Meeting Nazionale ITACARE-P 2025

La Cardiologia Riabilitativa e Preventiva come snodo fondamentale della cura della persona con cardiopatia

La valutazione del rischio cardiovascolare residuo e la relativa strategia terapeutica

Cesare Greco

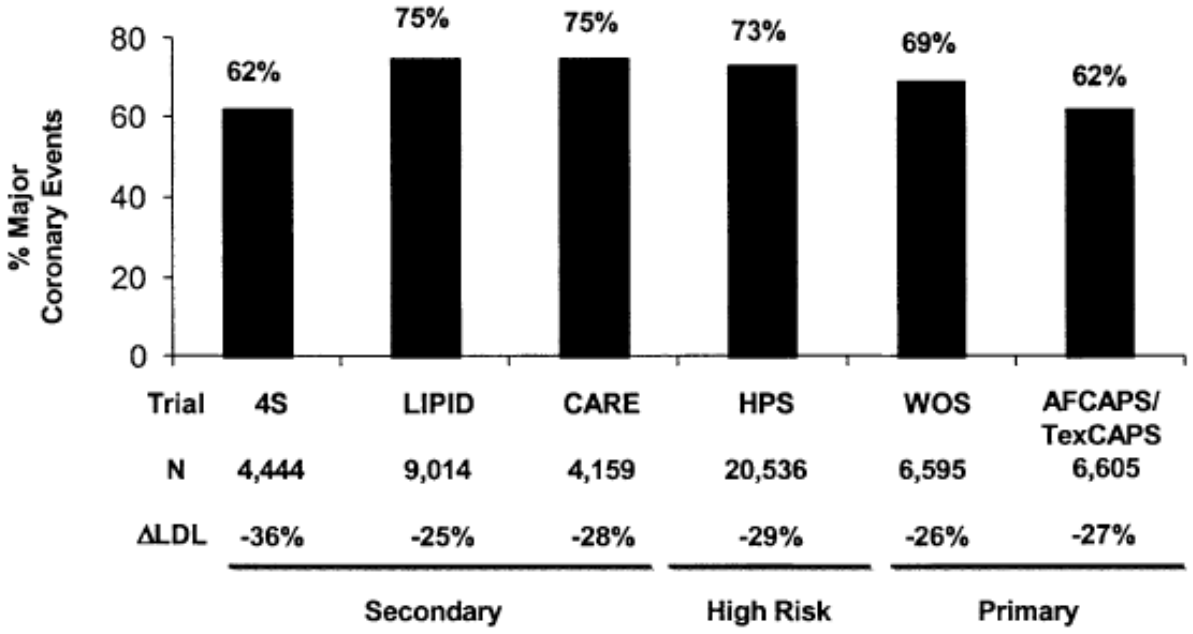
CENTRO CONGRESSI FRENTANI
Roma, 21-22 novembre 2025

The Forgotten Majority

Unfinished Business in Cardiovascular Risk Reduction

Peter Libby, MD

….the residual burden of cardiovascular morbidity and mortality



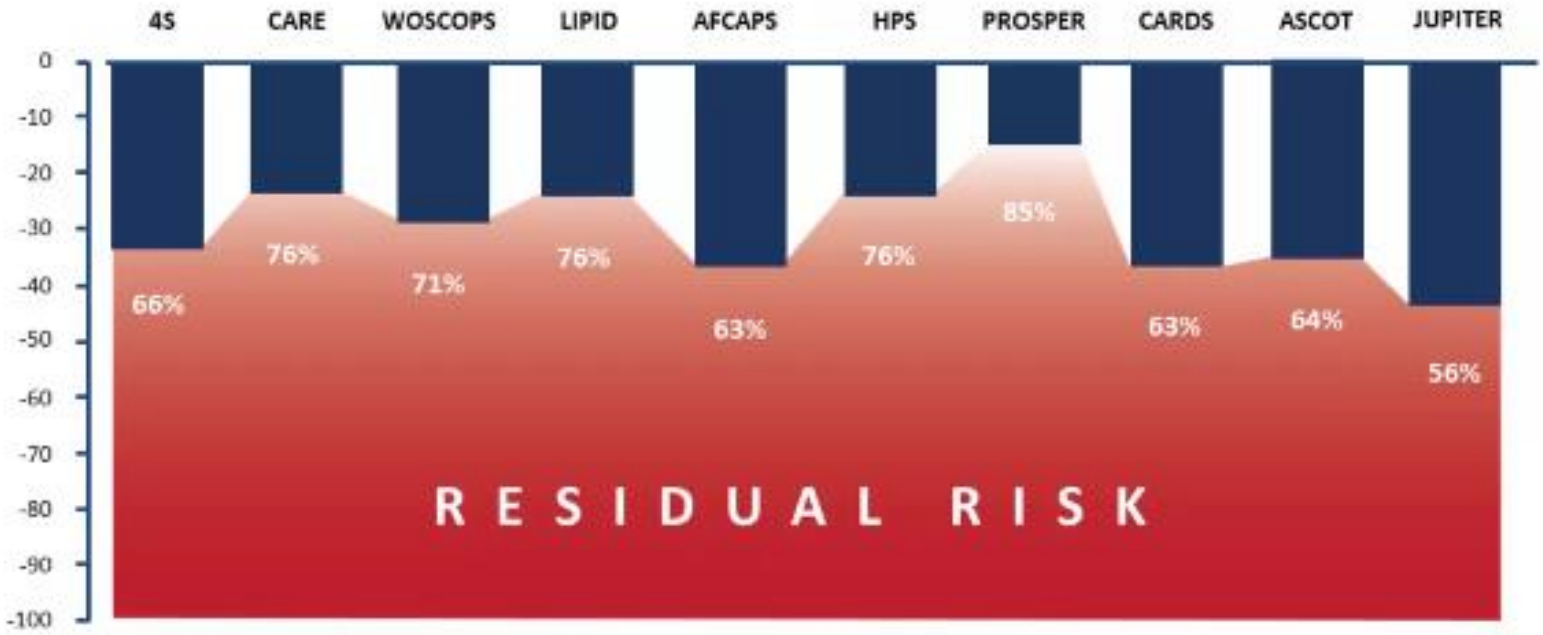
DO WE INTERVENE TOO LATE?

ARE OUR INTERVENTIONS TOO SHORT?

DO WE INTERVENE TOO LITTLE?

JACC 2005

Landmark Trials With Statin Monotherapy[1-10]



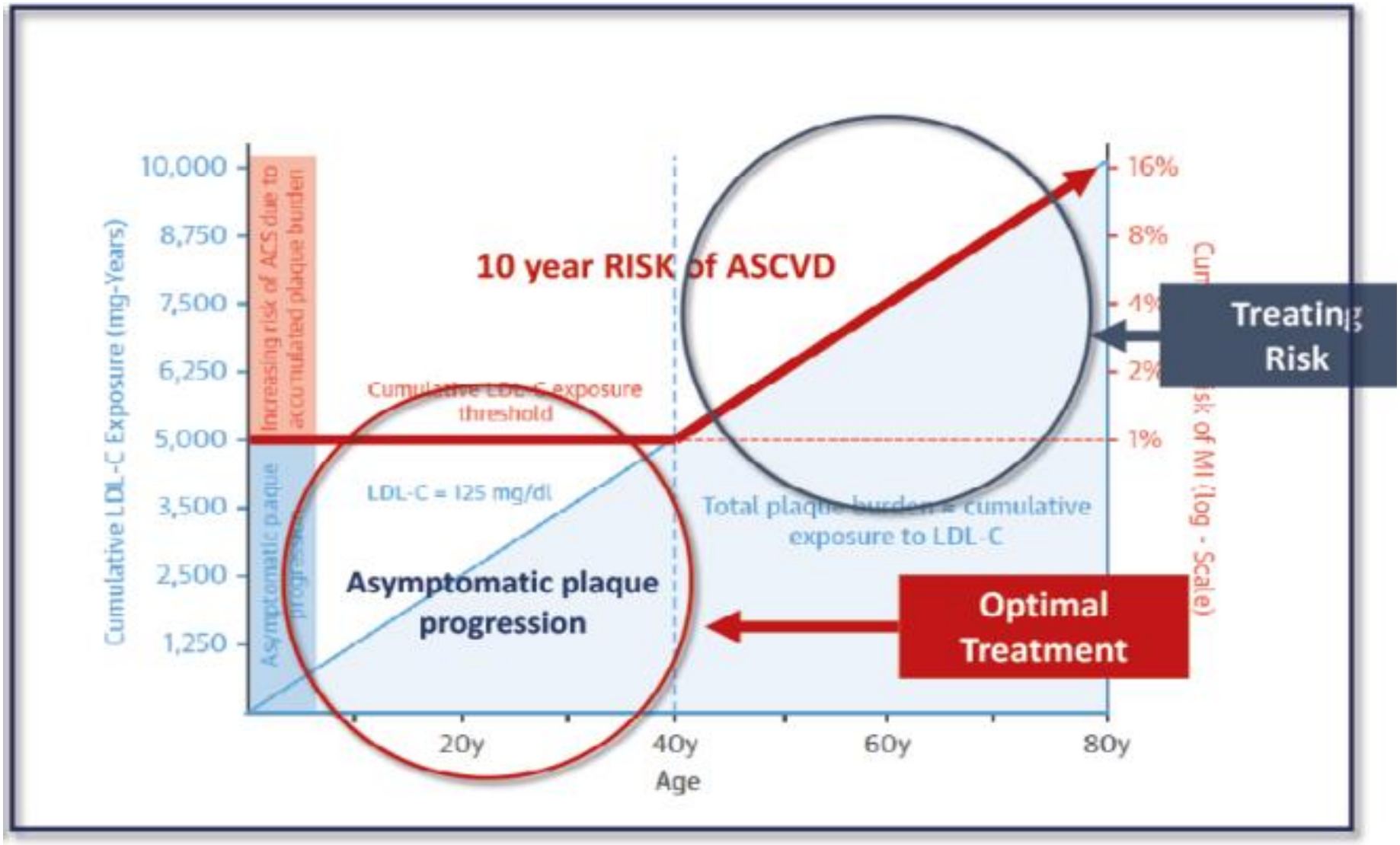
Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews

Table 2 Population demographics

Review	Participants (n)	Gender	% Male	Mean age
CTT 2012 and 2015	134 537	Women and men	59†	65.3 (women) 62.0 (men)
Mora *et al* 2010	13 154	Women	0	64‡
Ray *et al* 2010	65 229	Women and men	65	62

