Target Terapeutici per la Riduzione del Rischio Residuo

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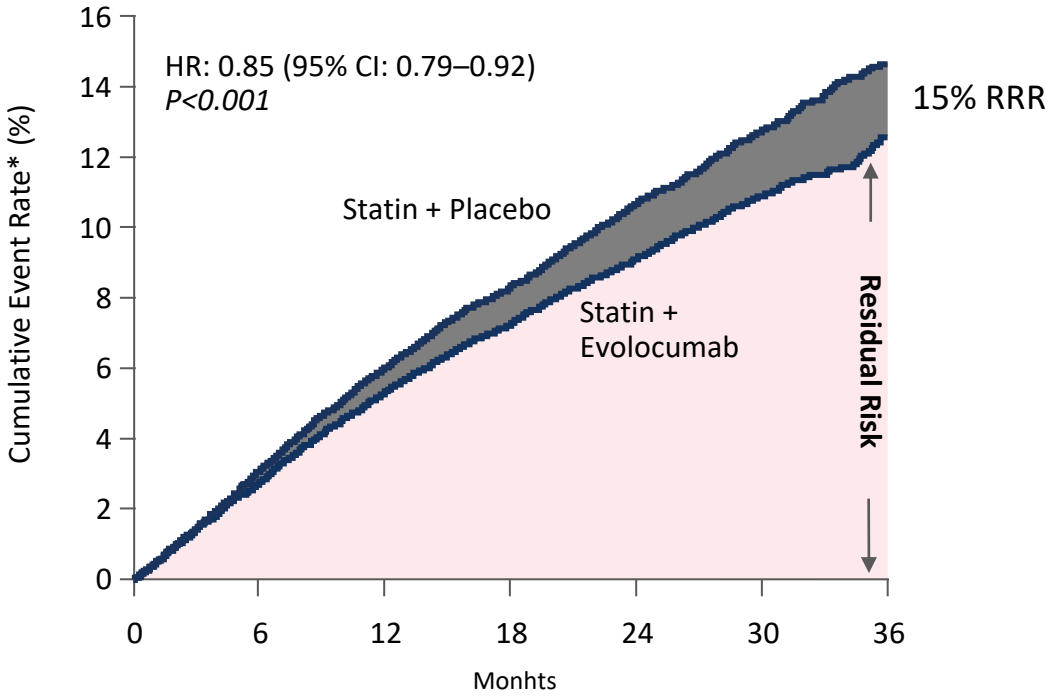
*R*esidual *R*isk in RCTs with PCSK9-I

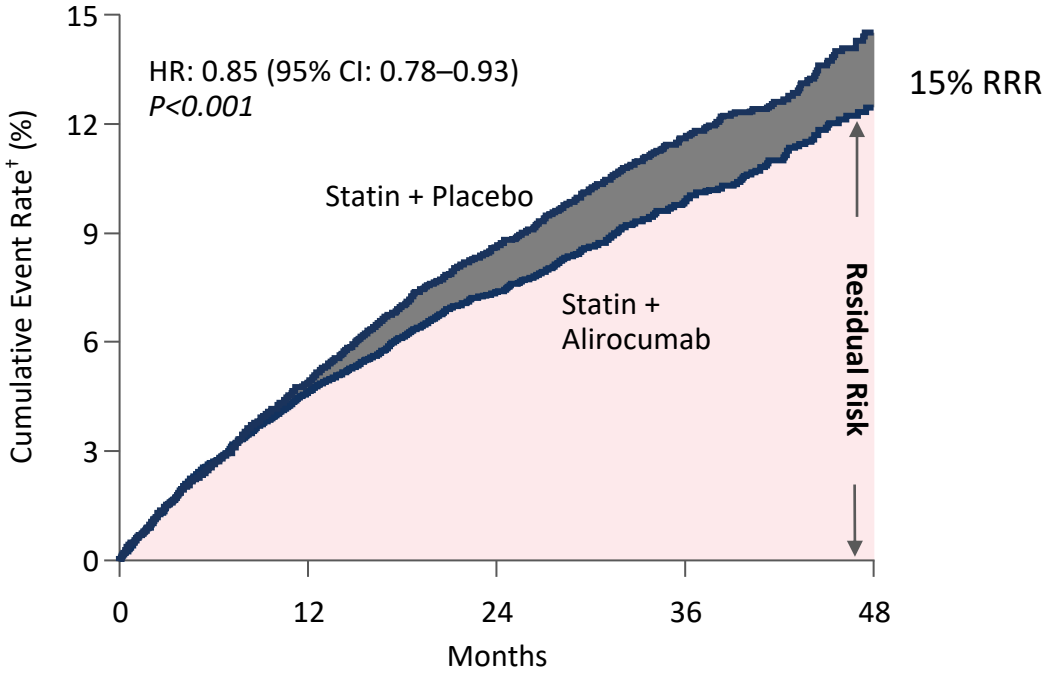
Incidence of MACE

FOURIER



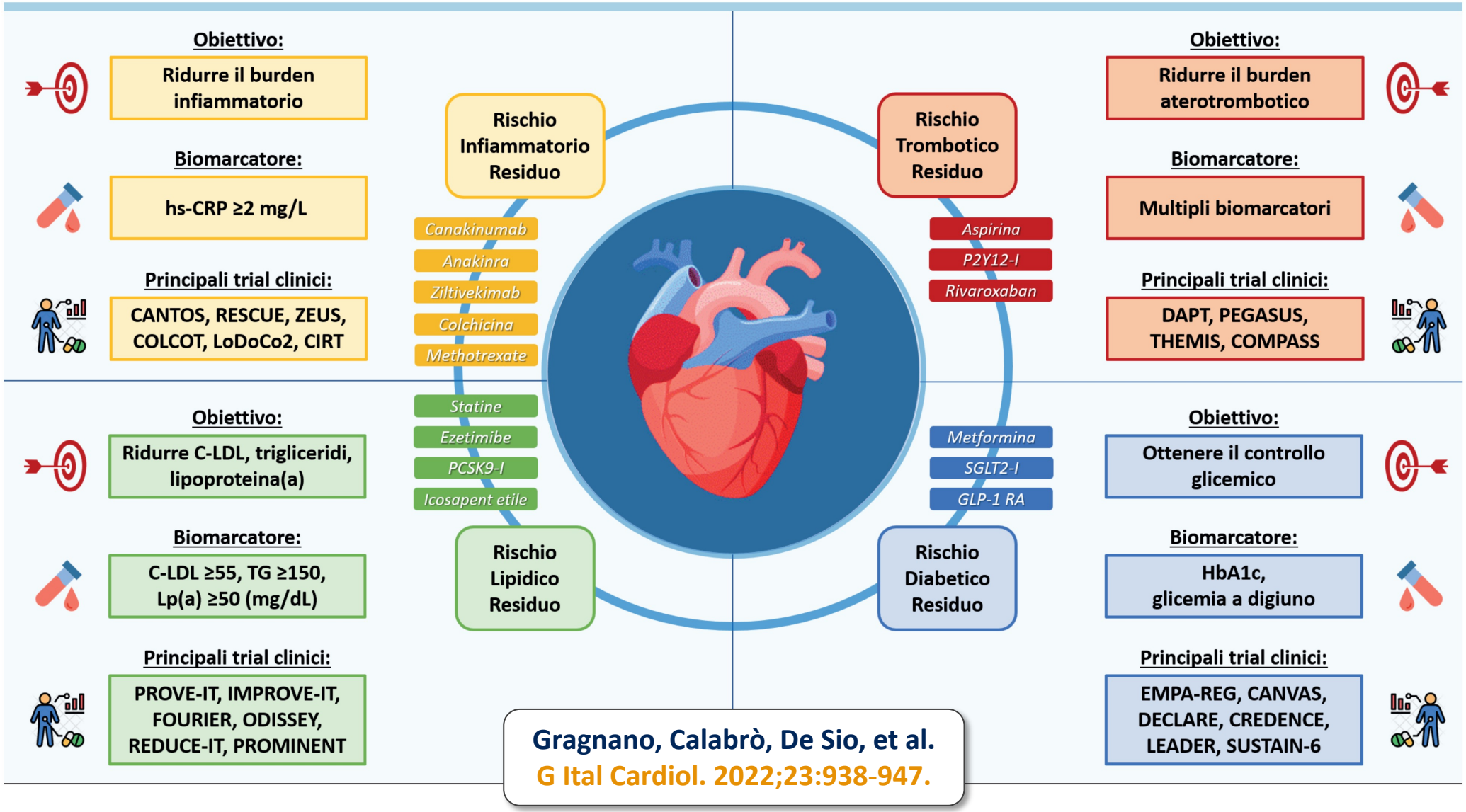
Mean LDL-C 30 mg/dL at 48 weeks

ODYSSEY OUTCOMES



Mean C-LDL 53 mg/dL at 48 months

Breaking Down the Principal Contributors to *R*esidual *R*isk

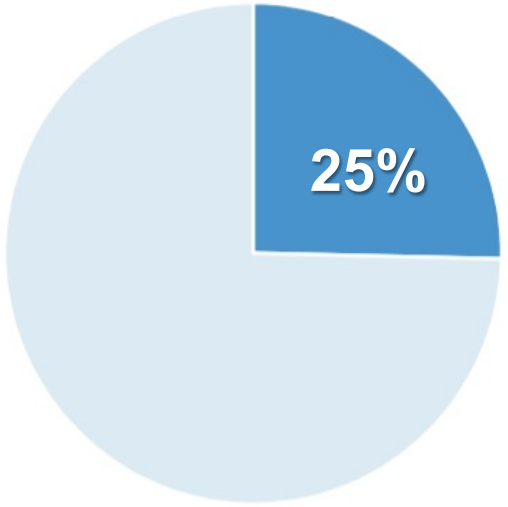


Gragnano, Calabrò, De Sio, et al.
G Ital Cardiol. 2022;23:938-947.

