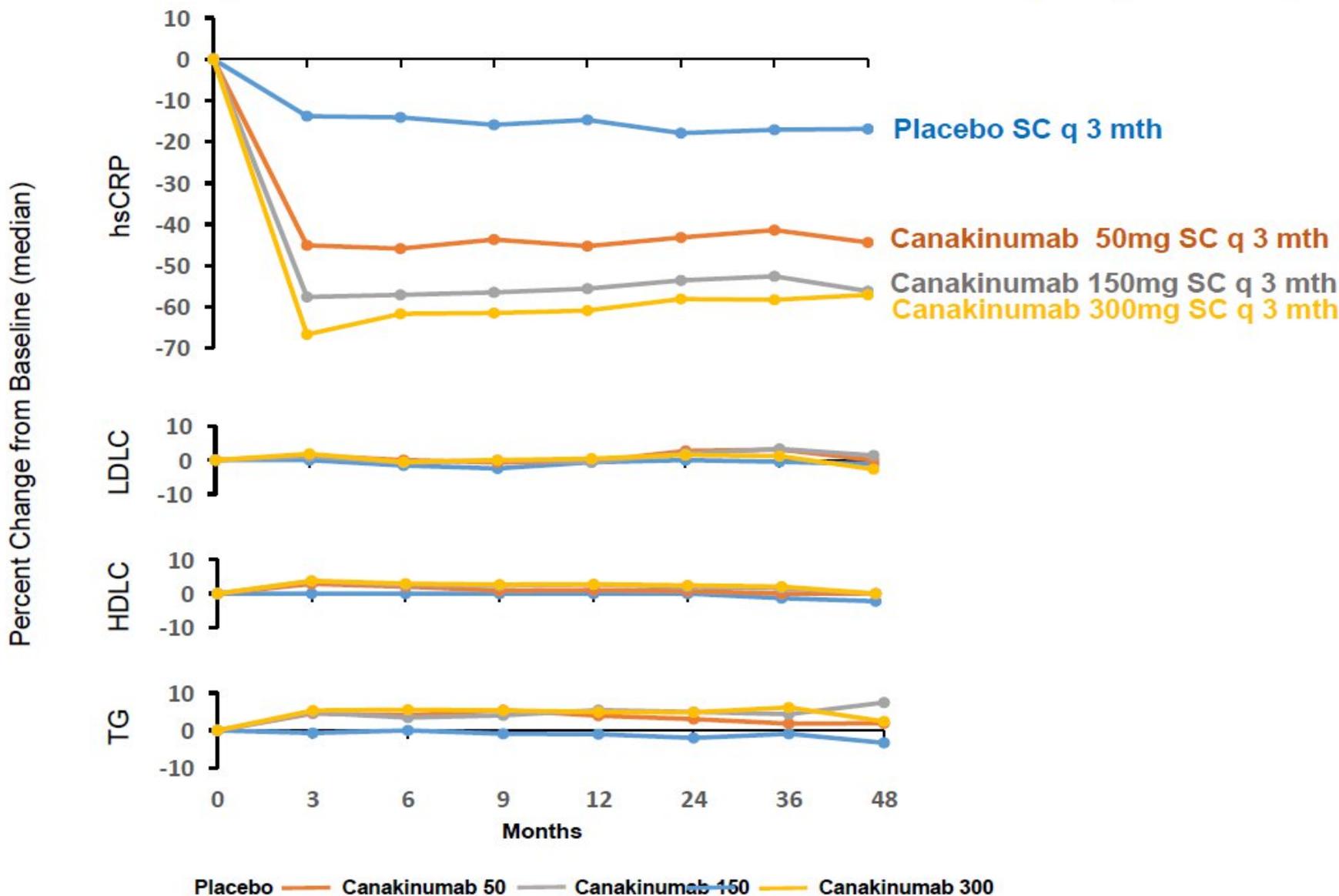
161
166

Effects of Interleukin-1 β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial



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



CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

Endpoint	Placebo (N=3347)	Canakinumab SC q 3 months			P-trend
		50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	
Primary	1.00	0.93	0.85	0.86	0.020
Secondary	1.00	0.90	0.83	0.83	0.002
Myocardial Infarction	1.00	0.94	0.76	0.84	0.028
Urgent Revascularization	1.00	0.70	0.64	0.58	0.005
Any Coronary Revascularization	1.00	0.72	0.68	0.70	<0.001
Stroke	1.00	1.01	0.98	0.80	0.17
Cardiac Arrest	1.00	0.72	0.63	0.46	0.035
CV Death	1.00	0.89	0.90	0.94	0.62
All Cause Mortality	1.00	0.94	0.92	0.94	0.39

SIGNIFICATIVE 23% REDUCTION IN ALL CAUSE MORTALITY WITH RIVAROXABAN VASCULAR DOSE 2.5 MG BID + ASA VS ASA IN CHRONIC CAD

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin N=8313	Aspirin N=8261	Rivaroxaban 2.5 mg bid + aspirin vs aspirin	
	N (%)	N (%)	HR (95% CI)	p-value
Net clinical benefit (CV death, stroke, MI, fatal or critical organ bleeding)	392 (5)	494 (6)	0.78 (0.69-0.90)	0.0003
All-cause mortality	262 (3)	339 (4)	0.77 (0.65-0.90)	0.0012
CV death	139 (2)	184 (2)	0.75 (0.60-0.93)	0.010
Non-CV death	123 (2)	155 (2)	0.79 (0.62-1.00)	0.048

For every 1000 patients with CAD treated with rivaroxaban plus aspirin, 13 MACE events would be prevented and 2 fatal or critical organ bleeds would be caused over a mean 23-month period.