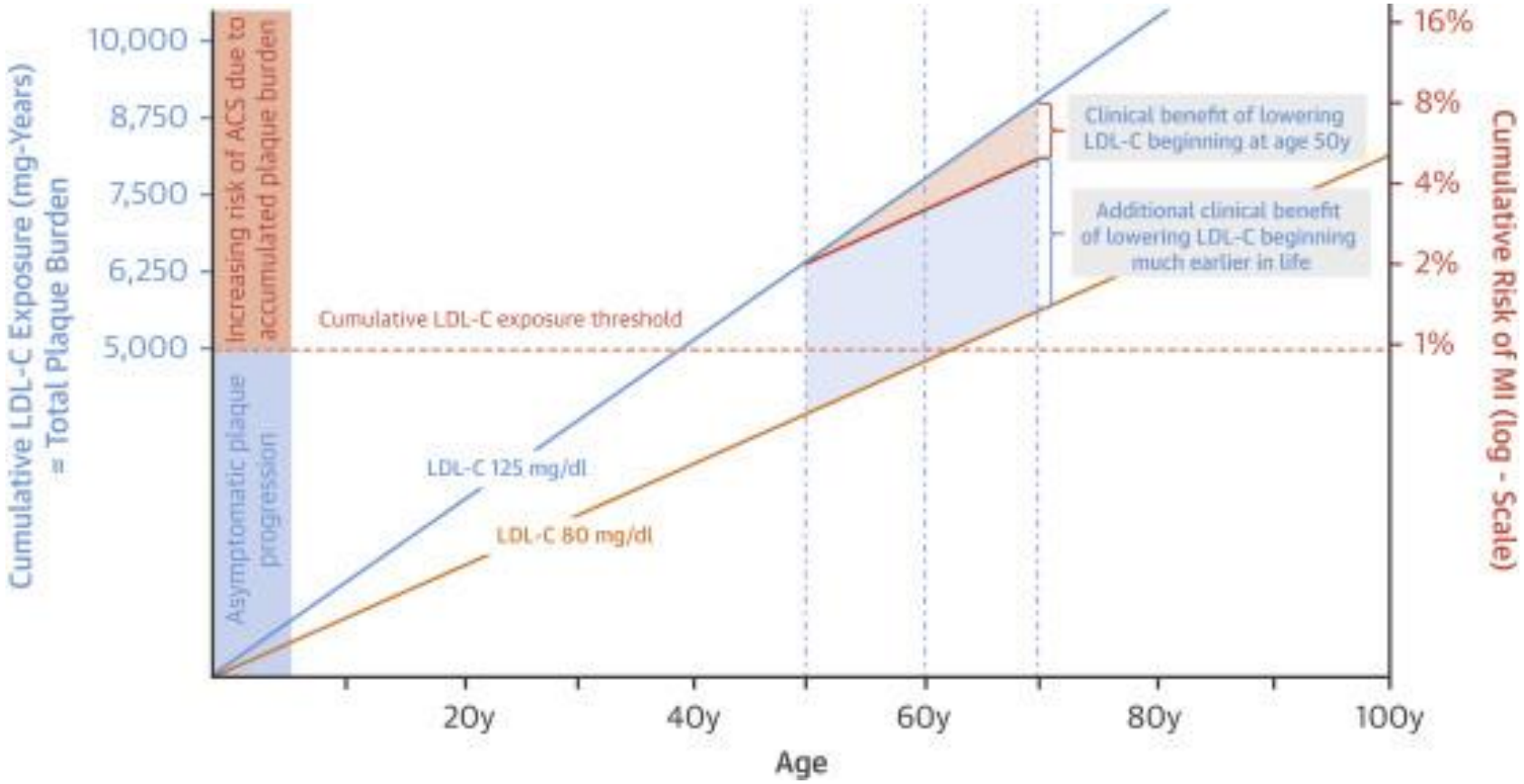
Byrne BMJ 2019

Should 10 year risk be replaced by exposure time?



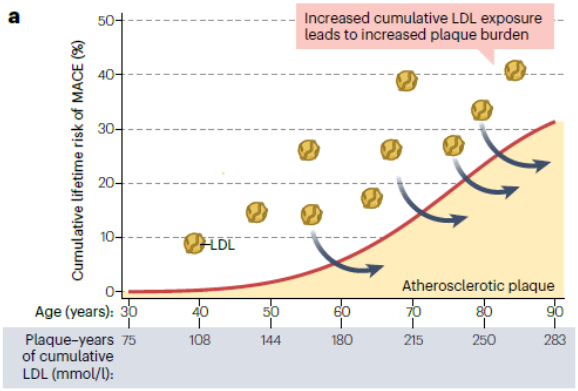
Graham EAJ 2024

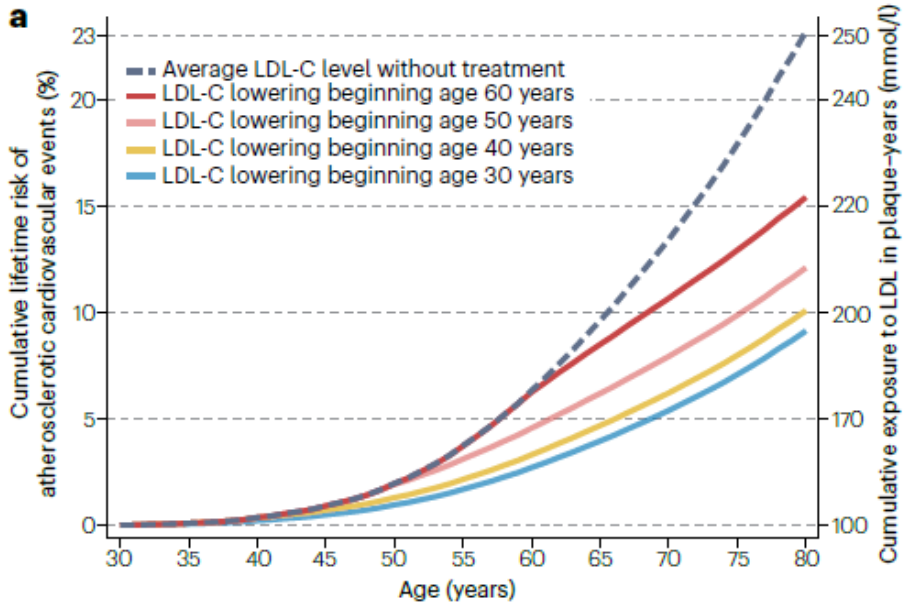
Impact of Lipids on Cardiovascular Health

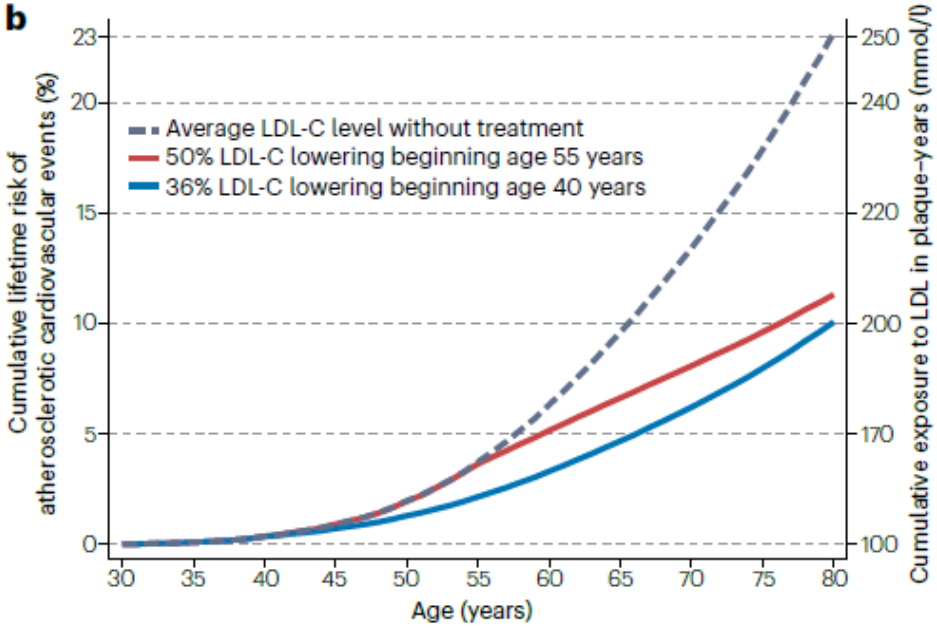


Ference JACC 2018

The LDL cumulative exposure hypothesis: evidence and practical applications







Ference Nature Reviews Cardiology 2024

The *Lancet* Commission on rethinking coronary artery disease: moving from ischaemia to atheroma