Triglycerides and Cardiovascular Risk

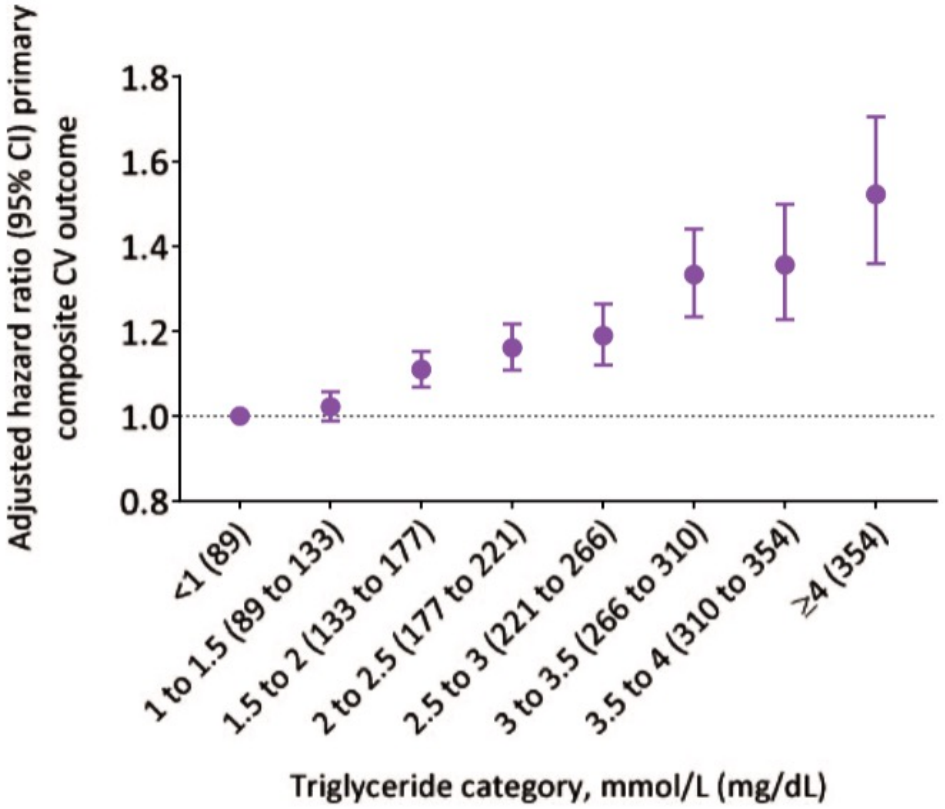
≈ 25% of ASCVD patients have low LDL-C but high TG levels

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



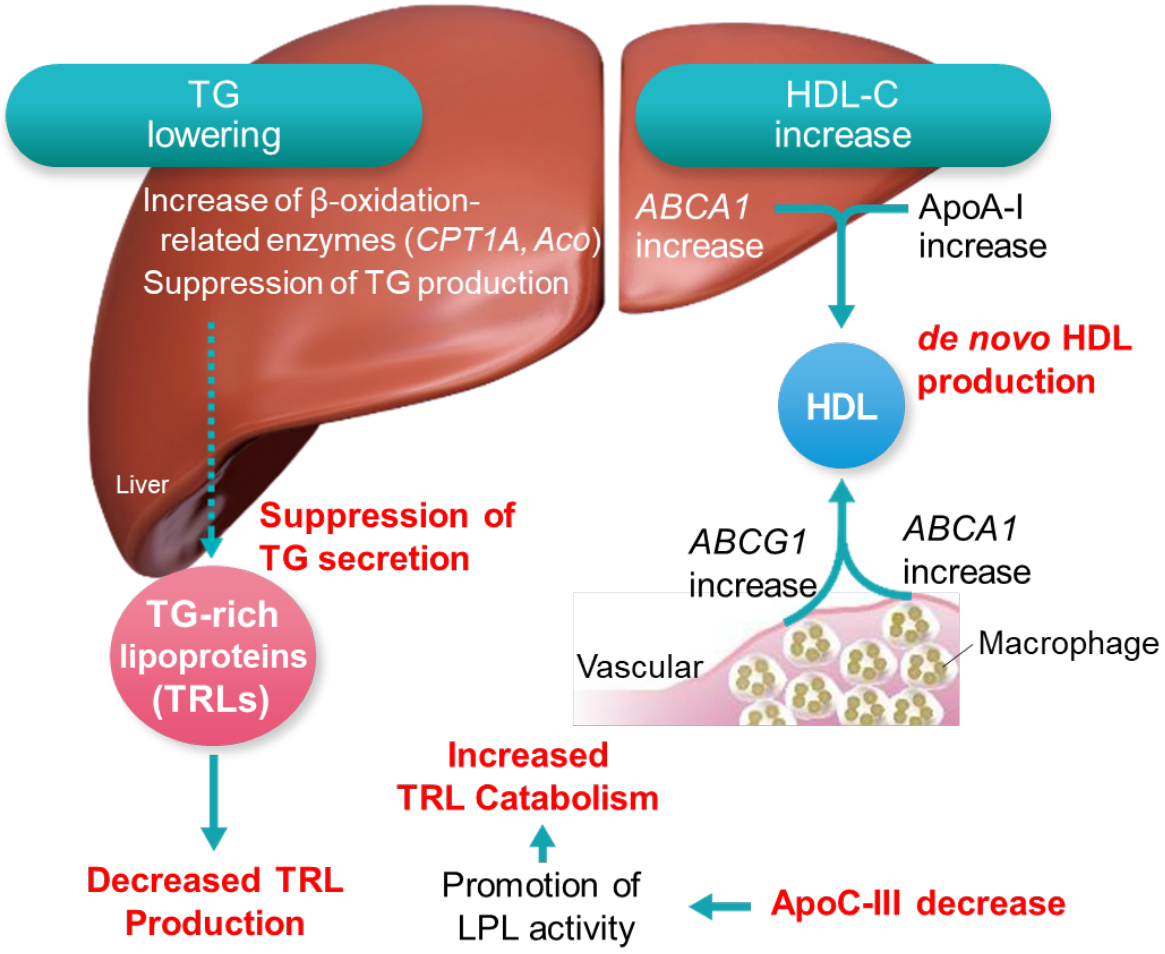
*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

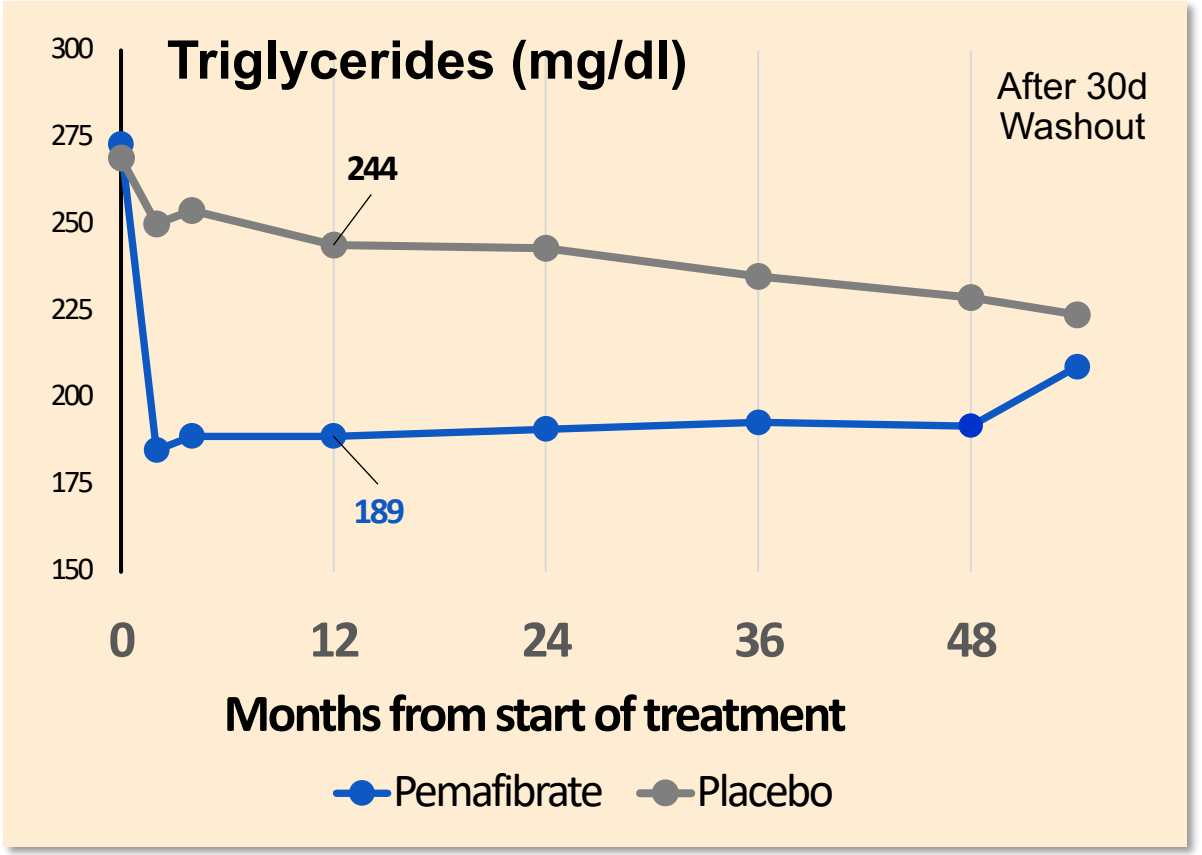
Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



Lawler PR et al. Eur Heart J. 2020;41(1):86-94.