Connolly SJ et al. Lancet. 2018; 391: 205-18

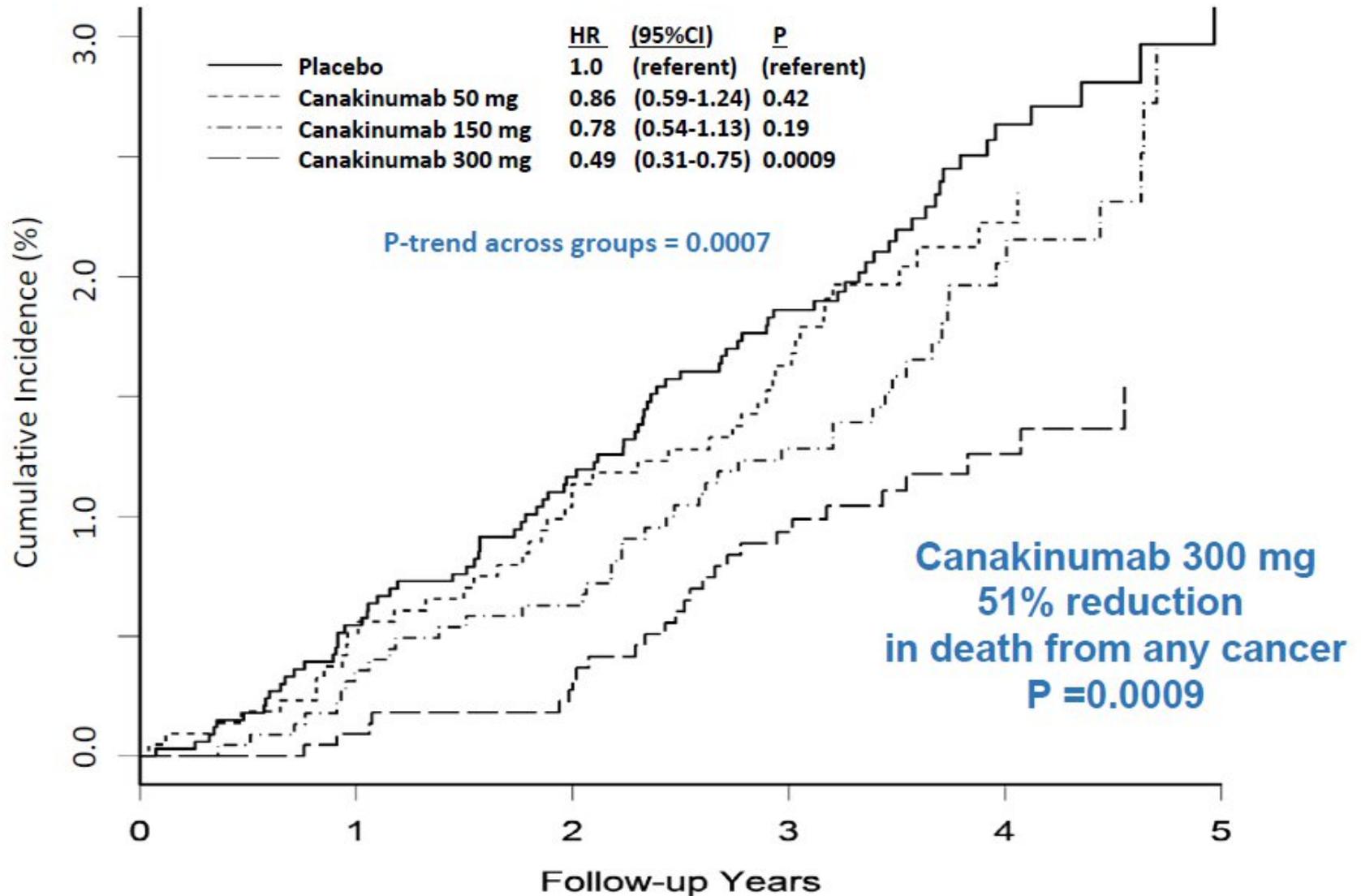


AGENDA

- * Quali sono i Target di LDL-C da raggiungere in Prevenzione Secondaria secondo le Linee Guida ESC 2021? (50% del valore iniziale di LDL-C oppure < 70 o < 55 mg%, rispettivamente per alto ed altissimo rischio)
- * Abbiamo i farmaci per raggiungere tali target? Si
- * Li raggiungiamo? Spesso no (EuroAspire V)
- * Se non li raggiungiamo, ci sono nuove prospettive terapeutiche? Si (Inclisiran)
- * Cosa intendiamo per “Rischio Cardiovascolare Residuo”? Quello legato a Lp(a) - IDL/VLDL e TRP - Infiammazione - Rischio trombotico
- * Quali prospettive in questo campo? Diversi trial effettuati da confermare e altri in progress per confermarne i risultati

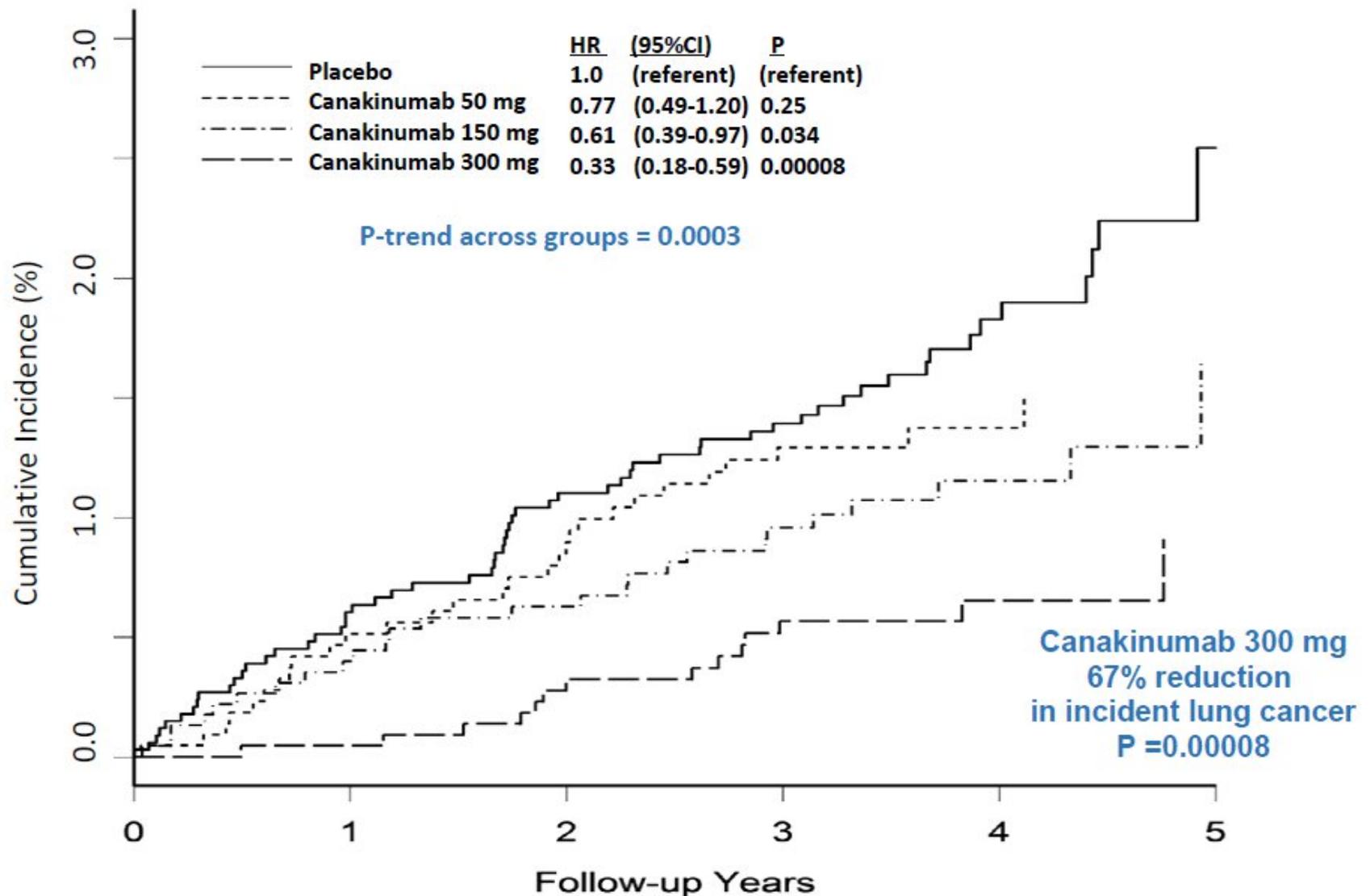
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality



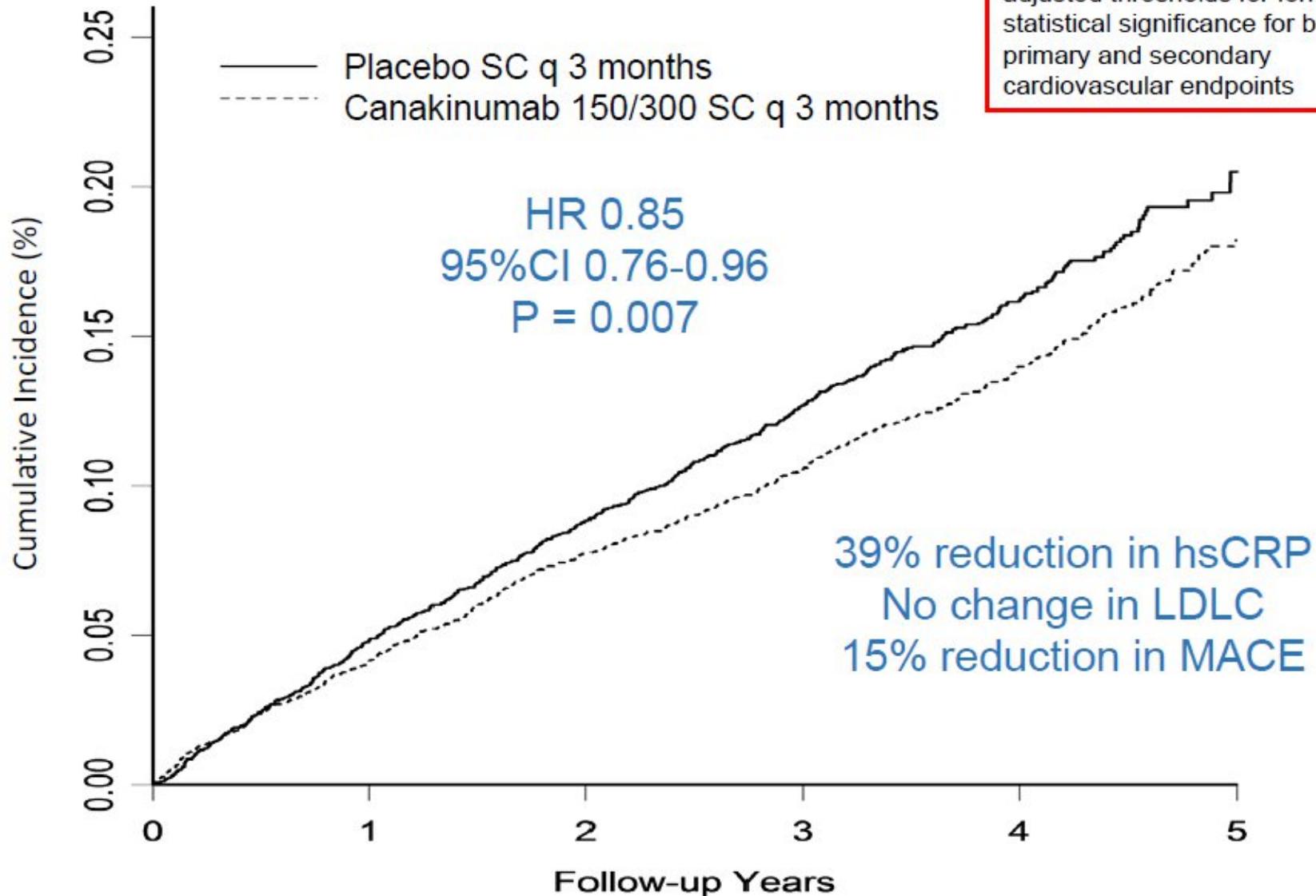
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Incident Lung Cancer