Global Burden of Disease Foresight and Results tools 1990-2021

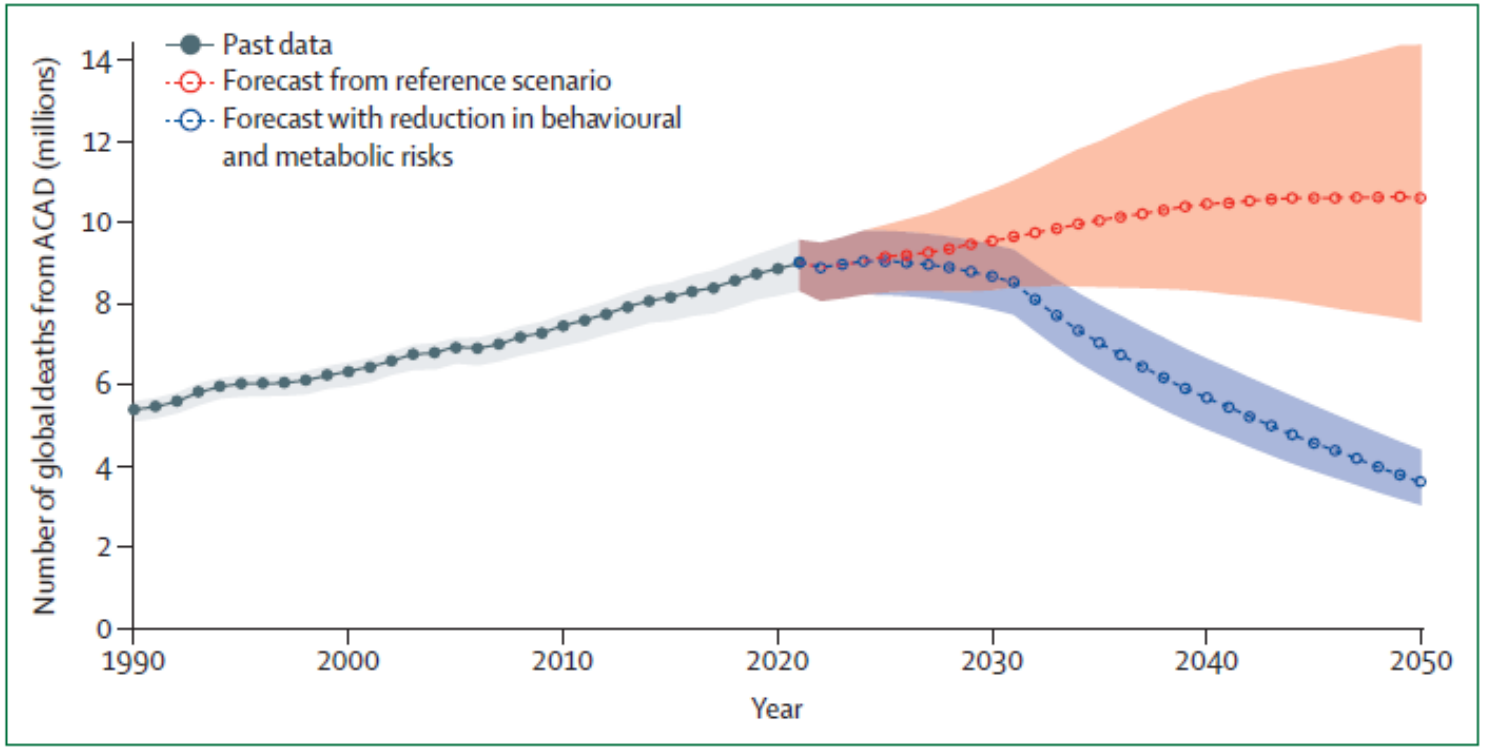


Figure 1: Number of deaths from ACAD from 1990 to 2021 and projection to 2050 with and without elimination of metabolic and behavioural risk factors

Lancet 2025

Addressing residual risk beyond statin therapy: New targets in the management of dyslipidaemias–A report from the European Society of Cardiology Cardiovascular Round Table

- Many patients will not achieve recommended lipid targets

- Types of residual risk and preventive strategies

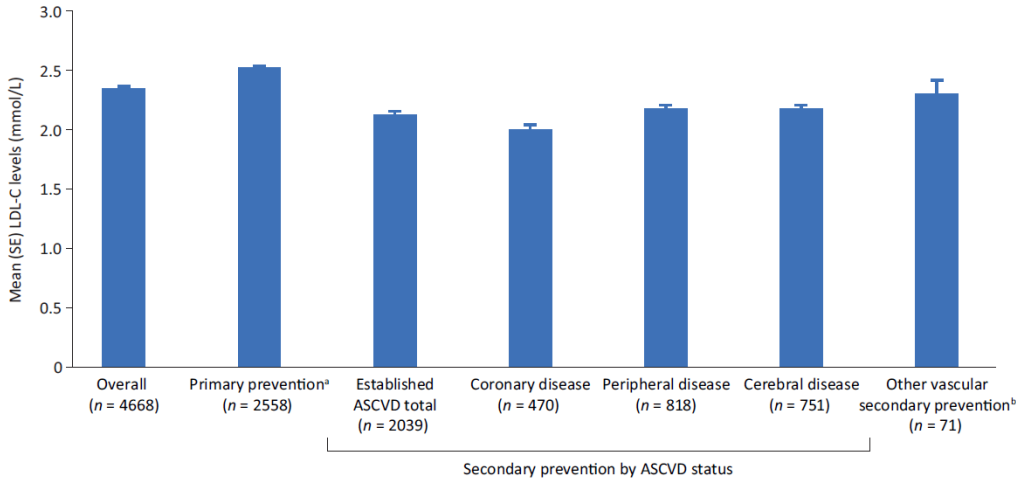
  Persistent elevated LDL
  Elevated triglycerides
  Elevated lipoprotein (a)
  Inflammation

- Role of imaging in assessing residual risk

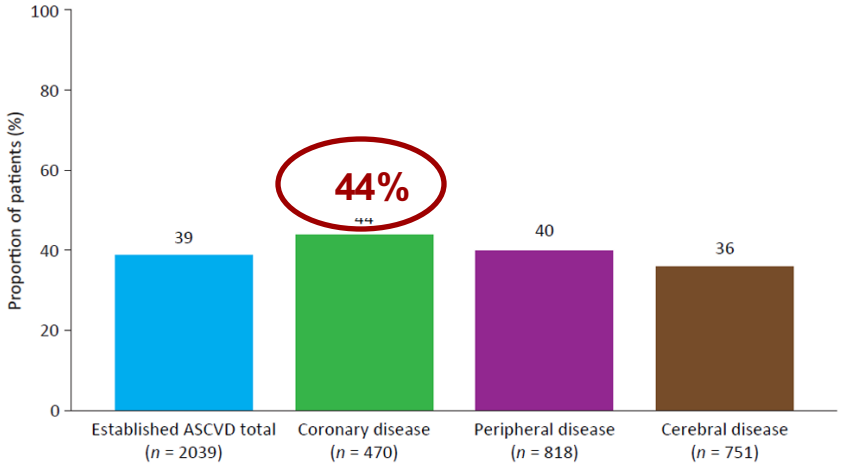
Mach J Clin Lipidol 2024

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

Most patients between 2.0 and 2.5 mmol/L
(between 77 and 100 mg/dL)



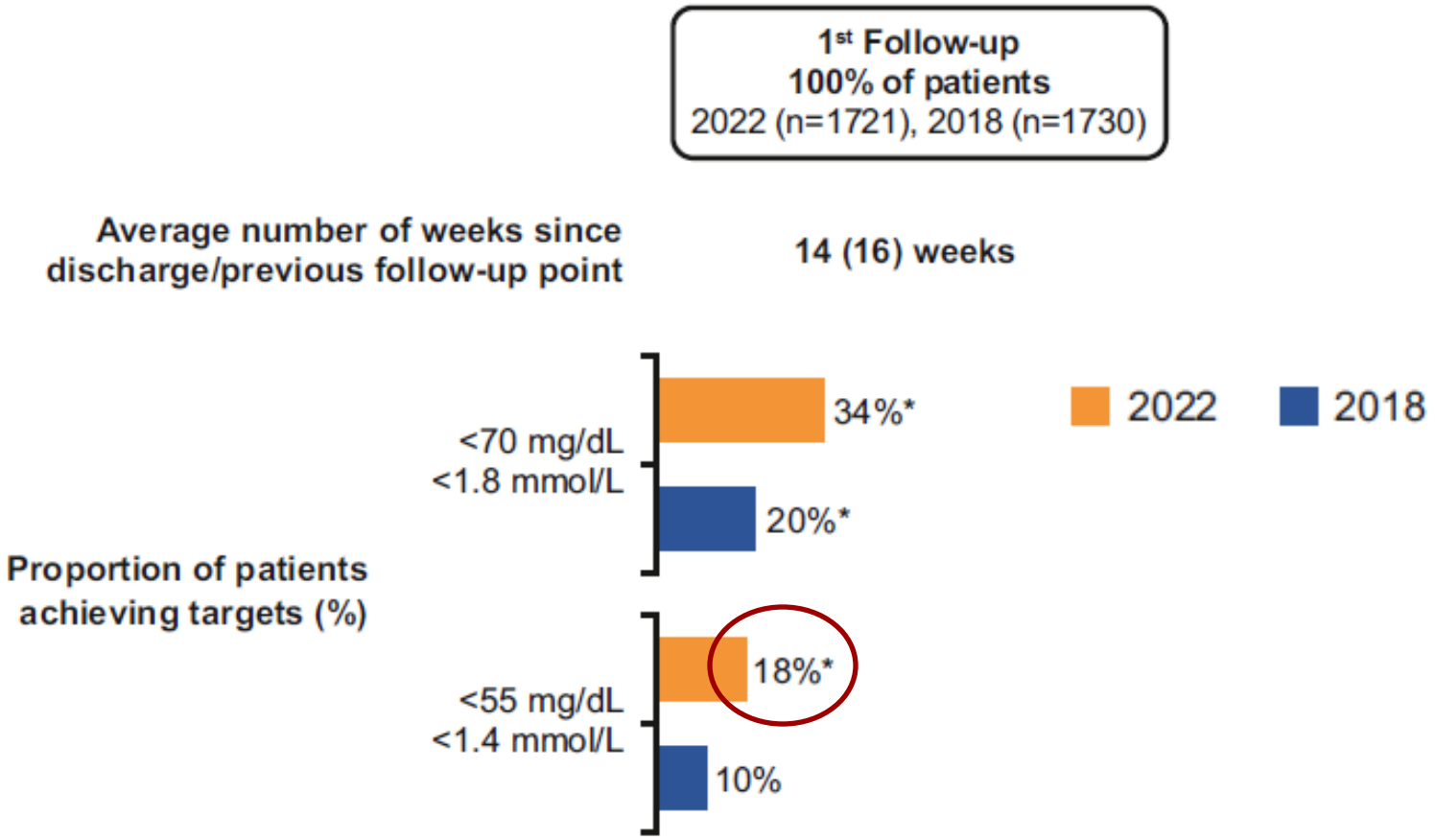
2016 ESC/EAS LDL-C goal (< 70 mg/dl) attainment in the ASCVD groups