Pemafibrate for the reduction of TGs

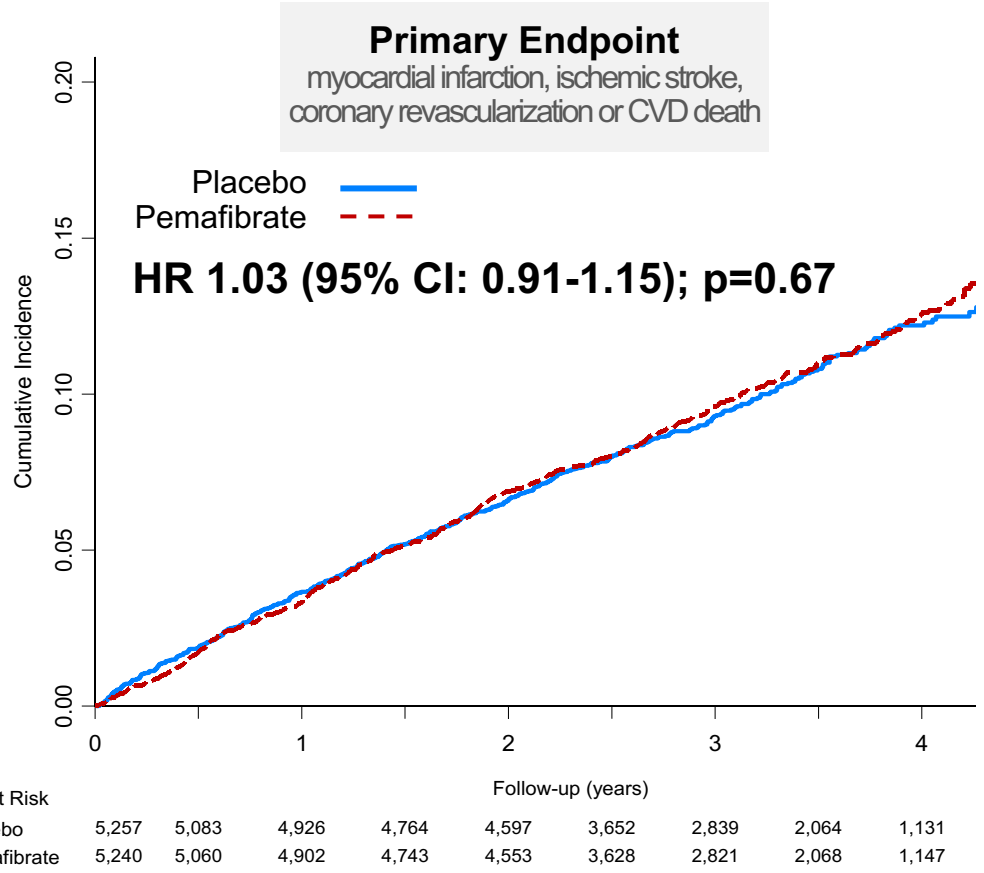


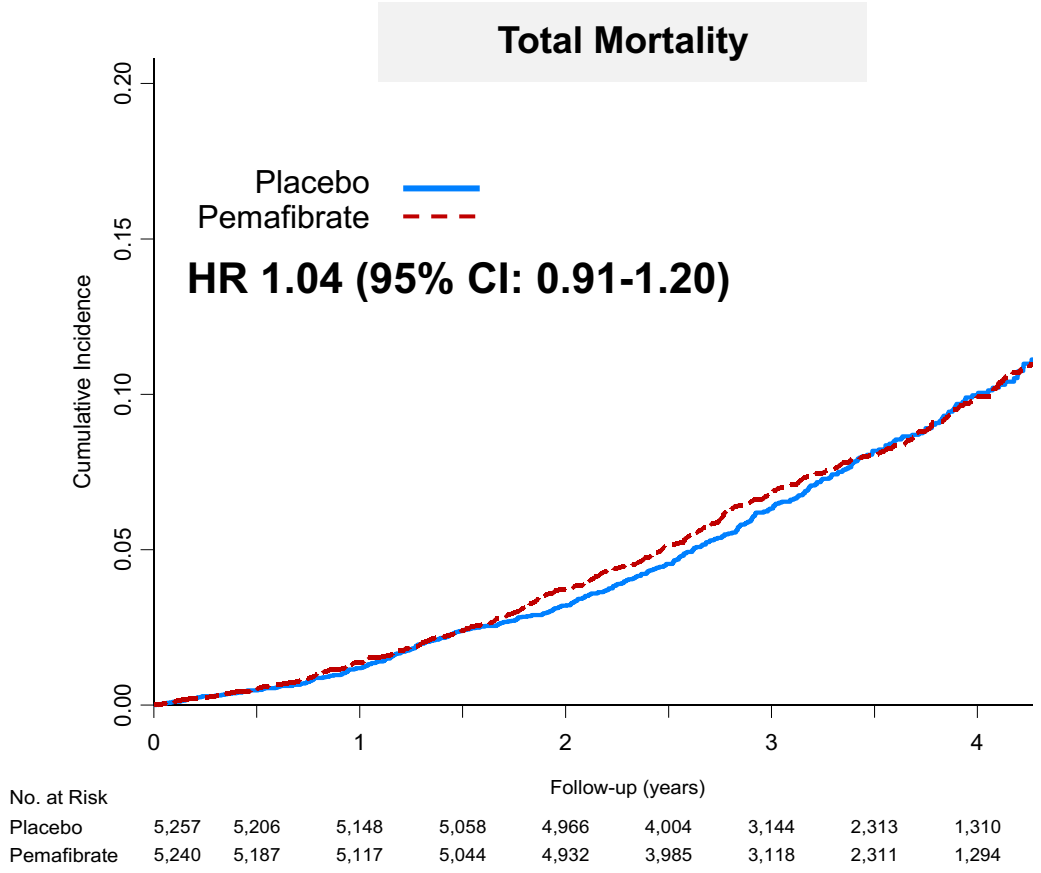


N Engl J Med 2022;387:1923-1934
Curr Atheroscler Rep 2020;221:5

Efficacy of Pemafibrate for CV Events

PROMINENT: Primary Endpoint and Mortality



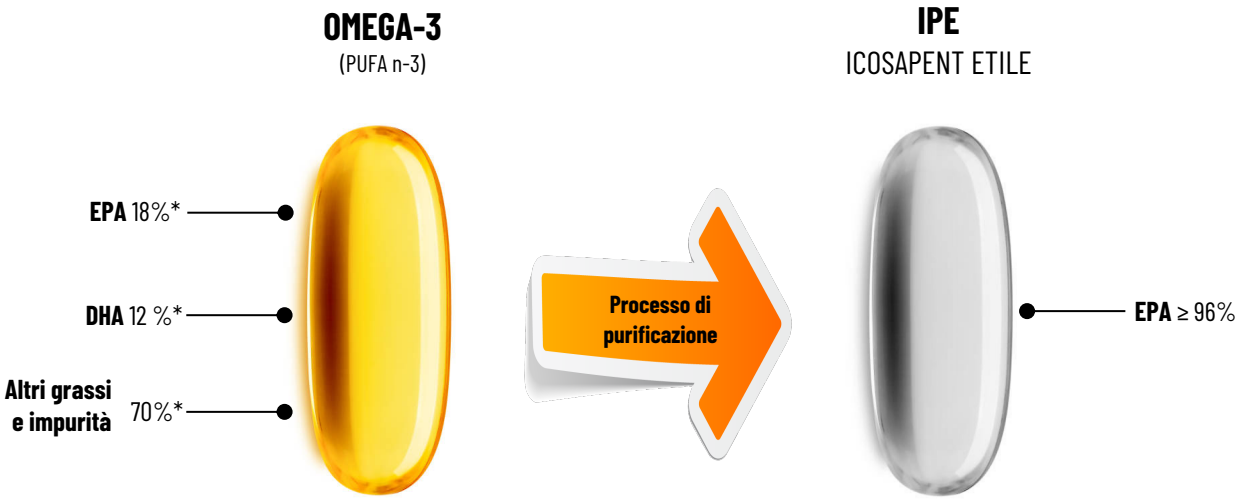


N Engl J Med 2022;387:1923-1934

Gli **OMEGA-3**
sono miscele contenenti:
(acidi grassi polinsaturi a catena lunga)

EPA
ACIDO EICOSAPENTAENOICO

DHA
ACIDO DOCOSAESAENOICO

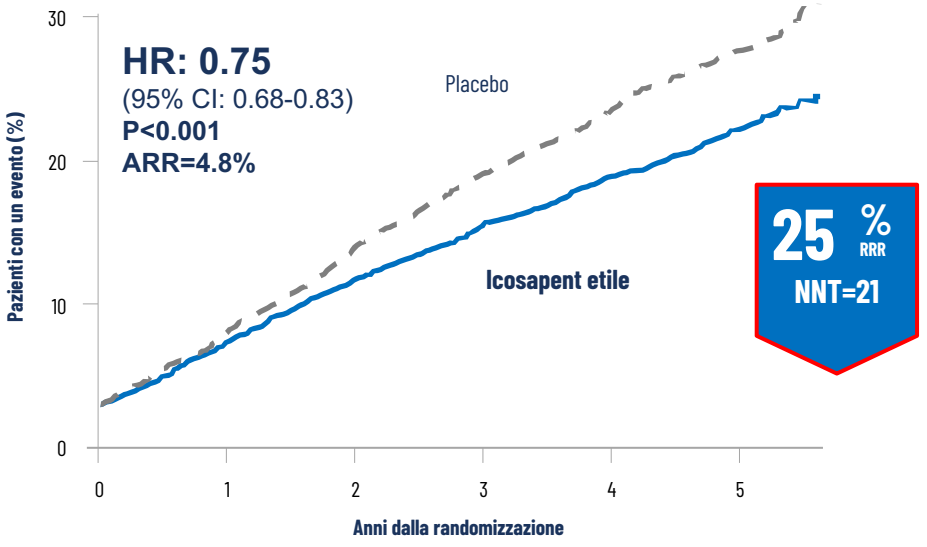


L'ICOSAPENT ETILE (IPE)
è l'estere etilico
dell'**acido eicosapentaenoico**
altamente PURIFICATO.
IPE è stato approvato come
una NUOVA entità chimica.

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia: REDUCE IT trial

Endpoint primario

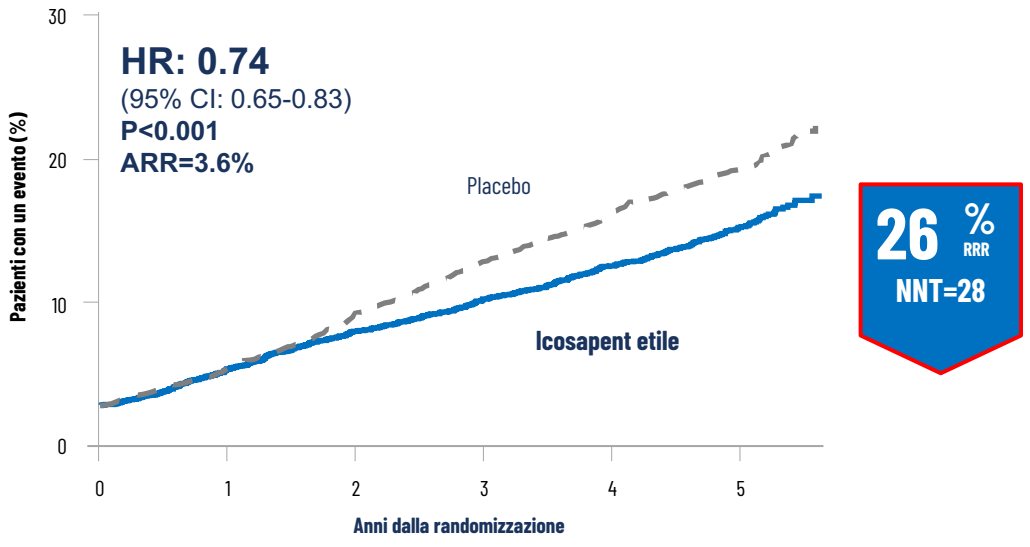
5-Point MACE: Morte CV, IM, ictus, rivascolarizzazione e angina instabile



N a rischio						
Placebo	4,090	3,743	3,327	2,807	2,347	1,358
Icosapent etile	4,089	3,787	3,431	2,951	2,503	1,430

Endpoint secondario

3-Point MACE: Morte CV, IM e ictus



N a rischio						
Placebo	4,090	3,837	3,500	3,002	2,542	1,487
Icosapent etile	4,089	3,861	3,565	3,115	2,681	1,562

Adapted from Bhatt DL, et al. N Engl J Med 2019; 380:11-22.