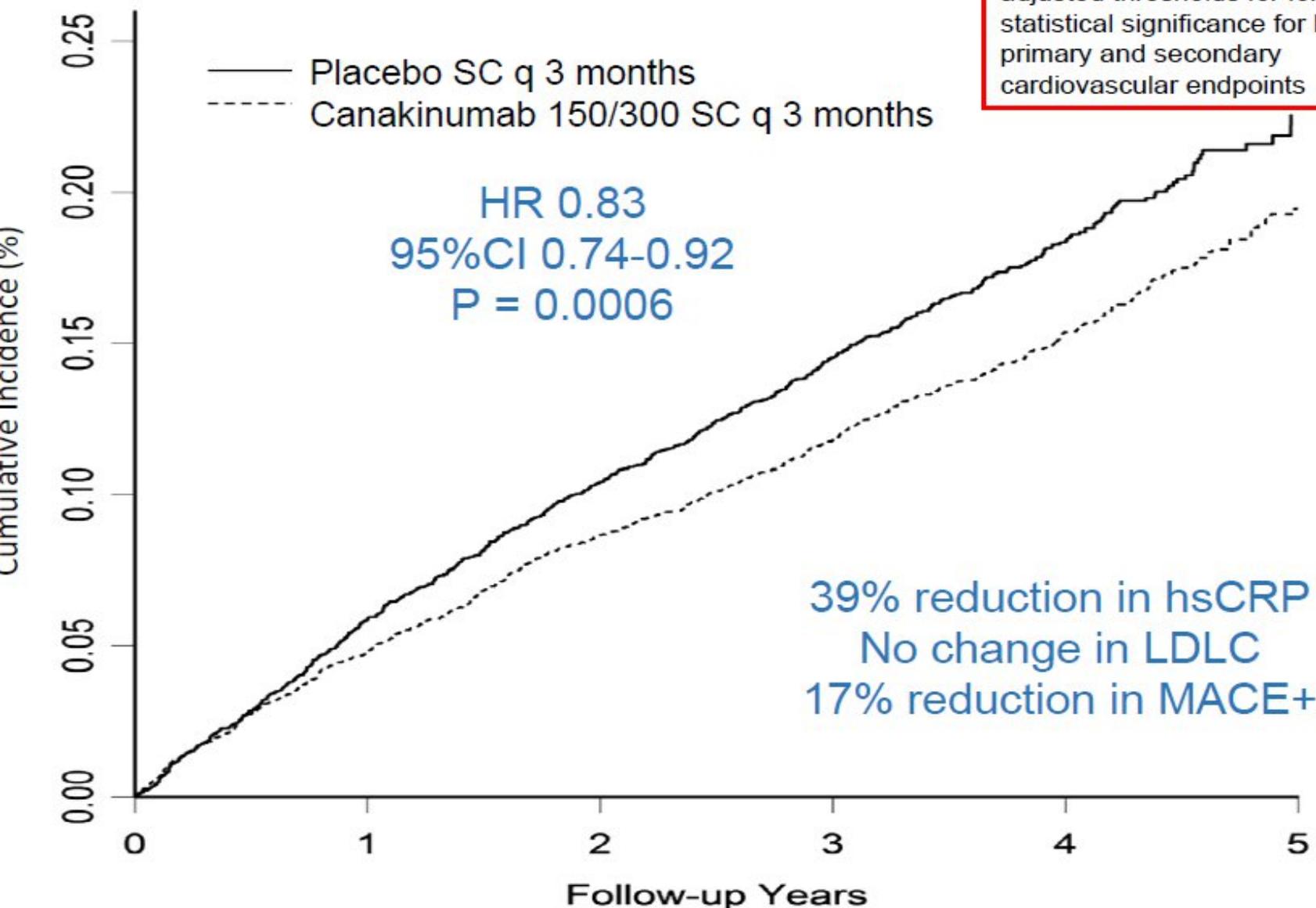


CANTOS: Primary Cardiovascular Endpoint (MACE)

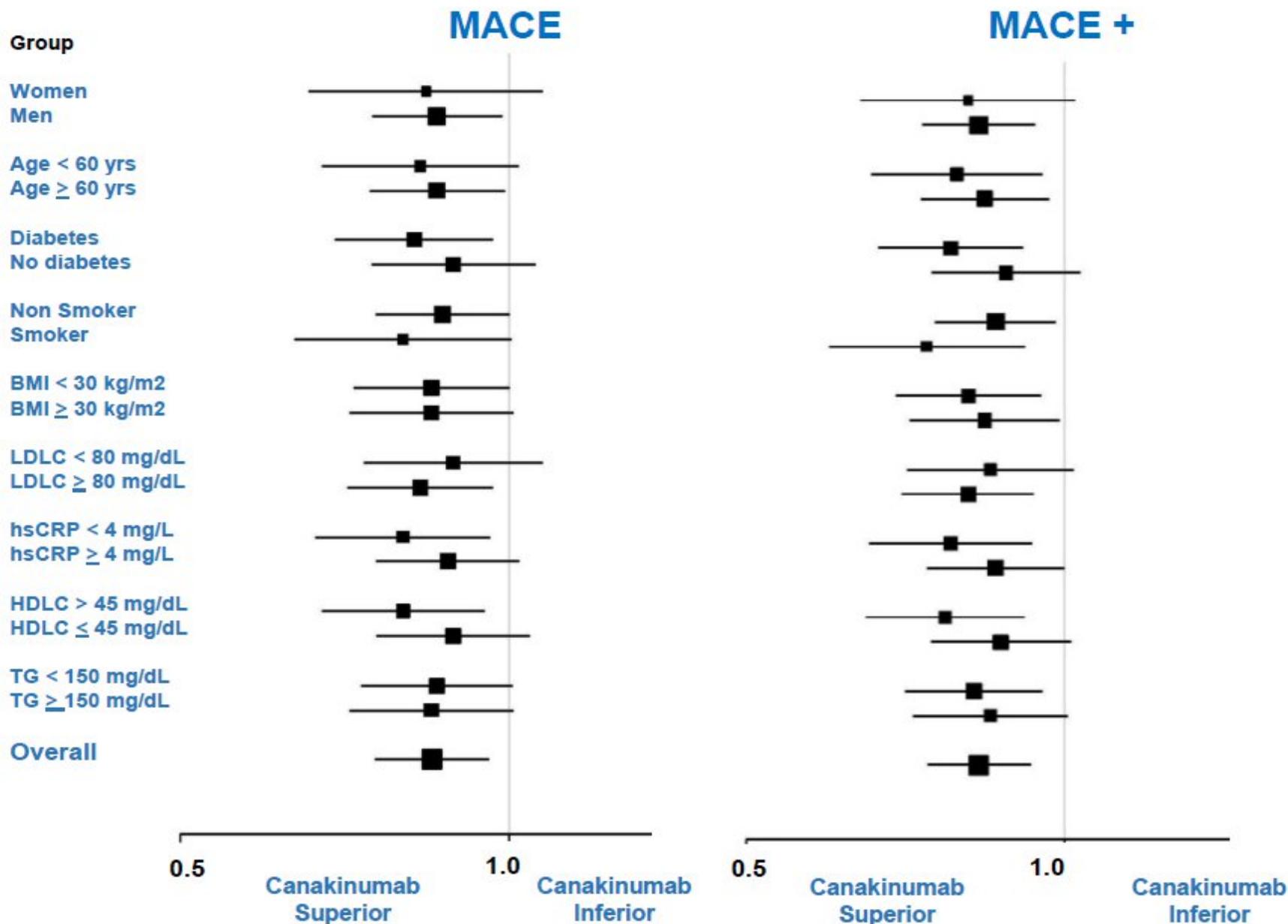
The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