Ray DA VINCI Eur J Prev Cardiol 2021

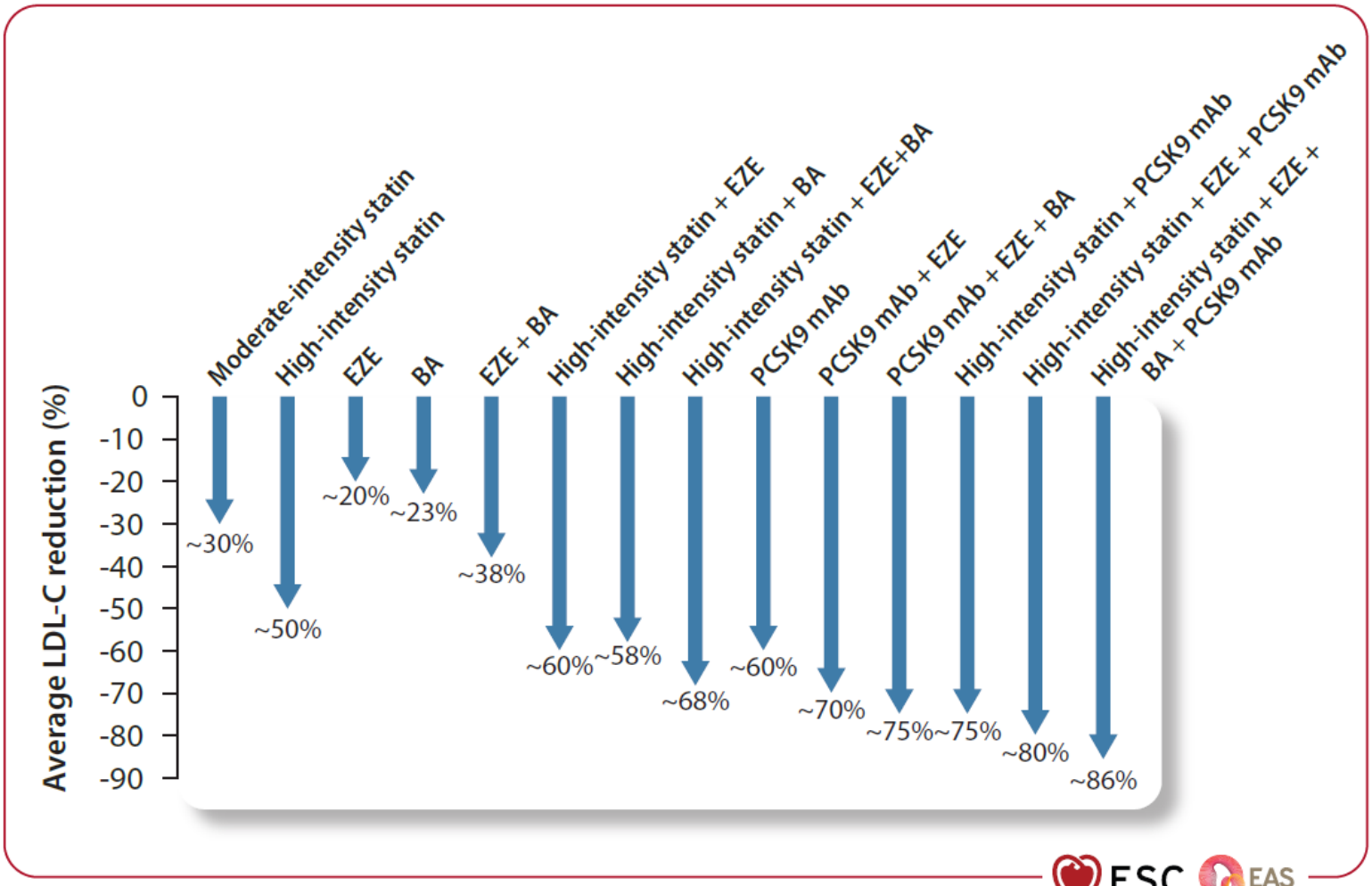
Many patients will not achieve recommended lipid targets

The effect of the 2019 ESC/EAS dyslipidaemia guidelines on low-density lipoprotein cholesterol goal achievement in patients with acute coronary syndromes: The ACS EuroPath IV project



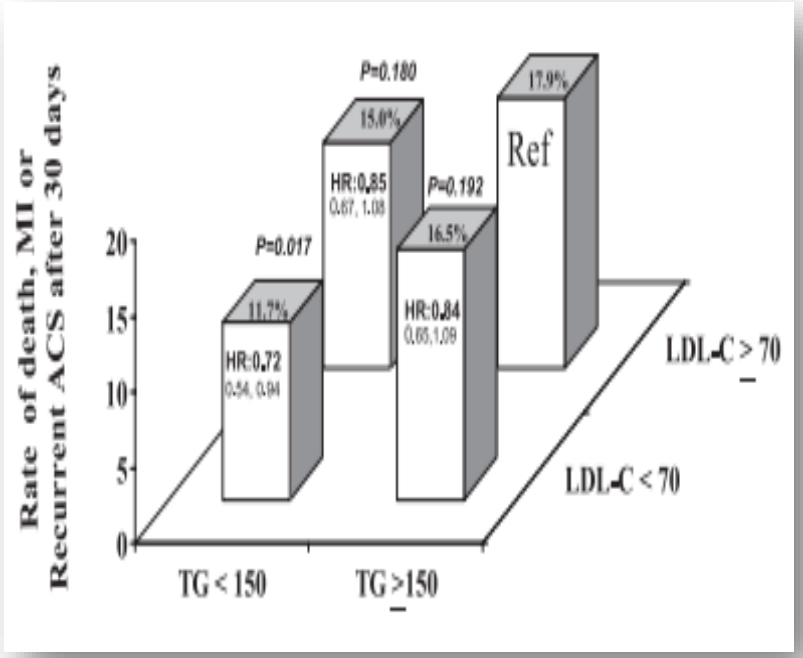
Laufs Vascular Pharmacol 2023

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

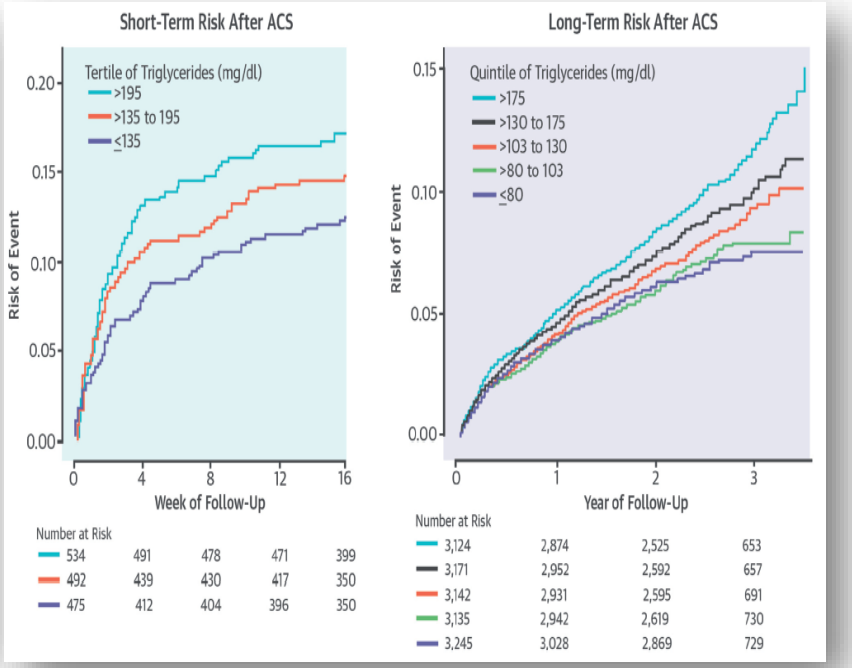


ESC EAS

Fasting TG Levels Predict Recurrent Ischemic Events in Patients with ACS or ASCVD Treated with High-Dose Statins



Prove-it[1]



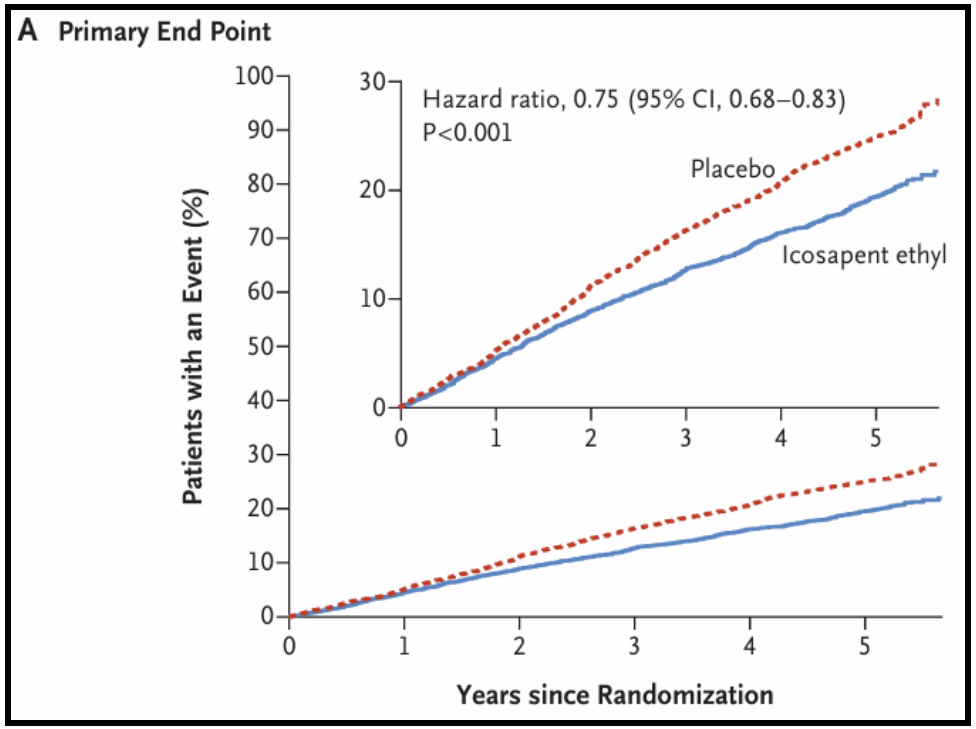
Miracl[2]

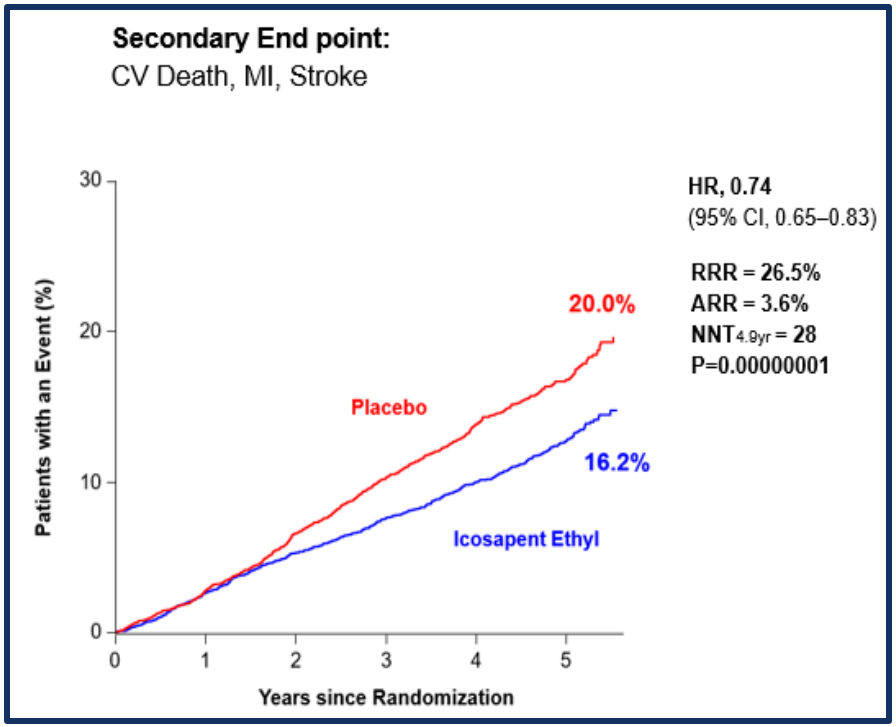
OUTCOMES[2]