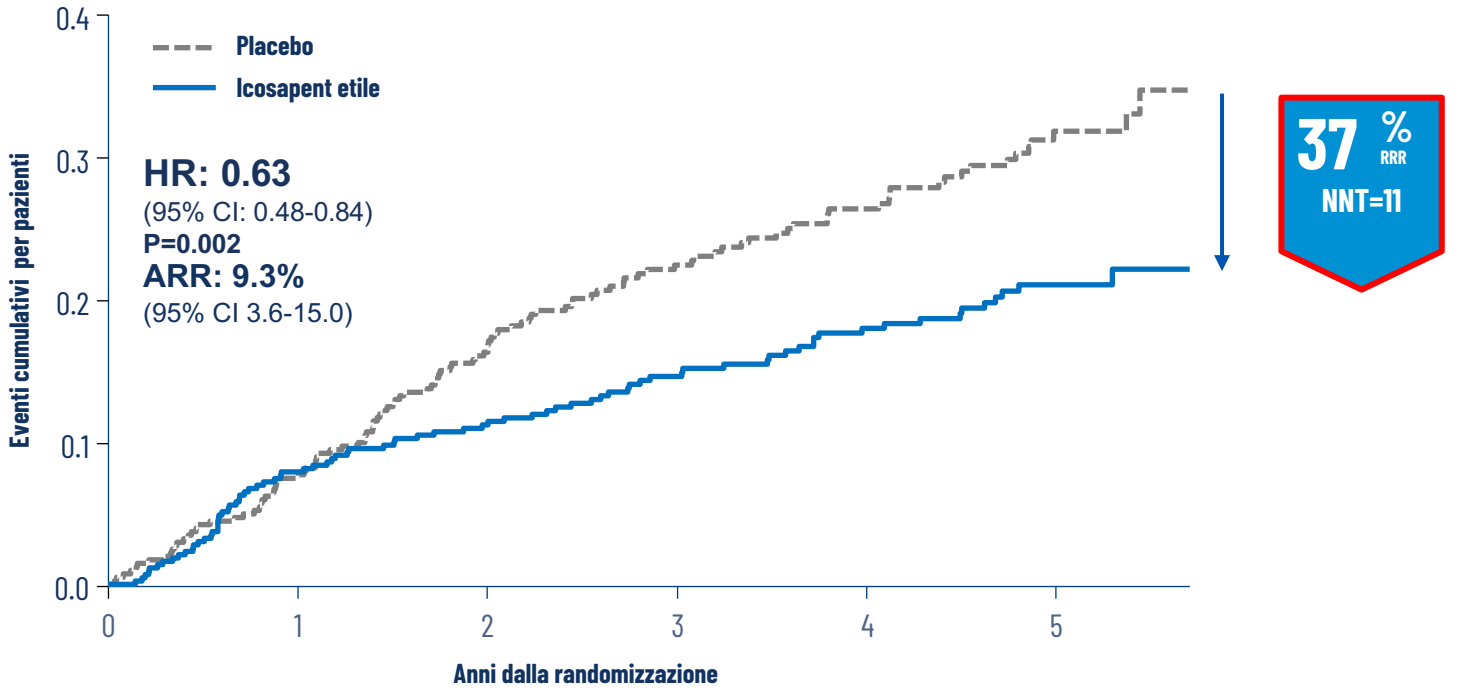
ARR, Riduzione rischio assoluto; CI, Intervallo di confidenza; CV, Cardiovascolare; HR, hazard ratio; MACE, Maggiori eventi avversi cardiovascolari; MI, Infarto del miocardio; NNT, number needed to treat; RRR, Riduzione rischio relativo

Icosapent Ethyl in Patients with Recent ACS

A sub-analysis of REDUCE-IT trial

Endpoint primario

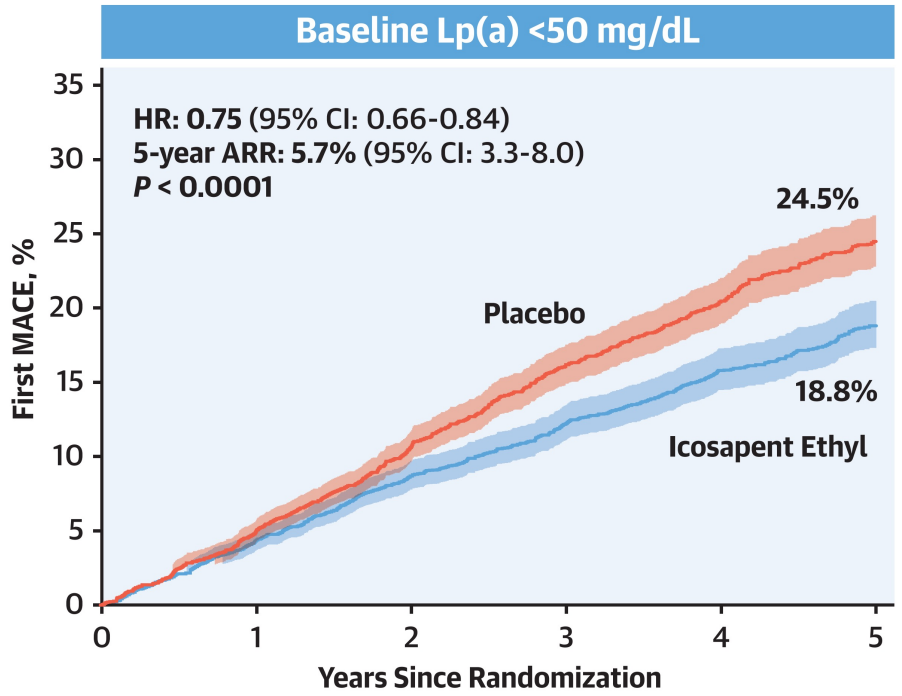
5-point MACE: morte CV, IM non-fatale, ictus non-fatale, rivascolarizzazione coronarica, ospedalizzazione per angina instabile

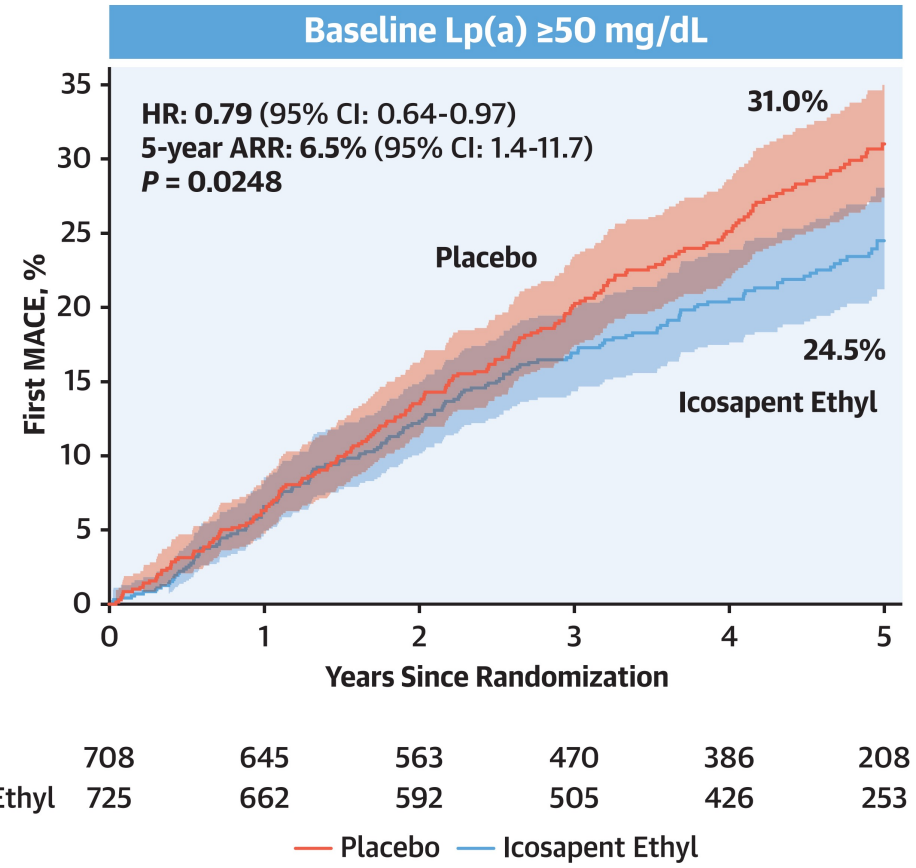


N° a rischio						
Placebo	407	395	373	311	253	150
Icosapent etile	433	425	402	338	284	142

Steg PG, et al. Eur Heart J. 2024:ehad889.

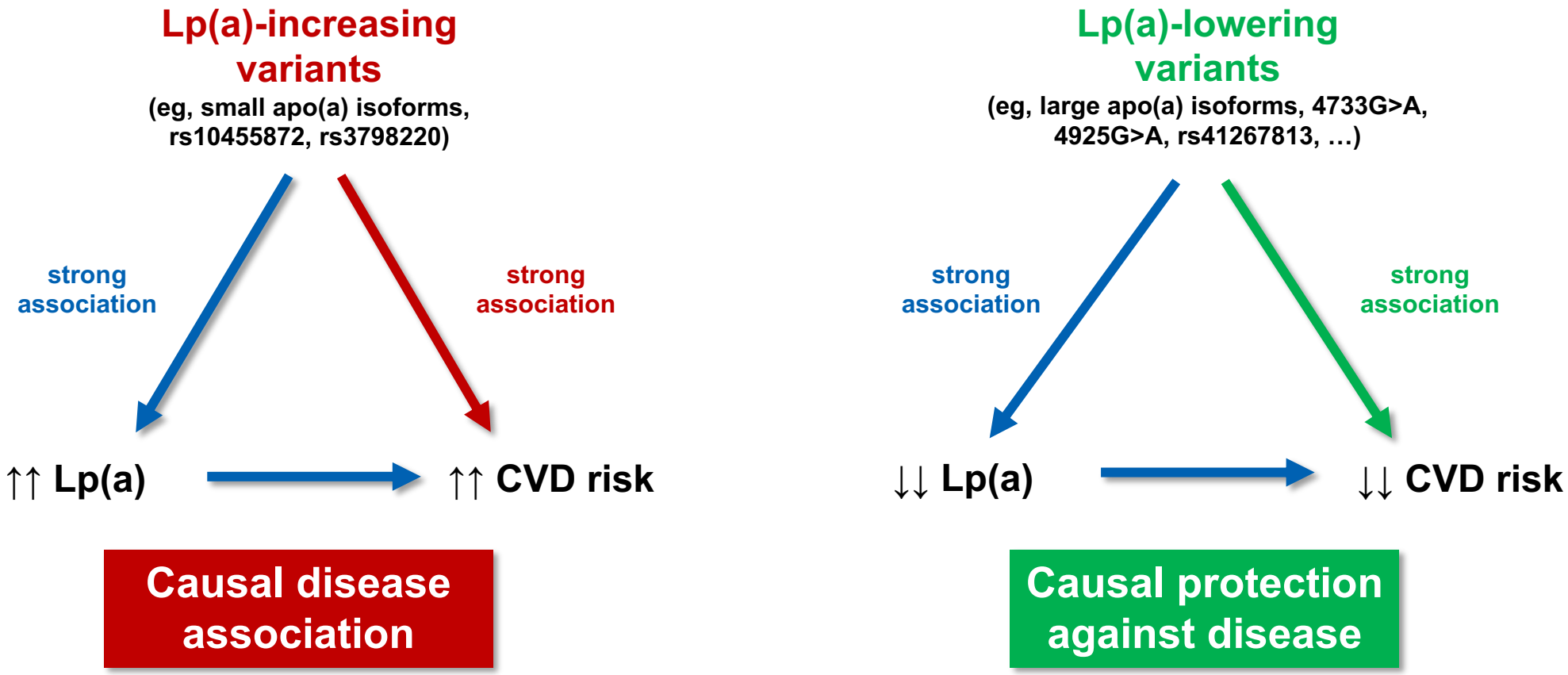
Lipoprotein(a) Levels and Cardiovascular Risk Reduction With Icosapent Ethyl