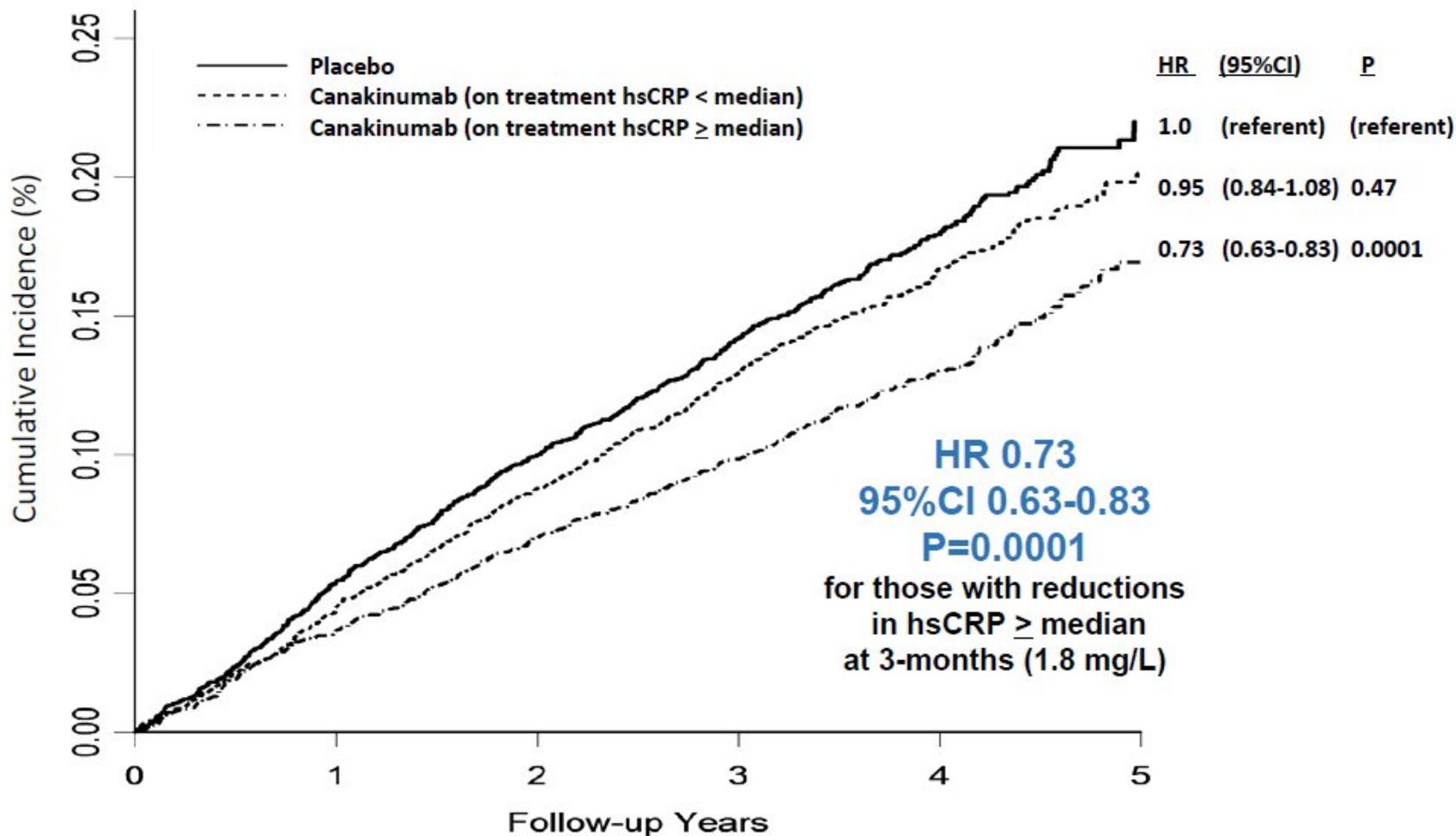
CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

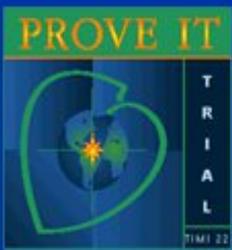


CANTOS: Consistency of Effect Across All Patient Groups



CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)





Subgroups: Reduction in All-Cause Mortality or Major CV Events

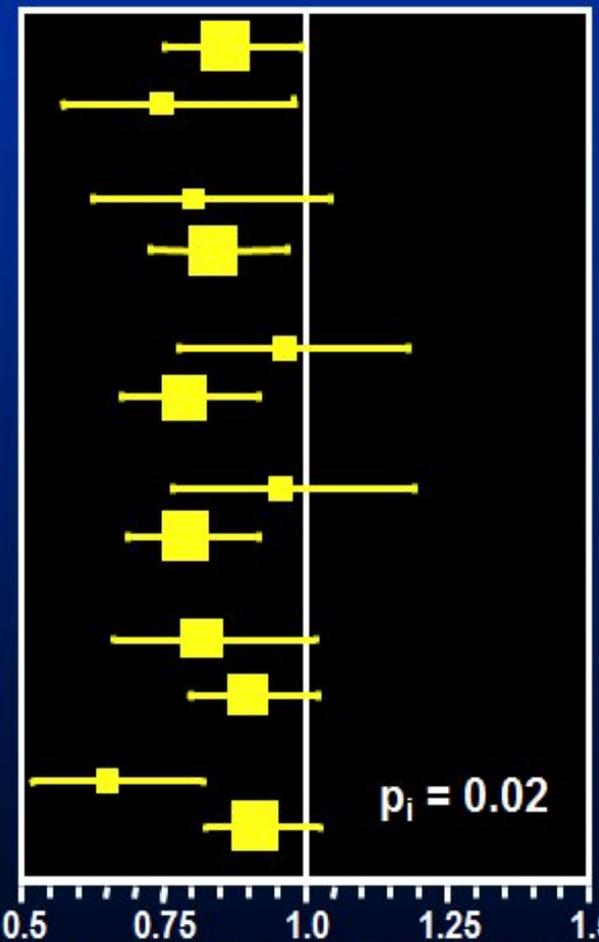
2 Year Event Rates

Atorva 80 **Prava 40**

23.0%	26.2%
20.3%	27.0%
28.8%	34.6%
21.0%	24.6%
28.1%	29.5%
20.1%	25.0%
27.5%	28.9%
20.6%	25.5%
21.7%	26.7%
23.1%	26.0%
20.1%	28.2%
23.5%	25.6%

% of Pts

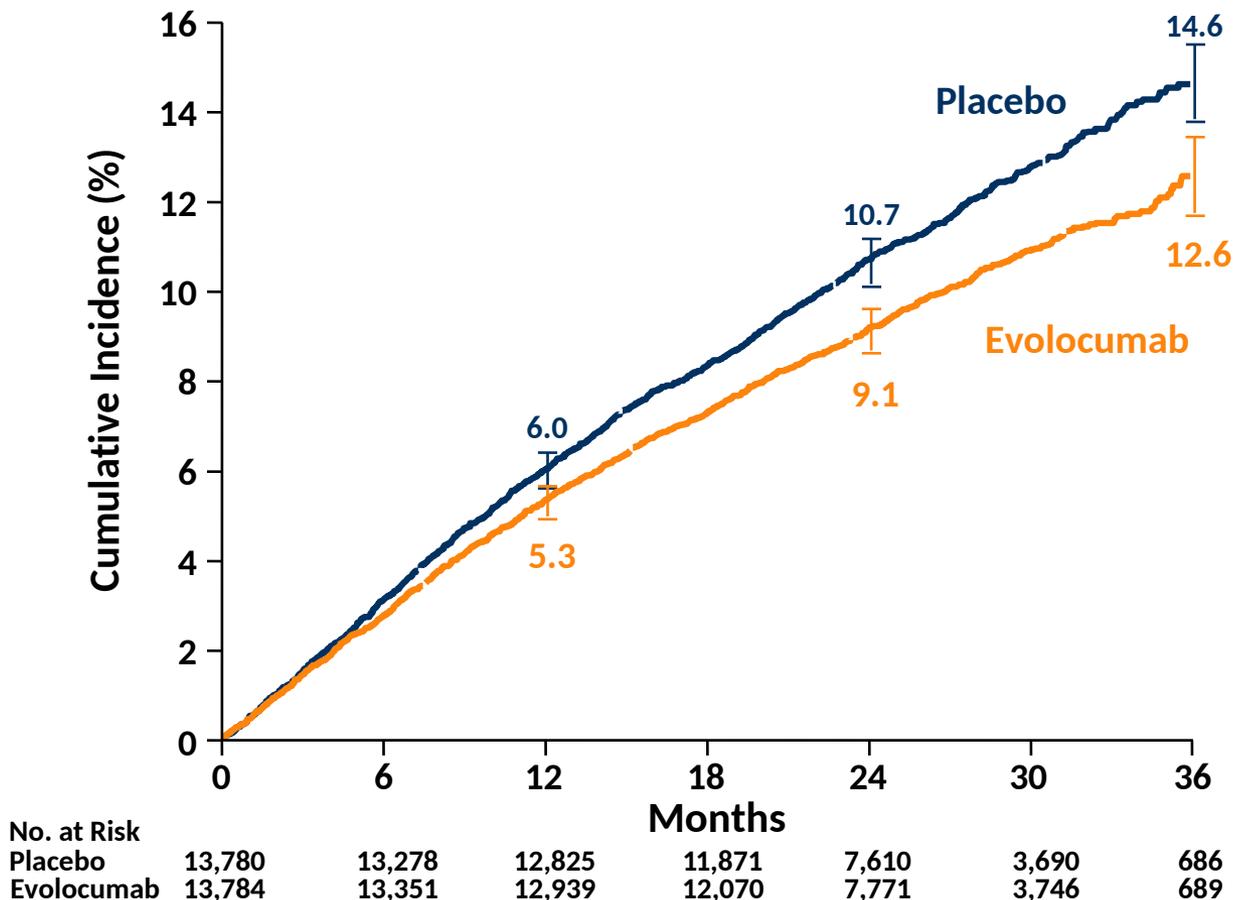
Male	78
Female	22
Diabetes	18
No Diabetes	82
Age ≥ 65	30
Age < 65	70
Prior Statin	25
No Prior Statin	75
HDL-C ≥ 40	44
HDL-C < 40	56
LDL-C ≥ 125	27
LDL-C < 125	73