1) Miller M, et al., J Am Coll Cardiol 2008;7:724
2) Schwartz GG, et al. J Am Coll Cardiol 2015;65:2267

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. Triglyceride 135-499 and LDL 41-100 mg/dl





Recommendations	Class[a]	Level[b]
High-dose icosapent ethyl (2 × 2 g/day) should be considered in combination with a statin in high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride level 135–499 mg/dL or 1.52–5.63 mmol/L) to reduce the risk of cardiovascular events.[8,111]	IIa	B
Volanesorsen (300 mg/week) should be considered in patients with severe hypertriglyceridaemia (>750 mg/dL or >8.5 mmol/L) due to familial chylomicronaemia syndrome, to lower triglyceride levels and reduce the risk of pancreatitis.[6,117]	IIa	B

Bhatt REDUCE-IT N Engl J Med 2019

Mach ESC Guidelines Update 2025

Cardiovascular Benefit of IPE is Independent of Basal C-LDL Levels

Primary Endpoint in subgroups	Icosapent etile n/N (%)	Placebo n/N (%)	HR (95%CI)	Int P value
Basal C-LDL				
• ≤1.73 mmol/L (67 mg/dL)	244/1481 (16.5%)	302/1386 (21.8%)	0.72 (0.61–0.85)	0.62
• >1.73 e ≤2.17 mmol/L (>67 e ≤84 mg/dL)	248/1347 (18.4%)	307/1364 (22.5%)	0.81 (0.68–0.96)	
• >2.17 mmol/L (> 84 mg/dL)	213/1258 (16.9%)	292/1339 (21.8%)	0.74 (0.62–0.89)	

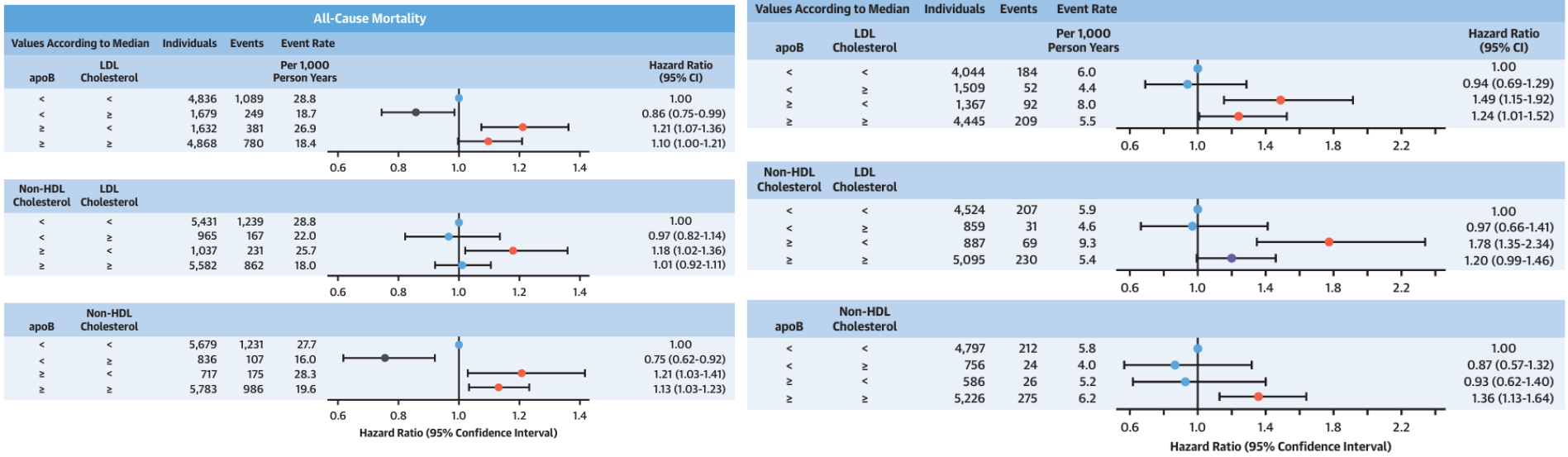
The CV benefit of IPE is also reported in patients in the lowest C-LDL quartile at baseline.
This indicates that the CV benefit associated with IPE is independent of C-LDL levels

Bhatt REDUCE-IT N Engl J Med 2019

Apolipoprotein B and Non-HDL Cholesterol Better Reflect Residual Risk Than LDL Cholesterol in Statin-Treated Patients

13,015 statin-treated pts in Copenhagen General Population Study 8 years median follow-up

FIGURE 2 Multivariable-Adjusted Hazard Ratios of All-Cause Mortality and Myocardial Infarction By Discordant Versus Concordant Categories of Apolipoprotein B, LDL Cholesterol, and Non-HDL Cholesterol in Statin-Treated Patients



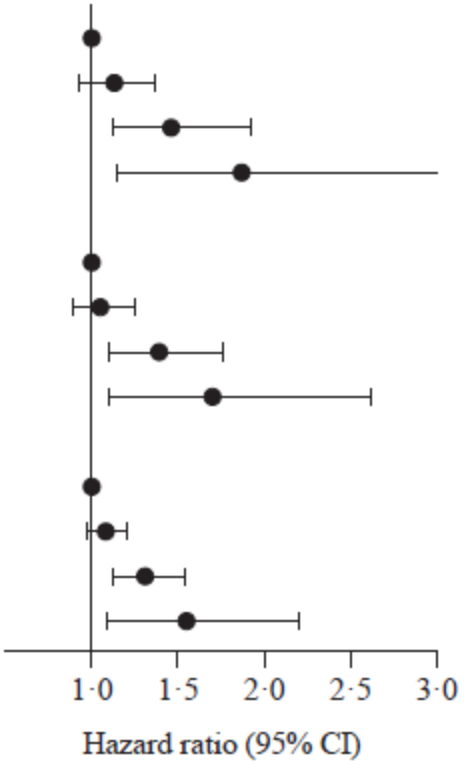
In statin-treated patients elevated apoB and non-HDL cholesterol, but not LDL cholesterol are associated with residual risk of all-cause mortality and myocardial infarction

Lindahardt JACC 2021

Non-HDL cholesterol and residual risk of cardiovascular events in patients with ischemic heart disease and well-controlled LDL cholesterol: a cohort study

Men

Non-HDL-C concentration (mmol/L)	Individuals (n)	Events (n)	Hazard ratio (95% CI)
Myocardial infarction			
<2·0	8,874	302	1·0
2·0-2·4	6,250	243	1·1 (0·9-1·4)
2·5-2·9	1,664	79	1·5 (1·1-1·9)
≥3·0	296	18	1·9 (1·1-3·1)
ASCVD			
<2·0	8,874	421	1·0
2·0-2·4	6,250	321	1·1 (0·9-1·2)
2·5-2·9	1,664	106	1·4 (1·1-1·8)
≥3·0	296	23	1·7 (1·1-2·6)
All-cause death			
<2·0	8,874	1,210	1·0
2·0-2·4	6,250	749	1·1 (1·0-1·2)
2·5-2·9	1,664	300	1·3 (1·1-1·5)
≥3·0	296	33	1·5 (1·1-2·2)