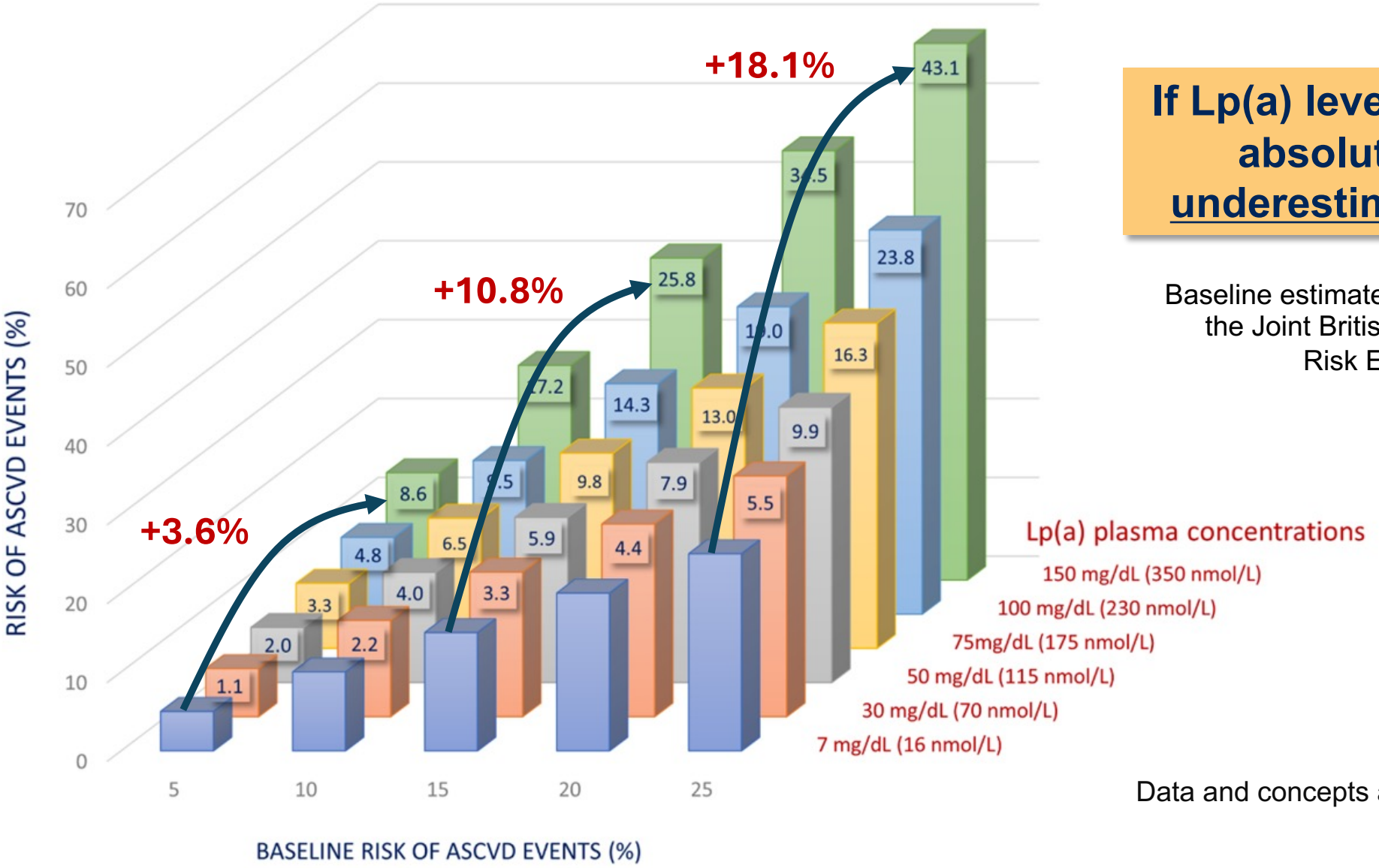


J Am Coll Cardiol. 2024 Mar 15:S0735.

Causal Association of Lp(a) levels with the Risk of Cardiovascular Diseases



Incremental Risk Caused by Higher Lp(a) levels



If Lp(a) level is not considered, absolute risk might be <u>underestimated</u> substantially

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

Data and concepts are provided by Brian Ference et al. using data from the UK Biobank

OCEAN(a)-DOSE: STUDY SCHEMA

Clinicaltrials.gov: NCT04270760

Patients aged 18-80 years with atherosclerotic disease & Lp(a) >150 nmol/L

N=281

**Subcutaneous administration*

RANDOMIZE 1:1:1:1:1

DOUBLE-BLIND, DOSE FINDING

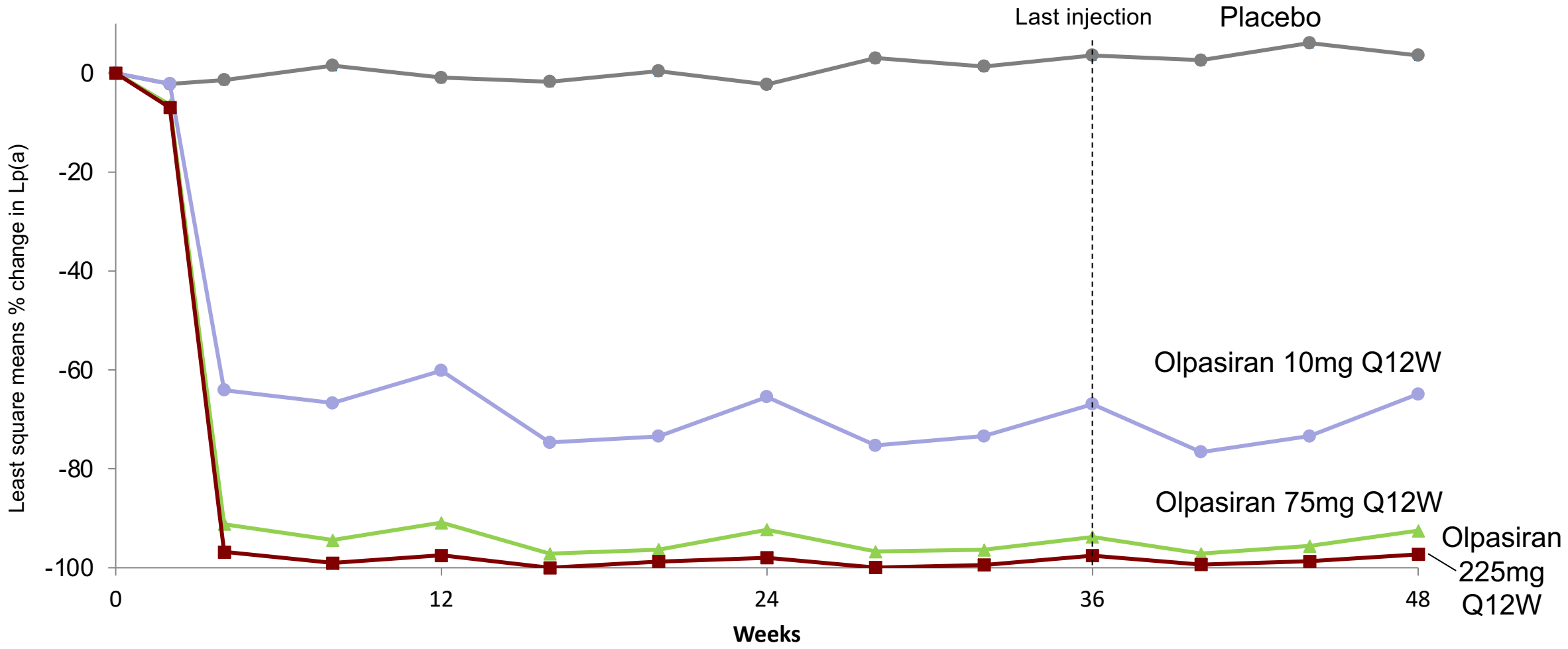
- **Olpasiran 10mg Q12W**
- **Olpasiran 75mg Q12W**
- **Olpasiran 225mg Q12W**
- **Olpasiran 225mg Q24W**
- **Placebo**

Primary Endpoint: % Change in Lp(a) from Baseline to Week 36

Key Secondary Endpoint: % Change in Lp(a) from Baseline to Week 48

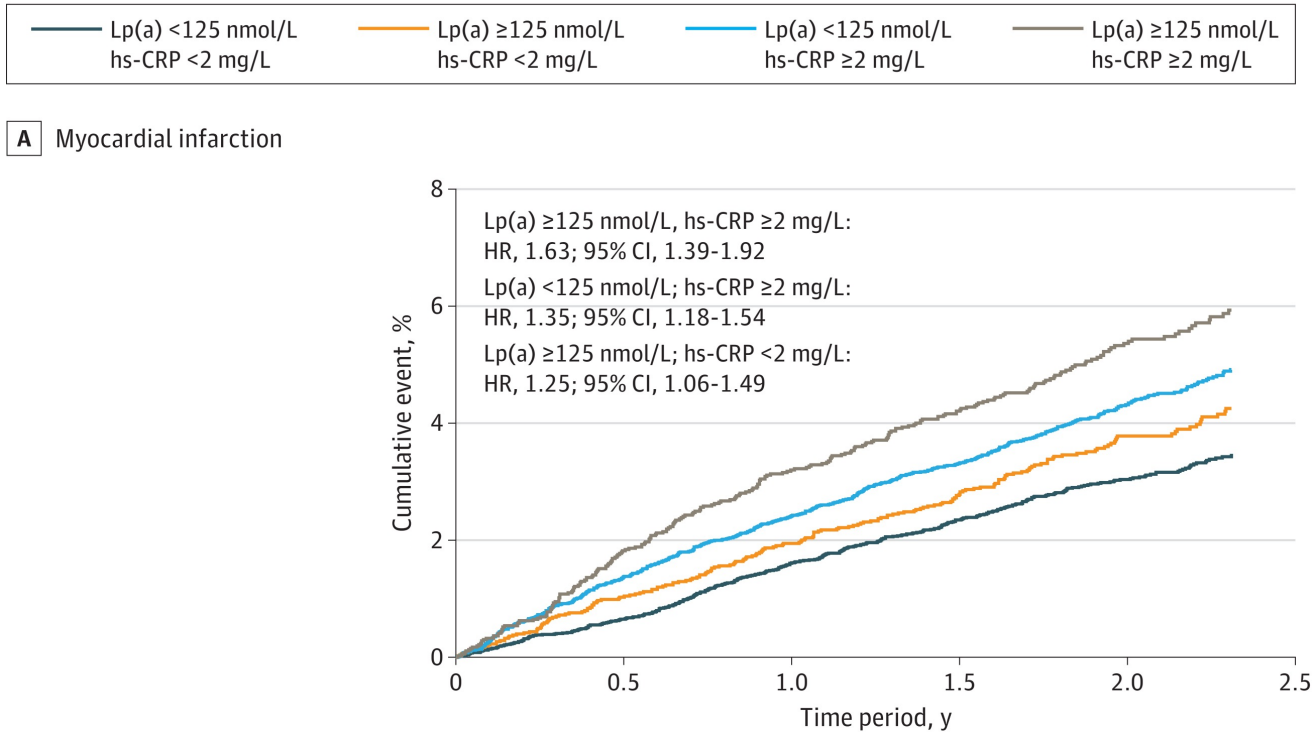
*__Olpasiran__ is a small interfering RNA that reduces lipoprotein(a) synthesis in the liver.