Atorvastatin 80 mg Better **Pravastatin 40 mg Better**

All $p_{\text{interaction}} = \text{NS}$
except as noted

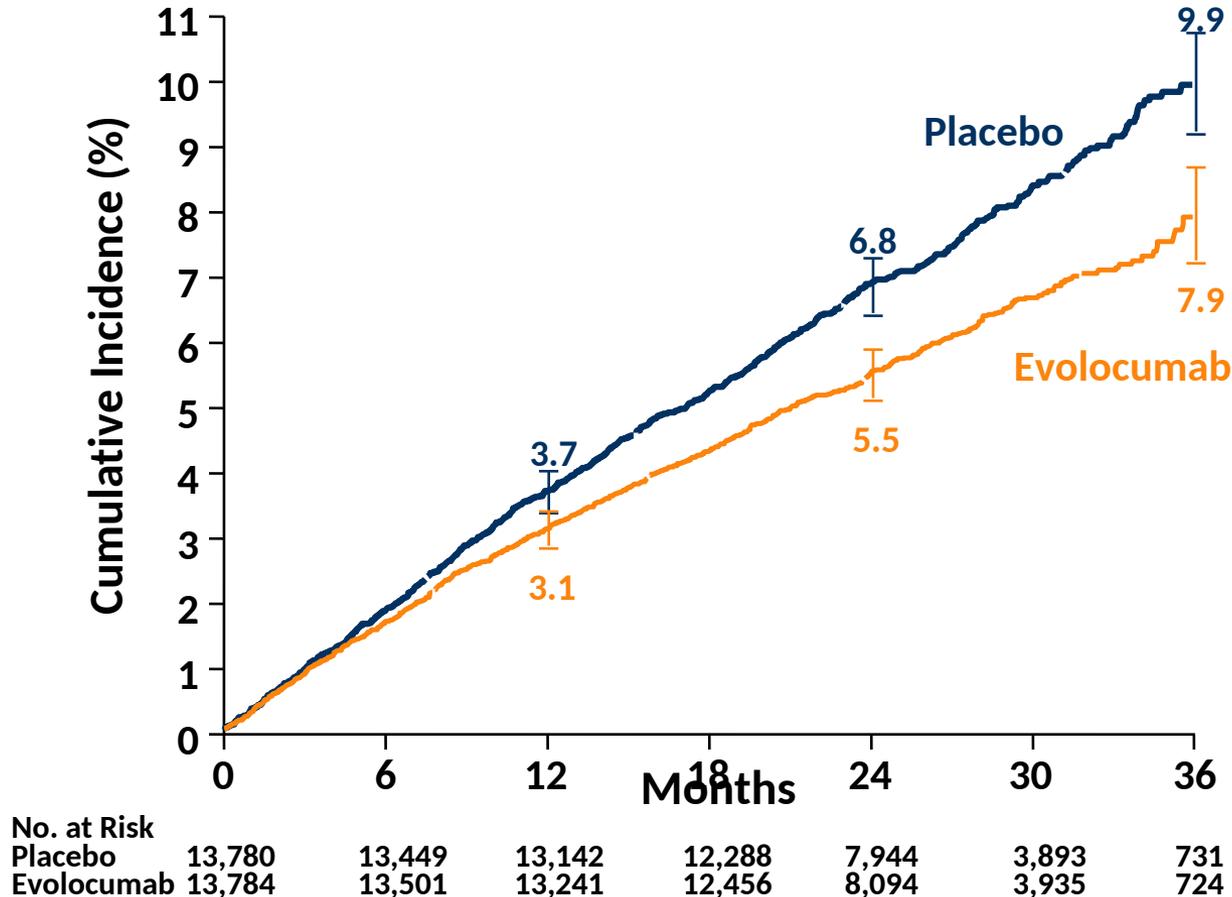
FOURIER Study - Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization



HR 0.85 (95% CI 0.79 to 0.92); P < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio
 Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Key Secondary Endpoint: Composite of CV Death, MI, or Stroke



HR 0.80 (95% CI 0.73 to 0.88); $P < 0.001$

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio

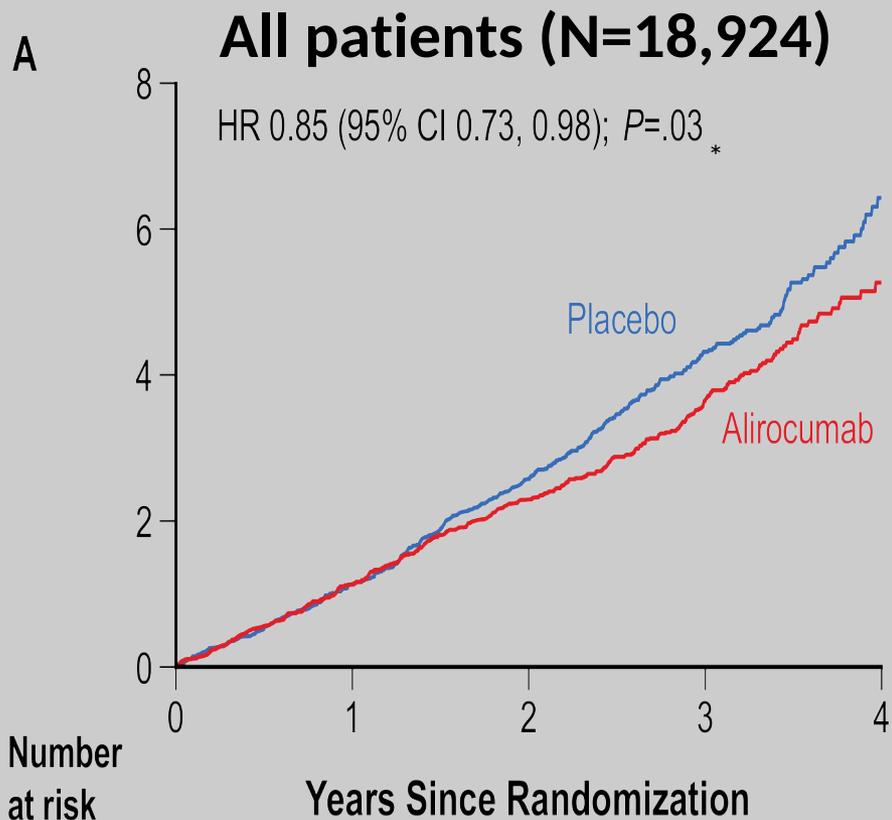
Sabatine MS, et al. *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

AMGEN[®]