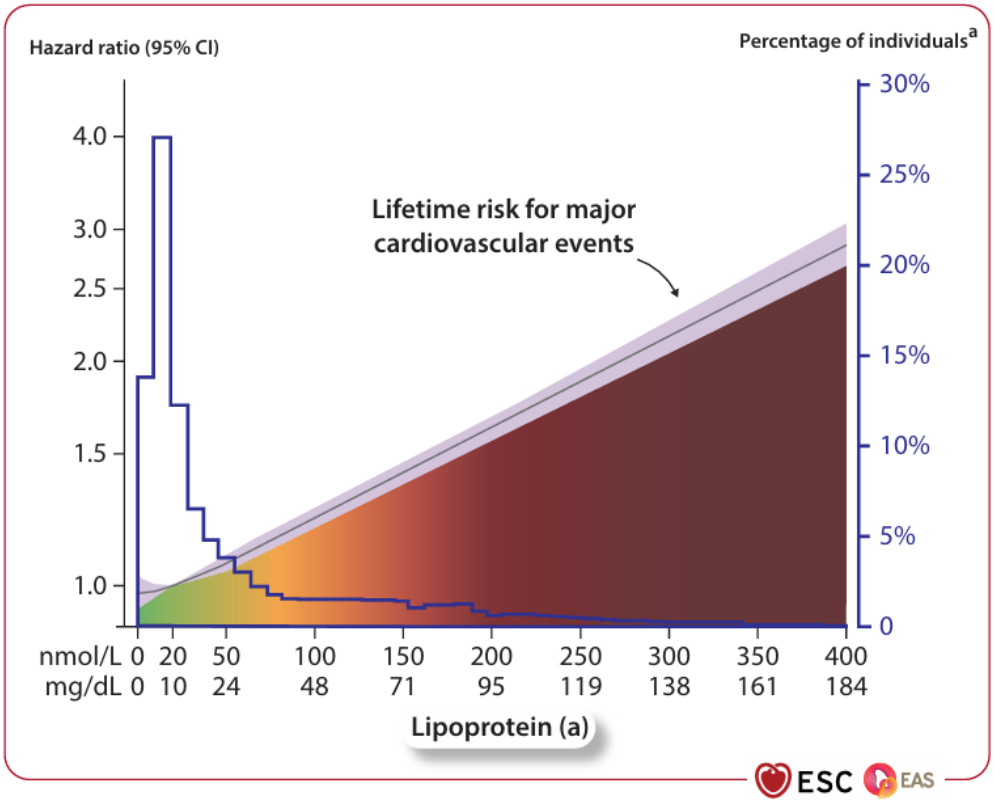


> 115 mg/dl

LDL-C ≤< 70mg/dl

Hansen Lancet 2024

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias



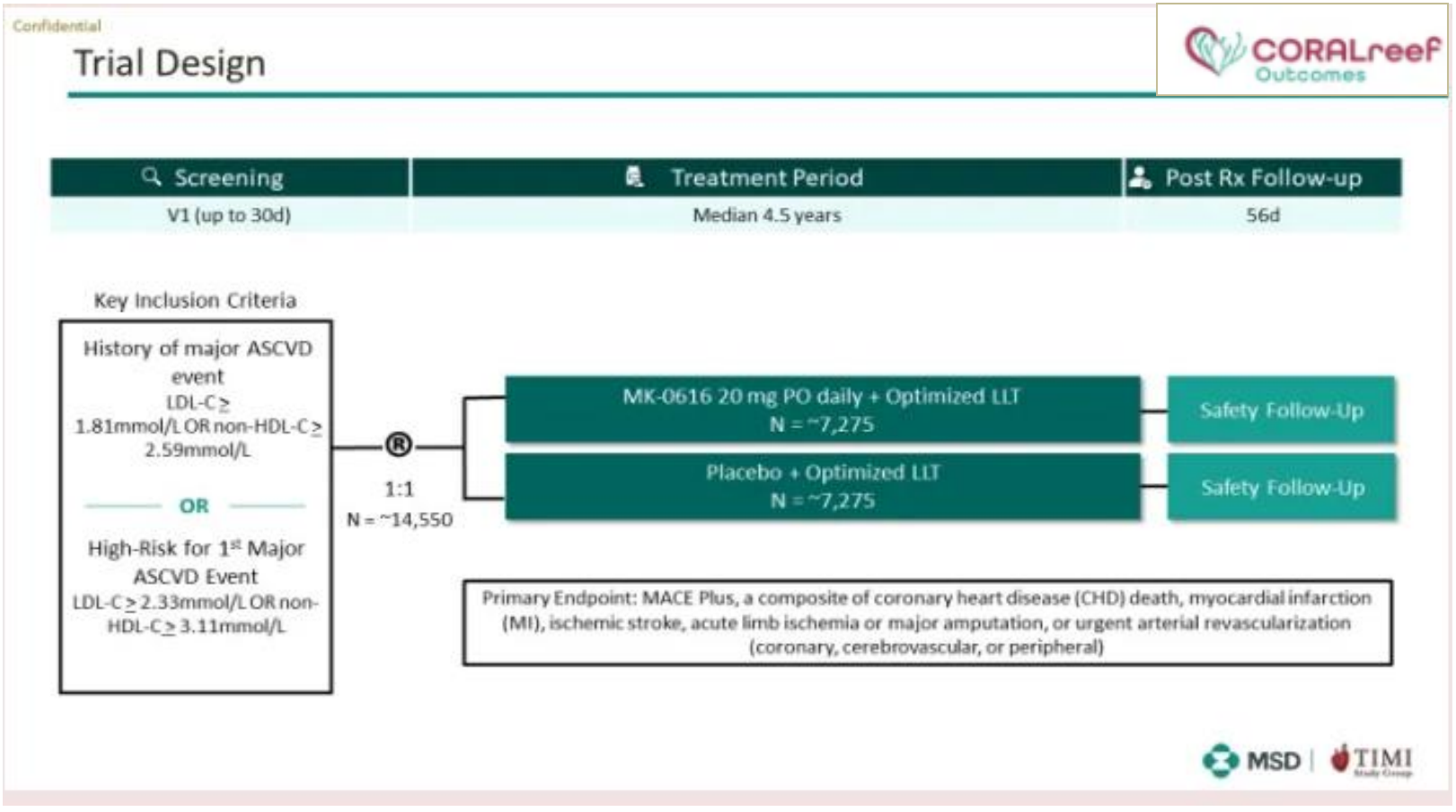
Recommendation Table 4 — Recommendations for measurement of lipoprotein(a) (see also Supplementary data online, Evidence Table 4)

Recommendations	Class[a]	Level[b]
Lp(a) levels above 50 mg/dL (105 nmol/L) should be considered in all adults as a CV risk-enhancing factor, with higher Lp(a) levels associated with a greater increase in risk.[37,101]	IIa	B

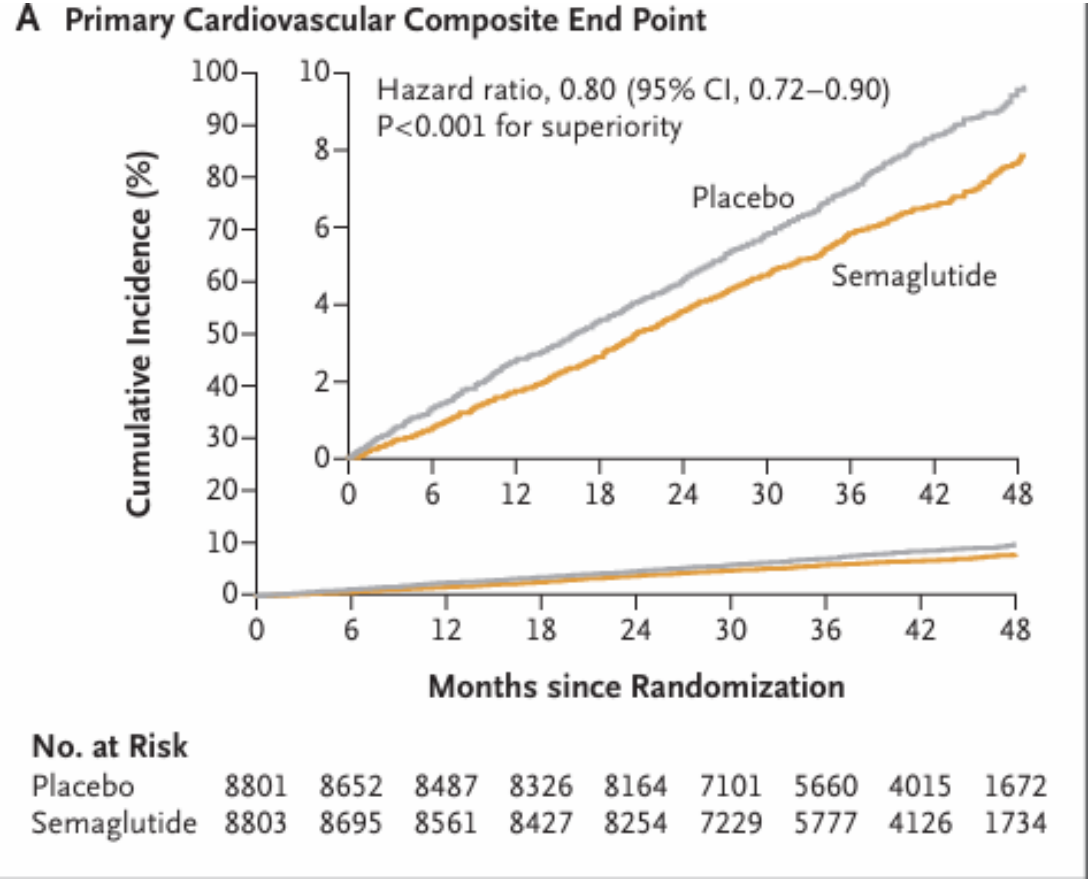
CORALreef Lipids study included 2,912 patients (mean age 62.8 years; 39% female) with a history of atherosclerotic cardiovascular disease (ASCVD) and LDL cholesterol ≥ 55 mg/dL or those at high risk for ASCVD and LDL cholesterol ≥ 70 mg/dL. Nearly 60% of patients had a prior ASCVD event and half had type 2 diabetes.

Two-thirds of **enlicitide** (proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor) treated patients had a more than 50% reduction in LDL cholesterol and achieved the recommended target of less than 55 mg/dL at 24 weeks, compared with just 1.2% in the placebo arm. Non-HDL cholesterol, apolipoprotein B, and lipoprotein(a) were all significantly reduced with enlicitide at 24 weeks (53.7%, 49.6%, and 29% reductions, respectively).

AHA Sessions 2025



Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes



17.604 pts 45 years of age or older who had preexisting cardiovascular disease and a body-mass index of 27 or greater but no history of diabetes.

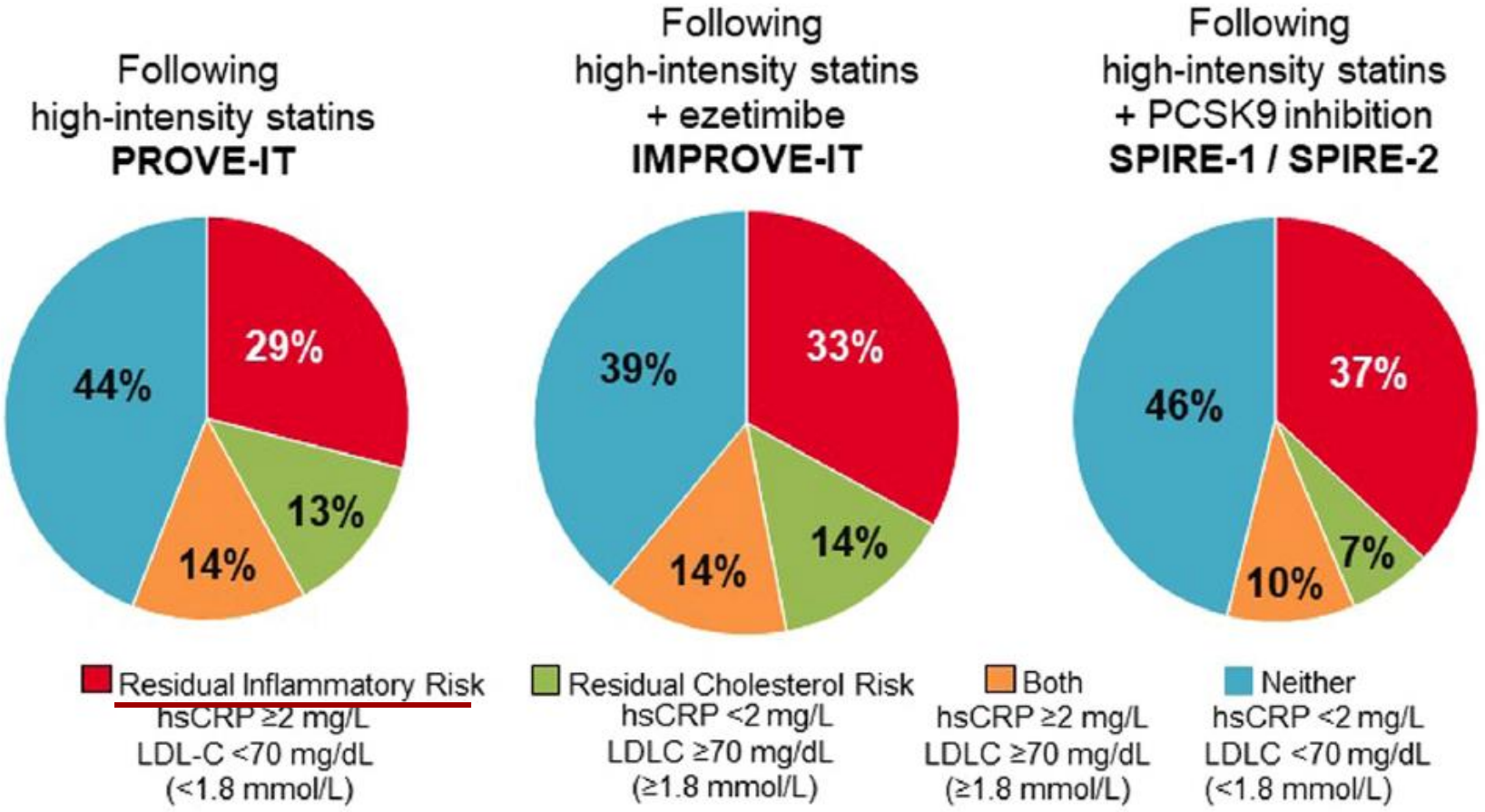
Lincoff New Engl J Med 2023

2024 ESC Guidelines for the management of chronic coronary syndromes

Recommendations	Class[a]	Level[b]
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit[c] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[86,688,695,697,700]	I	A
GLP-1 receptor agonists with proven CV benefit[d] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[710,711]	I	A
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI ≥27 kg/m^2) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke.[465]	IIa	B