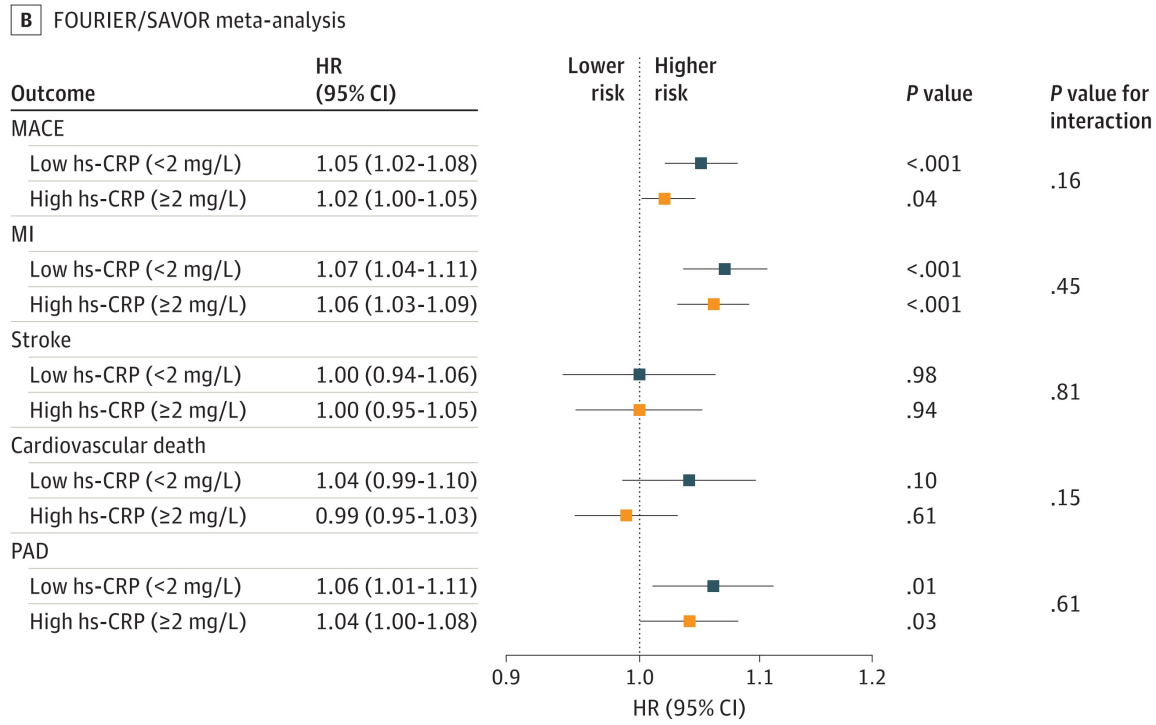
Changes in Lp(a) Through Follow-Up



Lp(a)-related Residual Risk

Lp(a), C-Reactive Protein, and CV Risk in Secondary Prevention

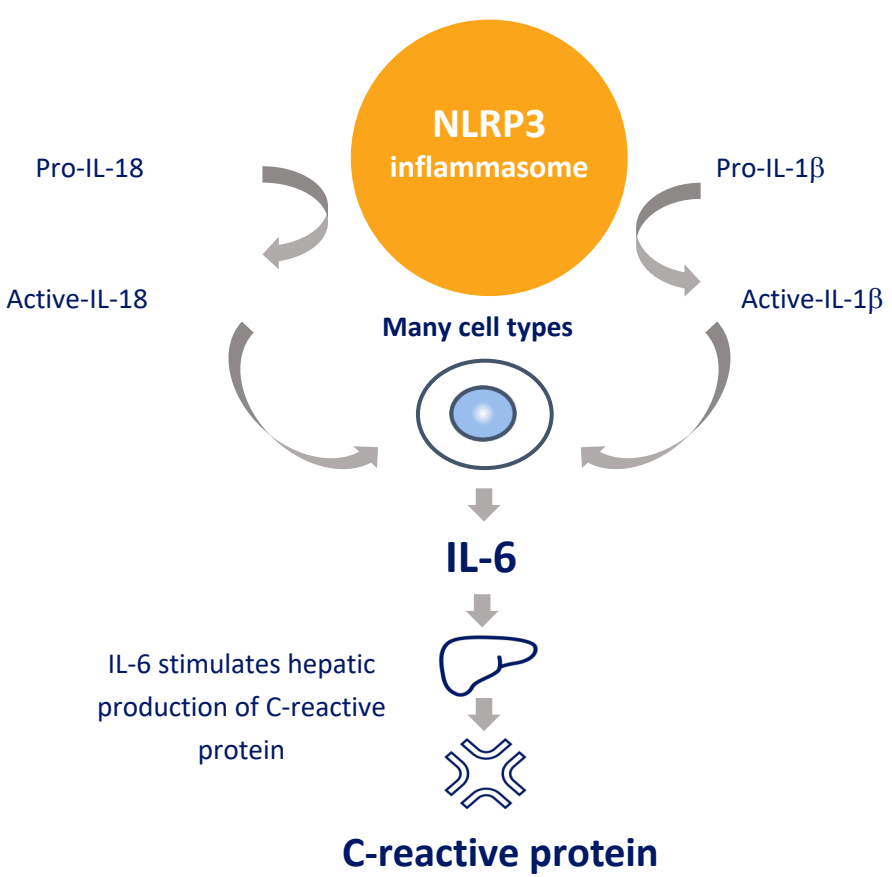


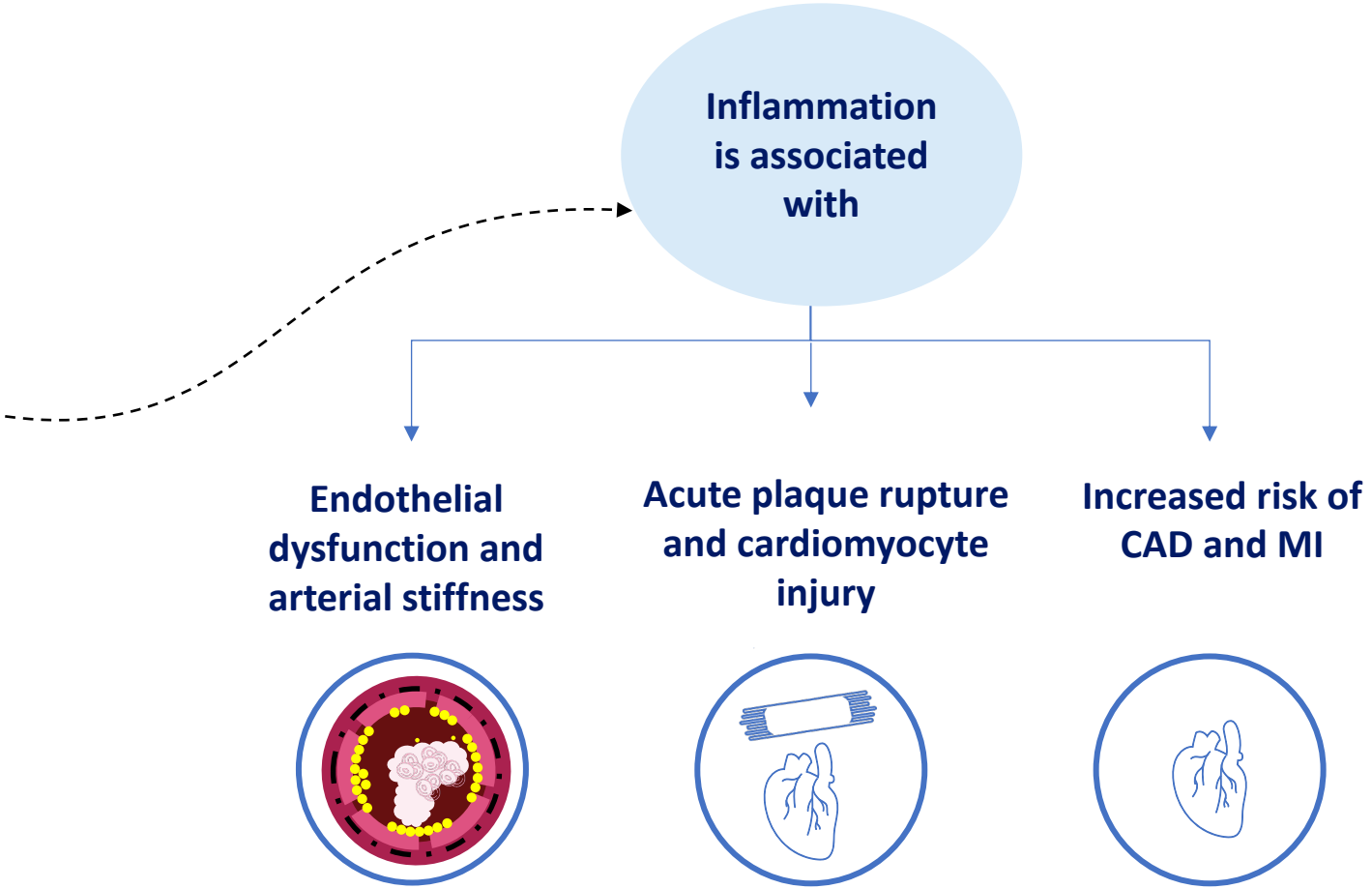


JAMA Cardiol. 2024 :e235605.