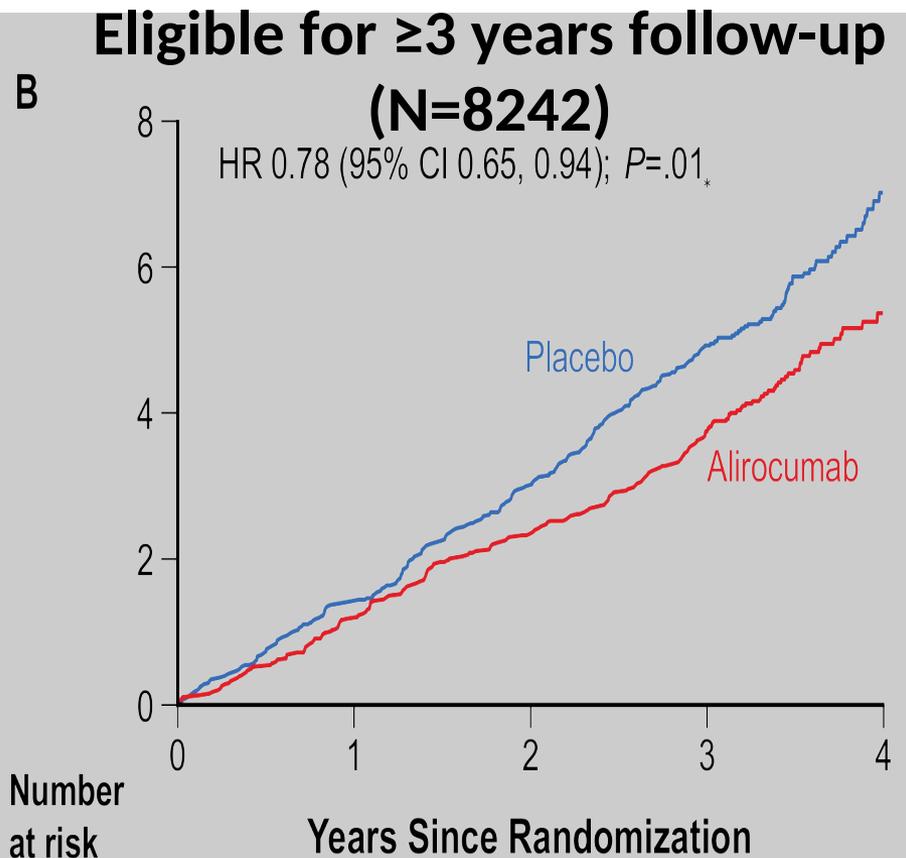
Cardiovascular



All-Cause Death: All Patients vs Patients Eligible for ≥ 3 Years of Follow-Up

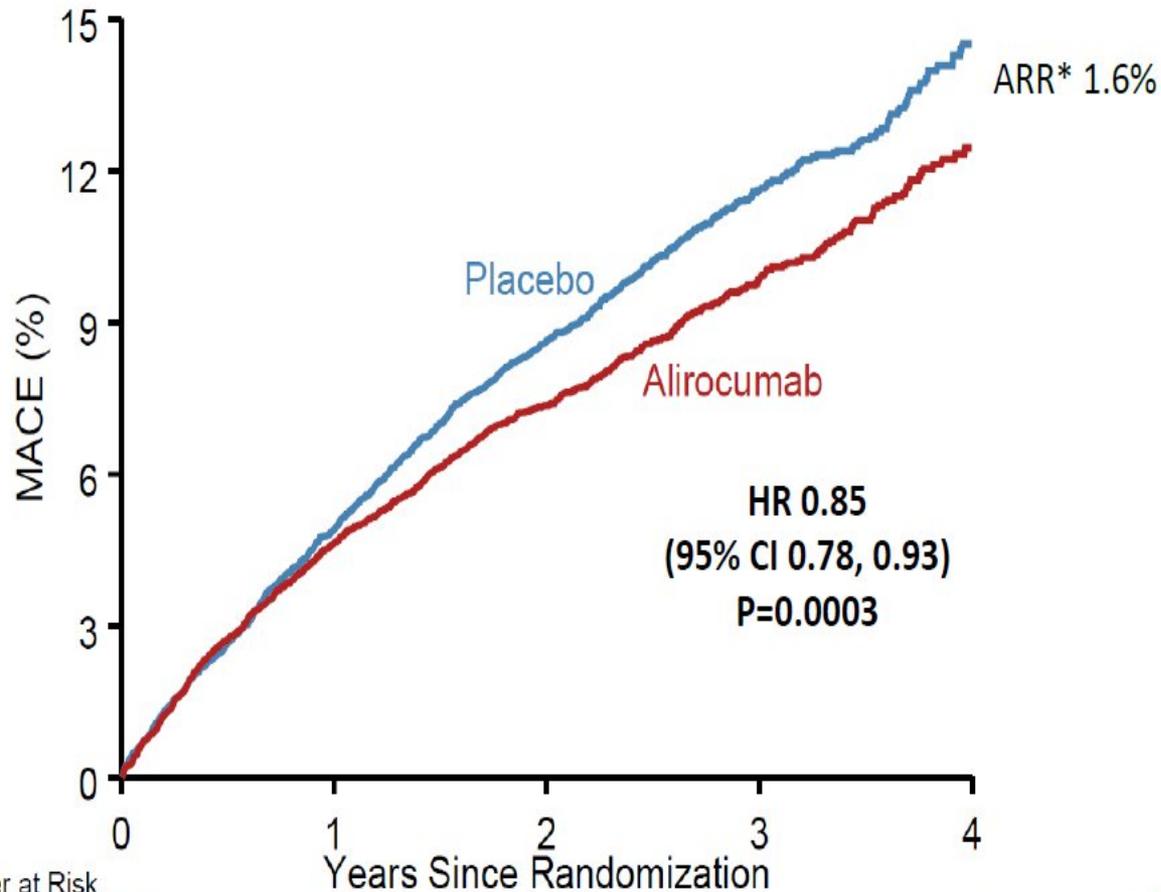


Placebo	9462	9219	8888	3898	737
Alirocumab	9462	9217	8919	3946	746



Placebo	4126	4061	3987	3898	737
Alirocumab	4116	4059	4007	3946	746

Primary Efficacy Endpoint: MACE



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

Number at Risk

Placebo 9462

Alirocumab 9462

Years Since Randomization

8805

8201

3471

629

8846

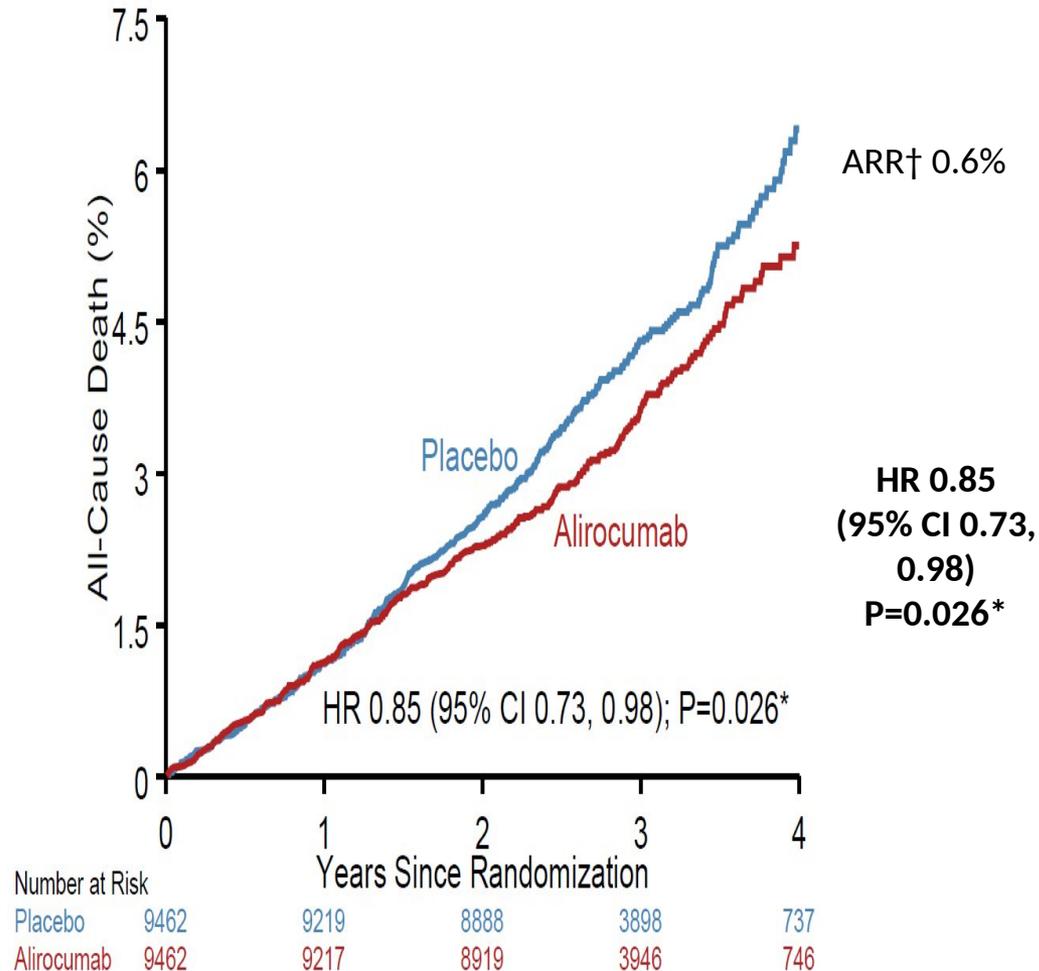
8345

3574

653

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

All-Cause Death



Schwartz GG et al, N Engl J Med. 2018; 379: 2097-107

Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial

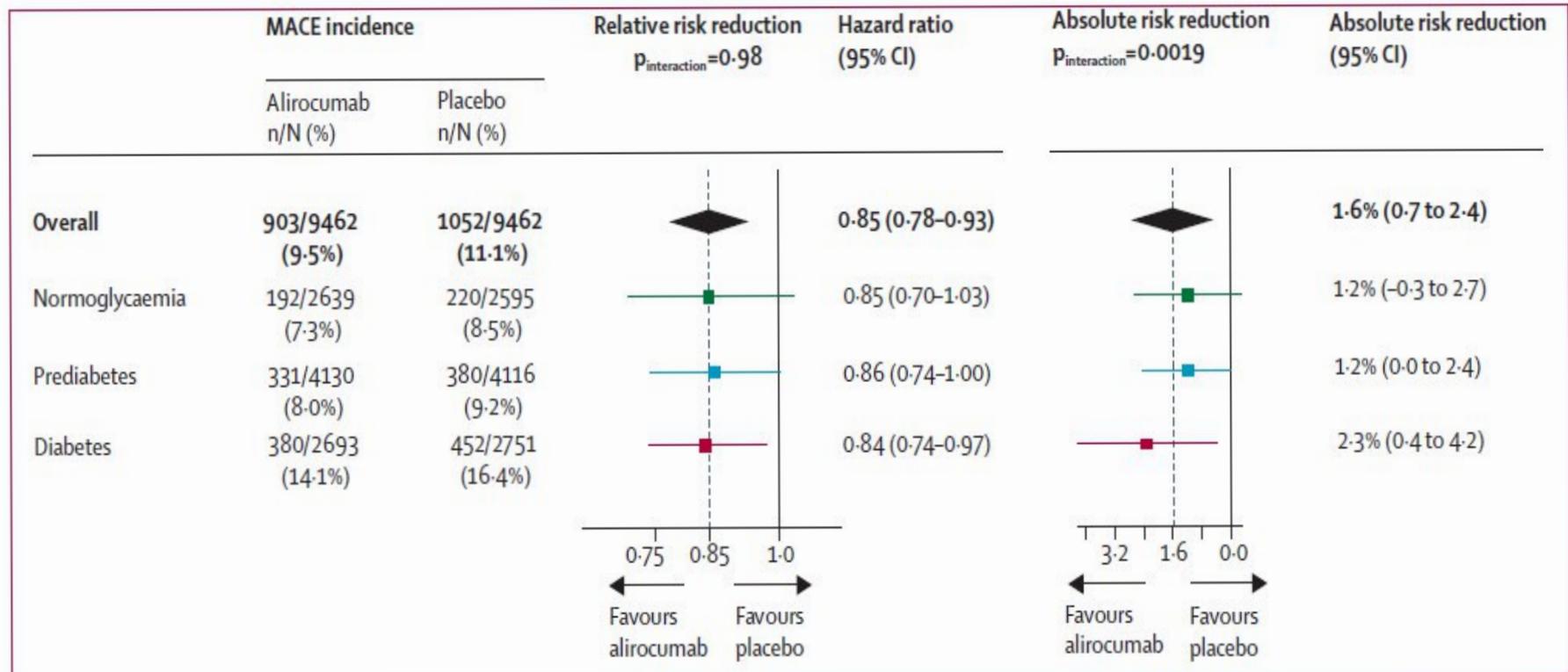


Figure 4: Relative and absolute risk reduction with alirocumab, by baseline glycaemic status
Median follow-up was 2.8 years (IQR 2.3-3.4). MACE=major adverse cardiovascular events.

INZIARE PRECOCEMENTE TERAPIA CON INIBITORI PCSK9

IL BENEFICIO E' TANTO MAGGIORE QUANDO SI INIZIA PRECOCEMENTE DOPO LA SCA

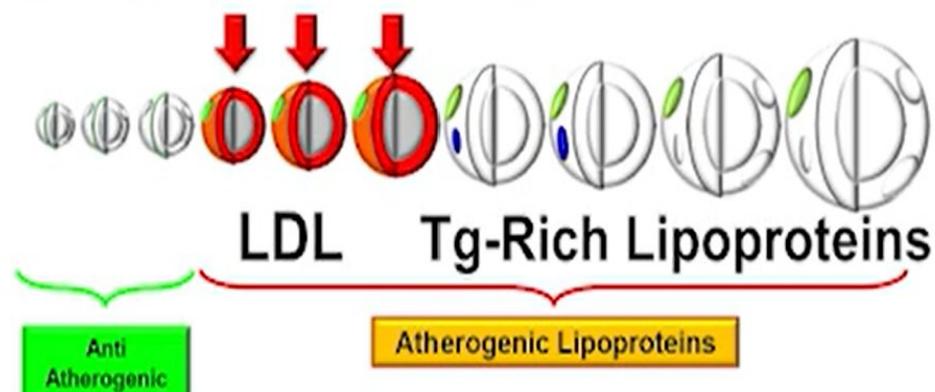
Subgroup	Patients	Incidence (%)		HR (95% CI)	
		Alirocumab	Placebo		
Index to randomization					
<2 months	6178	10.3	12.3	0.83 (0.71–0.96)	
2 to <6 months	9518	9.6	11.1	0.85 (0.75–0.96)	
≥6 months	3228	8.0	8.7	0.90 (0.71–1.14)	

2021 ESC Guidelines: LDL Cholesterol: #1 Lipid parameter for screening, diagnosis and management

➔ LDL-C analysis is recommended as the primary lipid analysis method for **screening, diagnosis, and management.**

I

C



European Heart Journal
(2021) 42, 3227-3337

Known Atherosclerotic Cardiovascular Disease

High Intensity Statin Therapy

Biologic Issue