Addressing residual risk beyond statin therapy: New targets in the management of dyslipidaemias–A report from the European Society of Cardiology Cardiovascular Round Table

Types of residual risk

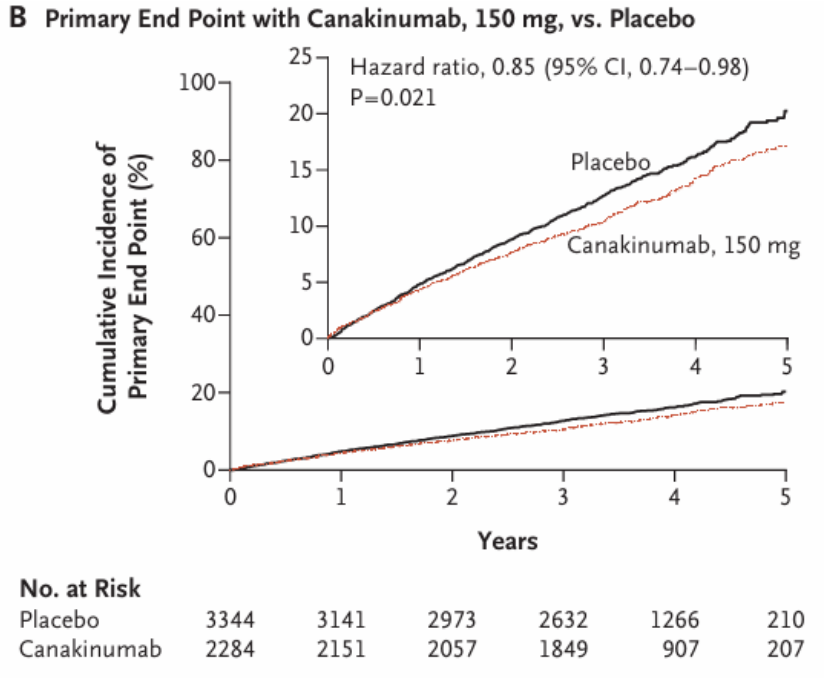


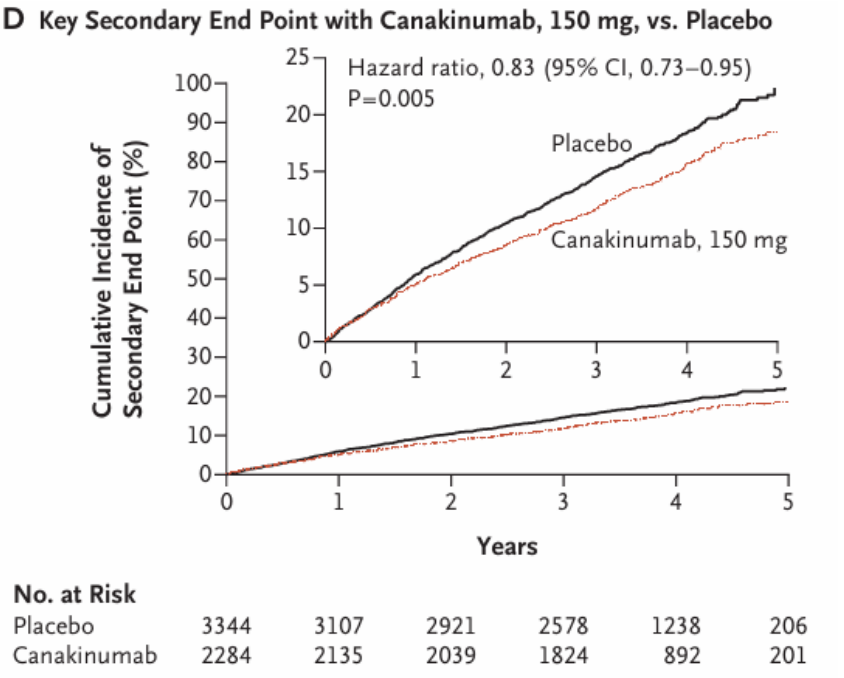
Mach J Clin Lipidol 2024

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter, treated of canakinumab (50 mg, 150 mg, and 300 mg sub cutaneously every 3 months) or placebo. At a median follow-up of 3.7 years, the primary end point was 4.50 events per 100 person-years in the placebo group, 3.86 events per 100 person-years in the 150-mg group,

The 150-mg dose met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P = 0.005).

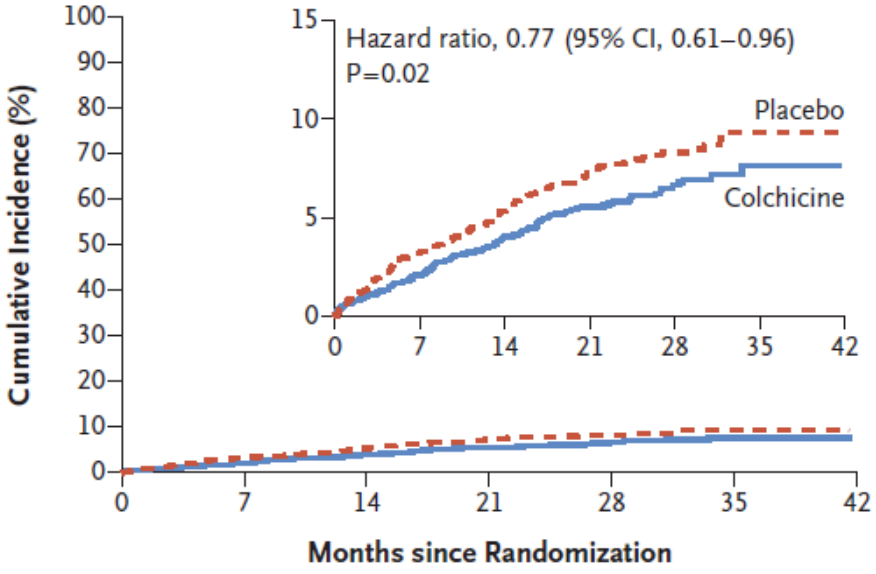




Ridker CANTOS N Engl J Med 2017

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Randomized, double-blind trial involving 4745 patients recruited within 30 days after a myocardial infarction and randomized to receive either low-dose colchicine (0.5 mg once daily) or placebo



No. at Risk							
Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

Recommendation	Class[a]	Level[b]
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.[714–716]	IIa	A

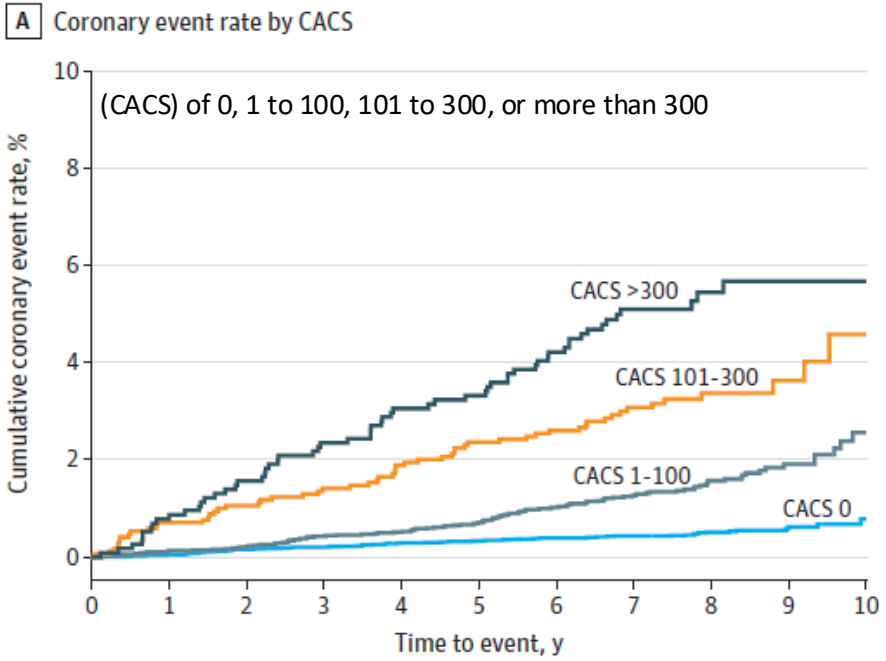
Tardiff N Engl J Med 2019

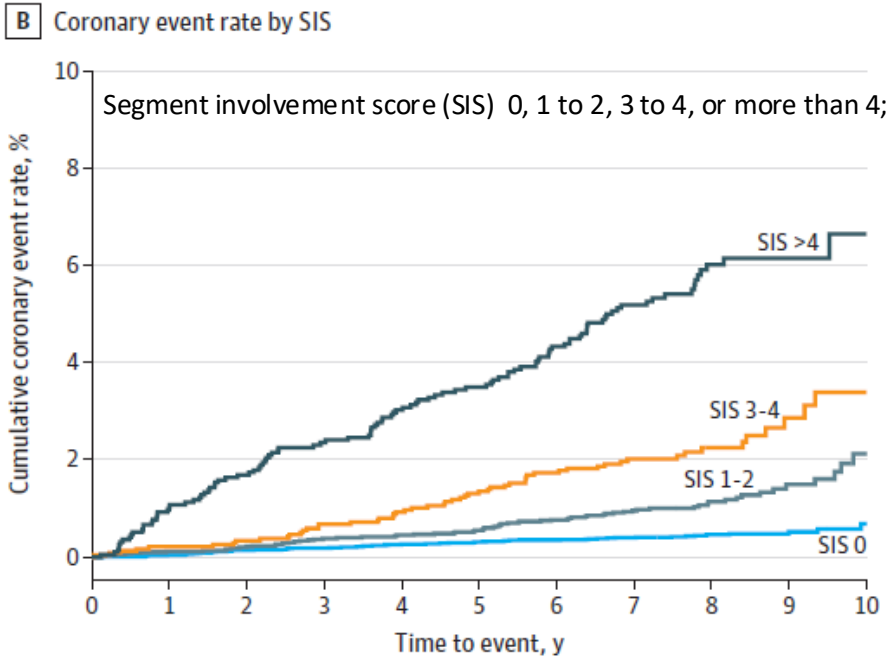
ESC Update 2025

Role of imaging in assessing residual risk

Coronary Computed Tomography Angiography in Prediction of First Coronary Events

Swedish Cardiopulmonary Bioimage Study (SCAPIS), a general population-based prospective study, was designed to extensively characterize more than 30000 individuals





net correct upward reclassification of 14.2% pts

10 years event rate = 1.24 %	No coronary event (n = 24 487)	Coronary event (n = 304)
SCORE2 risk, median (IQR), %[d]	4.1 (2.6-6.2)	6.6 (4.7-9.3)