In secondary prevention populations (FOURIER and SAVOR-TIMI 53), **higher Lp(a) levels** was associated with increased risk of MACEs, MI, and PAD **regardless of baseline hs-CRP level.**

Role of NLPR3 Inflammasome in Atherosclerosis





AGE, advanced glycation end products; CRP, C-reactive protein; IL-interleukin; Ox-LDL; oxidised low-density lipoprotein; SAA, serum amyloid A; Th, T-helper cell; Treg, regulatory T cells

1. Ridker PM et al. Circ Res 2016;118:145–156; 2. Esteve E et al. Diabetes Care 2007;30:939–945; 3. Mahmud A et al. Hypertension 2005;46:1118–1122; 4. Swerdlow DI et al. Lancet 2012;379:1214–1224; 5. Danesh J et al. PLoS Med. 2008;5:e78; 6. Sarwar N et al. Lancet 2012;379:1205–1213; 7. Ridker PM et al. Circulation 2000;101:1767–1772; 8. IL6R MR Consortium. Lancet 2012;379:1214–1224

Effect of Treatments Targeting the NLRP3 inflammasome pathway on CV risk in RCTs

Canakinumab

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

CANTOS reported a 15% **reduction in the primary composite endpoint* in the canakinumab 150 mg treatment group only vs. placebo**[1]

Colchicine

COLCOT

LODOCO2
LOW-DOSE COLCHICINE FOR SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

COLCOT reported a 23% **reduction in the primary composite endpoint†** with colchicine vs. placebo[2]

LoDoCo2 reported a **31% reduction in the primary composite endpoint‡** with colchicine vs. placebo[3]

Methotrexate

CIRT
CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

CIRT reported that **low-dose methotrexate did not reduce the risk of the primary composite endpoint§ vs. placebo** (HR 0.96 (95% CI: 0.79; 1.16))[4]

Results from CANTOS, COLCOT and LoDoCo2 **support the inflammatory hypothesis** of atherothrombosis

*Composite nonfatal AMI, nonfatal stroke or CV death; †Composite death from CV causes, resuscitated cardiac arrest, AMI, stroke or urgent hospitalisation for angina leading to coronary revascularisation; ‡Composite of CV death, AMI, ischaemic stroke or ischaemia-driven coronary revascularisation; §Composite nonfatal AMI, nonfatal stroke or CV death
reactive protein; LoDoCo2, Low-dose Colchicine 2 Trial; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3;
1. Ridker PM et al. N Engl J Med 2017;377:1119–1131; 2. Tardif JC et al. N Engl J Med 2019;381:2497–2505; 3. Nidorf SM et al. N Engl J Med 2020;383:1838–1847; 4. Ridker PM et al. N Engl J Med 2019;380:752–762

Colchicine in Current ESC Guidelines

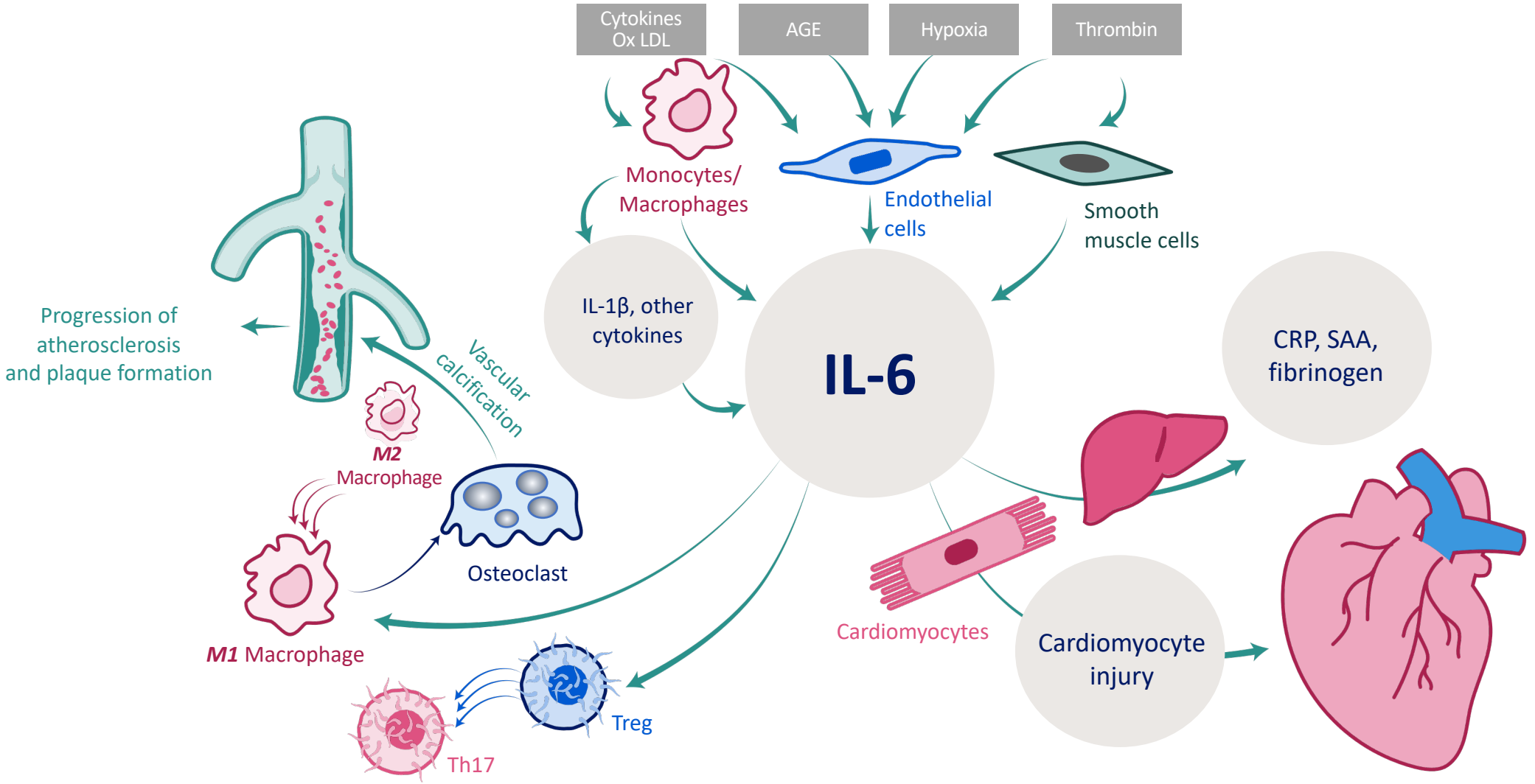
2021 ESC Guidelines on Cardiovascular Disease Prevention

Recommendations	Class	Level
Low-dose colchicine (0.5 mg o.d.) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.	IIb	A

2023 ESC Guidelines on Acute Coronary Syndrome

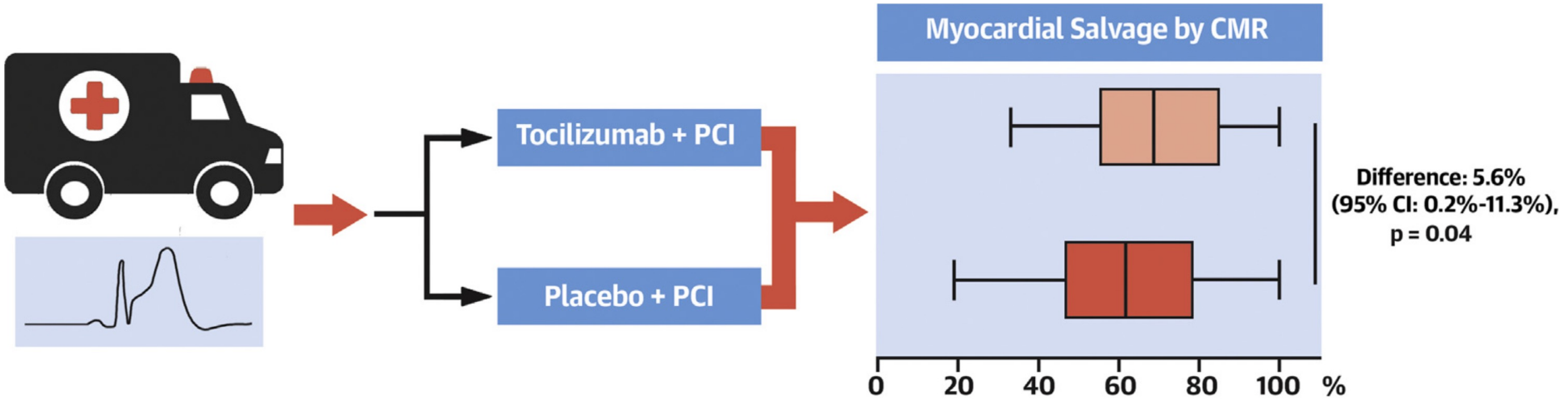
Recommendations	Class	Level
Low-dose colchicine (0.5 mg once daily) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy.	IIb	A

Role of IL-6 in Cardiovascular Disease



Anti-inflammatory Therapy with Tocilizumab for Patients with STEMI: ASSAIL-MI trial

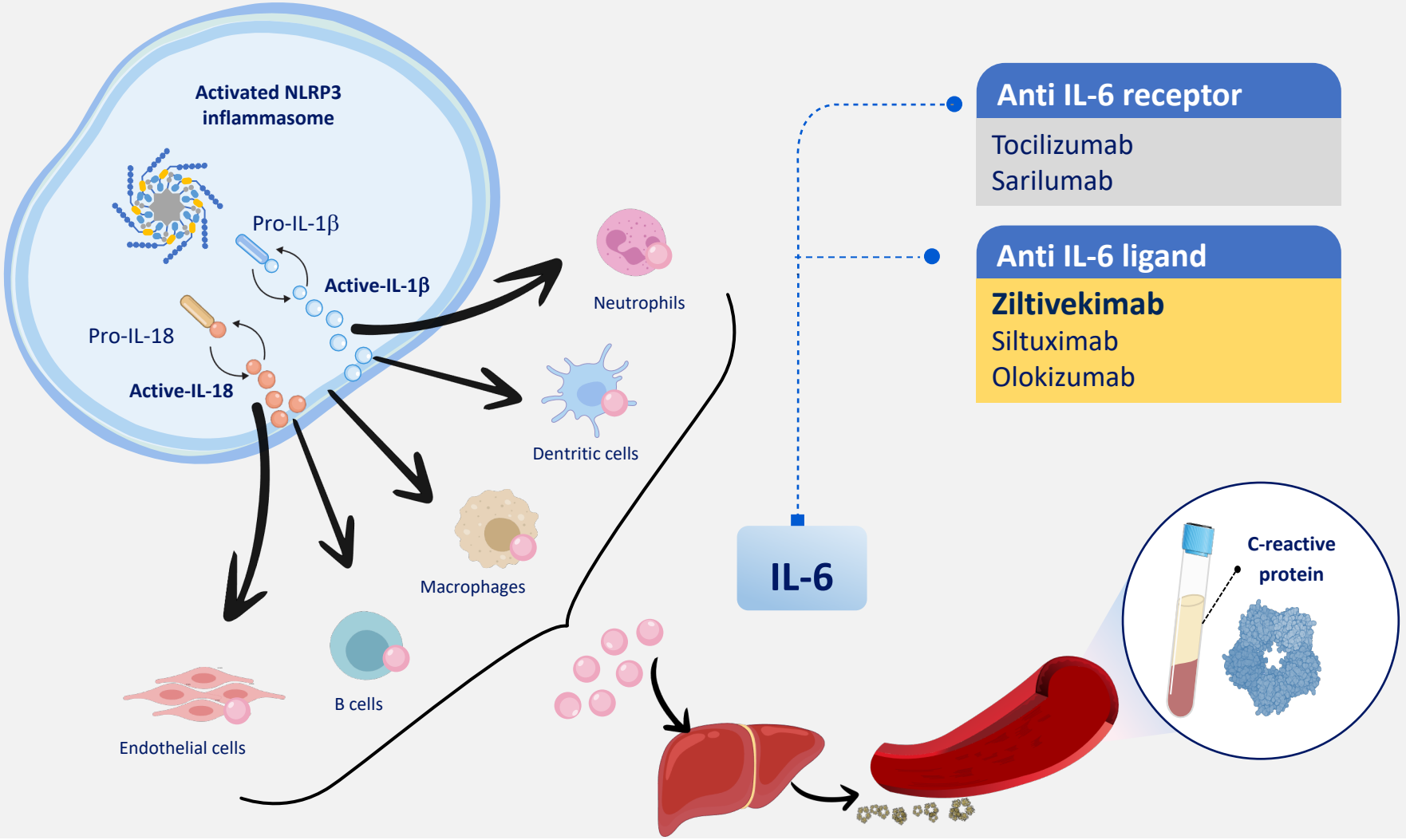
CENTRAL ILLUSTRATION Design and Primary Result of the ASSAIL-MI Trial



Broch, K. et al. J Am Coll Cardiol. 2021;77(15):1845-55.