Residual Cholesterol Risk

Residual Inflammatory Risk

Residual Thrombotic Risk

Residual Triglyceride Risk

Residual Lp(a) Risk

Critical Biomarker

LDL-C \geq 100 mg/dL

hsCRP \geq 2 mg/L

No simple biomarker

TG \geq 100 mg/dL

Lp(a) \geq 50 mg/dL

THE EVOLVING UNDERSTANDING AND APPROACH TO RESIDUAL CARDIOVASCULAR RISK MANAGEMENT

Devinder S, Dhindsa DS, et al. Front Cardiovasc Med 2020; 7: 88.
doi: 10.3389/fcvm.2020.00088. eCollection 2020.

In the JUPITER trial, rosuvastatin 20 mg daily reduced median high sensitivity C-reactive protein (hsCRP) by 37% as compared to placebo.

Interestingly, the magnitude of hsCRP reduction achieved with rosuvastatin was proportional to the reduction in CV.

Individuals who achieved hsCRP levels < 2 mg/L demonstrated a 55% reduction in the primary endpoint compared to those with hsCRP levels \geq 2 mg/L ($p = 0.007$); however, this benefit was not independent of LDL-C lowering.

Similarly, in PROVE-IT TIMI 22 Study, patients who achieved hsCRP levels < 2 mg/L sustained fewer recurrent CV events.

Whether the benefits of statins are related to LDL-C lowering, reduction in inflammation, or a combination of these factors remains a matter of debate.

INFLAMMATION AND CARDIOVASCULAR DISEASE: THE FUTURE

Arnold N, Koenig W et al. Eur Cardiol. 2021 Feb; 16: e20. Published online 2021 May 17.
doi: 10.15420/ecr.2020.50 PMID: PMC8157394 - PMID: 34093741

Interestingly, both a recent meta-analysis of 2,546 patients who were treated with a novel non-statin lipid-lowering drug class, namely PCSK9-I, as well as the two large PCSK9-I outcome trials FOURIER and ODYSSEY OUTCOMES, demonstrated that PCSK9-I had no significant effect on hsCRP despite profound LDL-C reduction (up to 50–60%).