Bergstrom JAMA 2025

Coronary CT angiography-guided management of patients with stable chest pain: 10-year outcomes from the SCOT-HEART randomised controlled trial in Scotland

Eligible patients were aged 18–75 years with symptoms of suspected stable angina due to coronary heart disease. Patients were randomly assigned (1:1) to standard of care plus CCTA or standard of care alone.

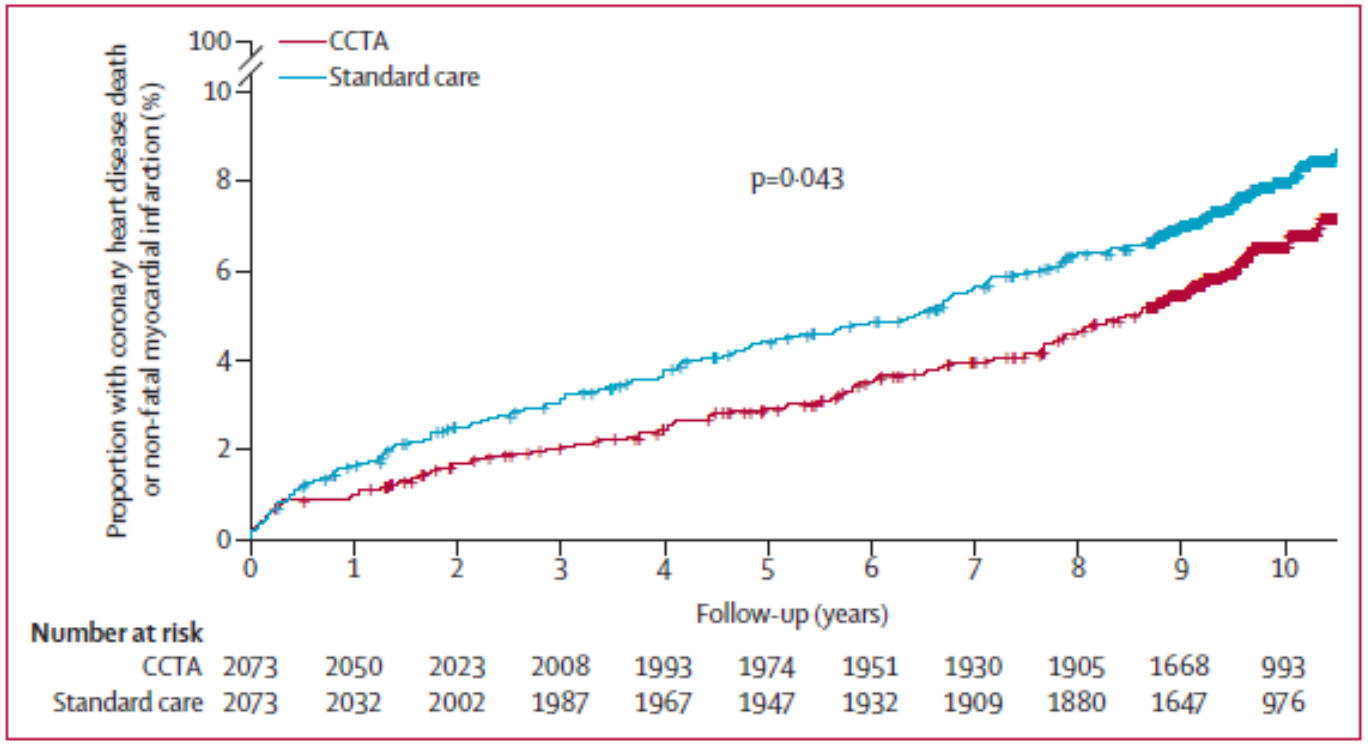


Figure 2: **Cumulative incidence for the primary outcome of coronary heart disease death and non-fatal myocardial infarction**

Williams SCOT-HEART 2025

Post–Myocardial Infarction Psychological Distress: A Scientific Statement From the American Heart Association

MECHANISMS BY WHICH PMPD MAY INCREASE CARDIAC RISK

Numerous mechanisms may contribute to the observed increase in adverse cardiac events in patients who develop PMPD. Psychological distress is known to be a risk factor for the development of cardiac risk factors, including smoking, diabetes, sedentary lifestyle, and obesity.[67] There is substantial evidence that depression after MI negatively affects multiple health behaviors that are important for reducing risk of recurrence. This may result in physical inactivity, inadequate sleep, poor diet, smoking, reduced adherence to cardiovascular medications, and poor attendance at cardiac rehabilitation.[68,69] Different

Levine Circulation 2025

Addressing residual risk beyond statin therapy: New targets in the management of dyslipidaemias–A report from the European Society of Cardiology Cardiovascular Round Table

Incoraggiare lo screening precoce nei giovani per l'ipercolesterolemia (e gli altri FRC)

Dare messaggi chiari sulla determinazione del rischio CV e sul suo trattamento

Far comprendere ai medici il bisogno di intensificare la terapia e seguirla per lungo tempo

Lavorare con industria ed istituzioni nel campo della prevenzione CV

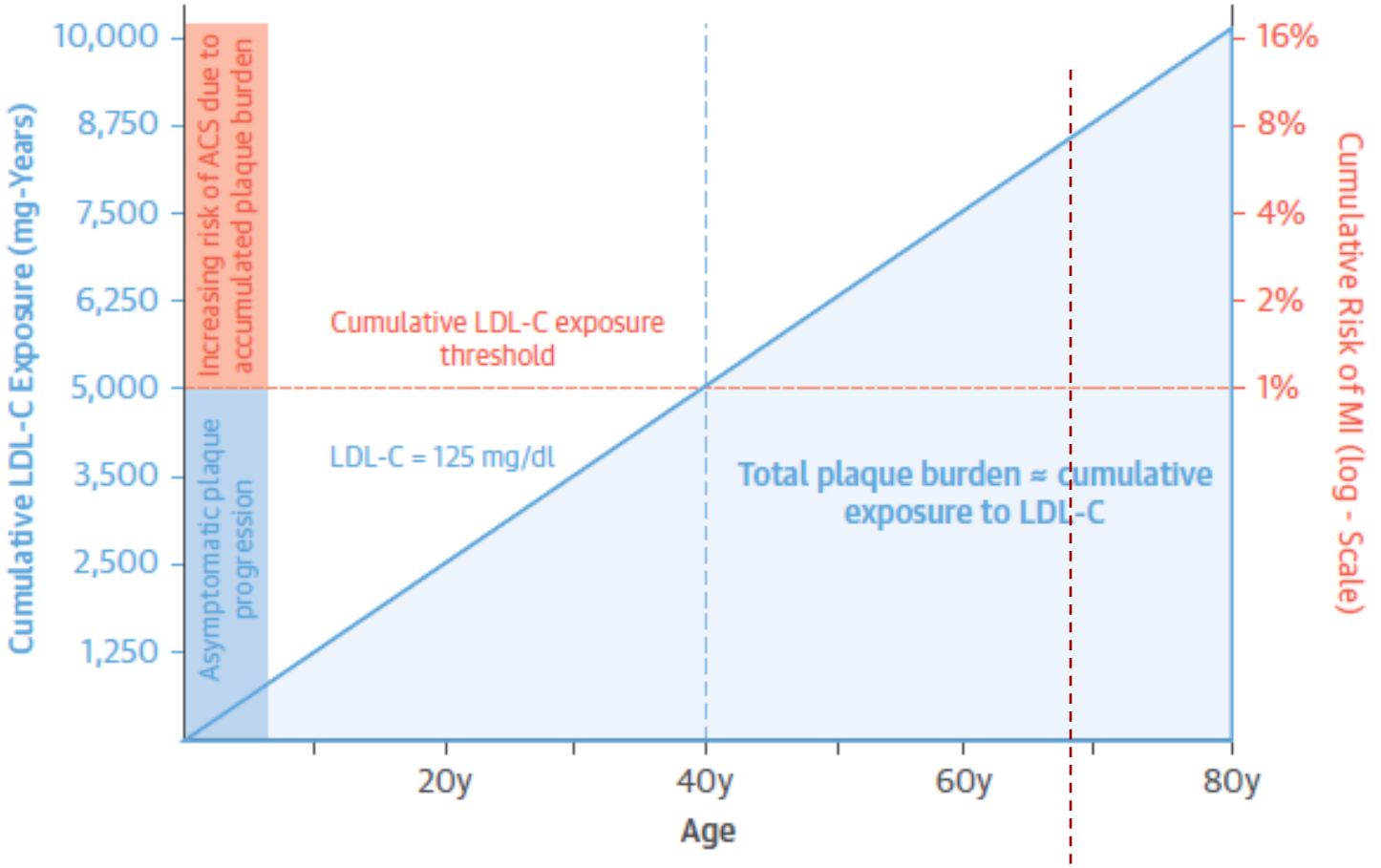
Incoraggiare uno stile di vita salutare dalla giovane età

Usare l'imaging per individuare l'aterosclerosi e migliorare i risultati della prevenzione CV

Fine

Impact of Lipids on Cardiovascular Health

Effect of Cumulative Exposure to LDL on Plaque Burden and Risk of Cardiovascular Disease



Sum of their LDL-C level at all ages up to their current age and is equivalent to calculating the area under the curve for LDL-C levels by age measured in plaque–years (mmol/ litre or mg/decilitre)

Ference JACC 2028