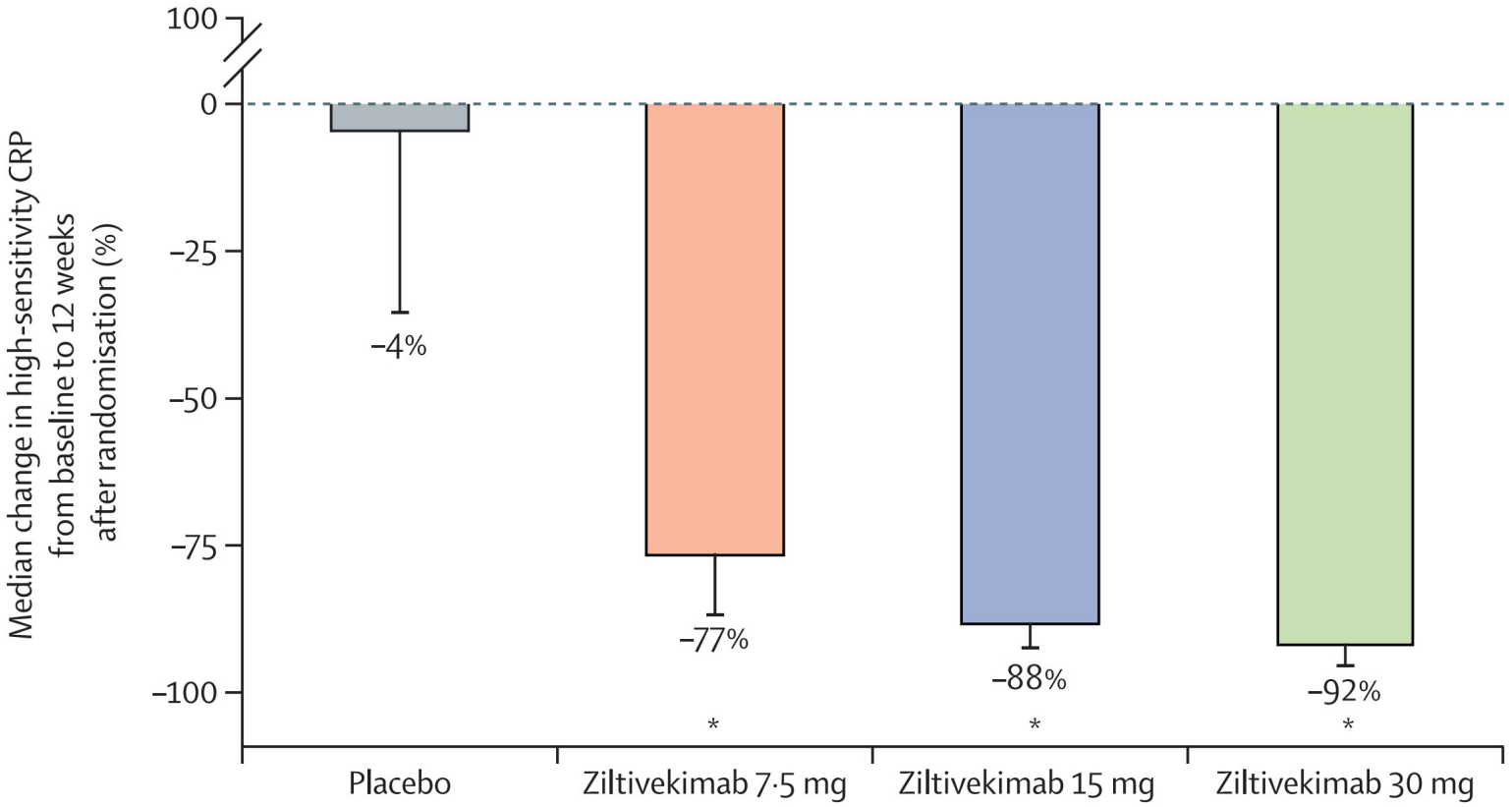
In the ASSAIL-MI trial, we randomized 199 patients with acute ST-segment elevation myocardial infarction (illustrated by ambulance and ST-segment elevation in electrocardiogram) to prompt treatment with the interleukin-6 receptor inhibitor tocilizumab or placebo during percutaneous coronary intervention (PCI). As illustrated in the bar chart, the primary endpoint, the myocardial salvage index as measured by cardiac magnetic resonance imaging (CMR), was higher in patients allocated to tocilizumab (between-group difference 5.6% [95% confidence interval: 0.2% to 11.3%] of left ventricular volume; $p = 0.04$). ASSAIL-MI = ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction.

Ziltivekimab Targets IL-6 ligand



Adapted from Ridker PM et al. Circulation 2020;141:787–789

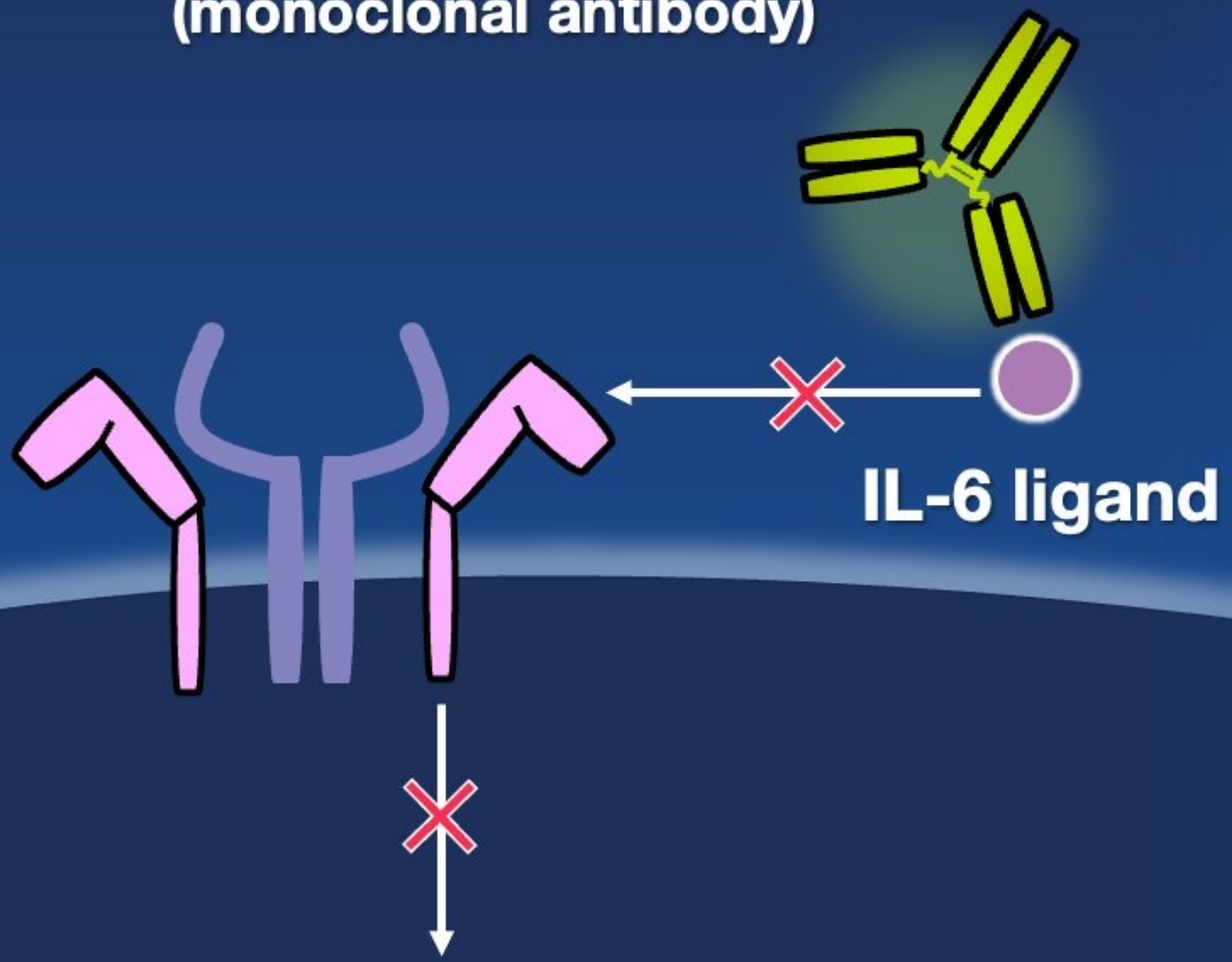
Anti-inflammatory Therapy with Ziltivekimab for Atherosclerotic Disease: RESCUE trial



In 264 patients with moderate to severe CKD and hsCRP ≥2 mg/dl, **ziltivekimab** (a fully human monoclonal antibody against the IL-6 ligand) **markedly reduced biomarkers of inflammation and thrombosis** relevant to ASCVD.

Lancet. 2021;397:2060-2069.

Ziltivekimab
(monoclonal antibody)



ARTEMIS Trial

- Phase 3, event-driven
- 10000 patients with recent type 1 acute myocardial infarction
- Randomized to ziltivekimab 30/15 mg plus SOC or placebo
- Primary endpoint: Cardiovascular death, MI, or stroke

CONCLUSIONS

- Despite great strides in cardiovascular secondary prevention, **many patients remain at high risk of recurrent CV events.**
- **Residual risk** results from a combination of **multiple risk factors (inflammation, Lp(a), triglycerides, etc)**.
- Adoption of **GDMT (intensive LDL-C lowering)** is the first step to address cardiovascular risk, but it is not sufficient.
- In secondary prevention, **new therapeutic targets** using novel strategies should be addressed to improve patient prognosis.
- Novel therapies need to be **personalized (precision medicine).**

Thank you!

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