Nonetheless, post-hoc data from FOURIER and SPIRE in patients at high risk on statin treatment consistently documented that inflammation still plays an important prognostic role, even in subjects with very low LDL-C concentrations (< 20 mg/dl), in whom hsCRP was able to independently modify CV risk.

This supports the notion that additional anti-inflammatory treatment in these patients might provide benefit beyond aggressive lipid lowering.

RESIDUAL CARDIOVASCULAR RISK AT LOW LDL: REMNANTS, LIPOPROTEIN(a), AND INFLAMMATION

Hoogeveen RC, Ballantyne CM. *Clinical Chemistry* 2021; 67: 143–153

PCSK9-I, evolocumab and alirocumab, reduce Lp(a) concentration by 23%–27%. In patients with higher baseline Lp(a), PCSK9-I provided greater absolute Lp(a) reduction and greater absolute risk reduction for CV events. In a subgroup analysis from Odyssey Outcomes, Lp(a) reduction with alirocumab independently contributed to ASCVD reduction beyond the effects of reductions in LDL-C and non-HDL-C.

Beyond residual cholesterol risk, these results support the concept of residual inflammatory risk. Residual inflammatory risk is not uncommon; in both PROVE IT and IMPROVE-IT, almost one-third of statin-treated patients had hs-CRP >2 mg/L. More than one-third of the patients in the PCSK9 CV outcomes trials met the eligibility criteria for CANTOS despite achieving very low LDL-C (CRP > 2 mg%).

Evidences from epidemiologic and genetic studies, as well as randomized clinical trials, suggest that remnant lipoproteins, Lp(a), and inflammation are causally related to risk of ASCVD in individuals already treated with statin therapy. Novel therapies to reduce circulating concentrations of TGRL, Lp(a), and inflammatory markers in these individuals show promising results, although their efficacy in reducing residual CV risk is still under investigation with several clinical trials currently ongoing.

ADDRESSING DYSLIPIDEMIC RISK BEYOND LDL-CHOLESTEROL.

Tall AR, ... , Goldberg IJ et al. J Clin Invest. 2022;132 (1): e148559.

Despite the success of LDL-lowering drugs in reducing cardiovascular disease (CVD), there remains a large burden of residual disease due in part to persistent dyslipidemia characterized by **elevated levels of triglyceride-rich lipoproteins (TRLs) and reduced levels of HDL**. This form of dyslipidemia is increasing globally as a result of the rising prevalence of **obesity and metabolic syndrome**.

Large clinical trials of such agents in patients with high CVD risk and elevated levels of TRL will be required to demonstrate efficacy of these approaches.

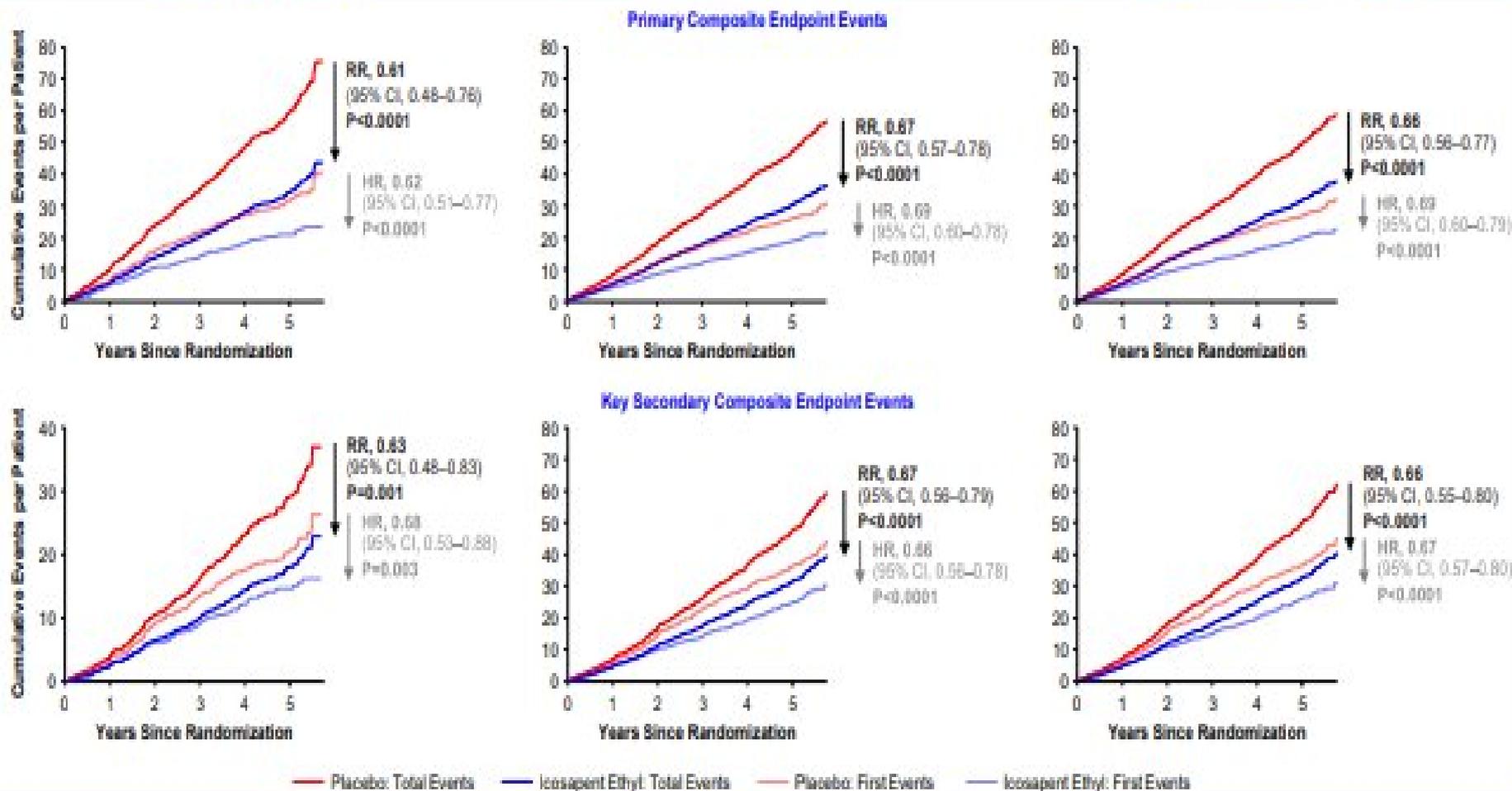
RESULTS (cont.)

Substantial and Consistent Reductions in First and Total (First and Subsequent) Primary and Key Secondary Endpoint Events Across Various Definitions of Dyslipidemia:
 Similar relative risk reductions of 31-39% across dyslipidemia definitions

REDUCE-IT Prespecified
 (TG ≥ 200 + HDL-C ≤ 35 mg/dL)

Guideline-Informed
 (TG ≥ 150 + HDL-C $< 40/50$ mg/dL)

STRENGTH-Informed
 (TG ≥ 180 + HDL-C $< 42/47$ mg/dL)



Ranked secondary end points

	Colchicine (N = 2762)	Placebo (N = 2760)	Hazard Ratio (95% CI)	P Value
1. Cardiovascular death, Myocardial infarction, or Ischemic stroke	115 (4.2)	157 (5.7)	0.72 (0.57-0.92)	0.007
2. Myocardial infarction or Ischemia-driven coronary revascularization	155 (5.6)	224 (8.1)	0.67 (0.55-0.83)	<0.001
3. Cardiovascular death or Myocardial infarction	100 (3.6)	138 (5.0)	0.71 (0.55-0.92)	0.010
4. Ischemia-driven coronary revascularization	135 (4.9)	177 (6.4)	0.75 (0.60-0.94)	0.012
5. Myocardial infarction	83 (3.0)	116 (4.2)	0.70 (0.53-0.93)	0.014
6. Ischemic stroke	16 (0.6)	24 (0.9)	0.66 (0.35-1.25)	0.198
7. Death from any cause	73 (2.6)	60 (2.2)	1.21 (0.86-1.71)	
8. Cardiovascular death	20 (0.7)	25 (0.9)	0.80 (0.44-1.44)	

Pathophysiology of TG-rich lipoproteins in the progression of atherosclerosis

