ASPC
The American Society for Preventive Cardiology

Understanding Inflammation in Atherosclerotic Cardiovascular Disease (ASCVD)

The Rise of Inflammatory Biomarkers

This educational presentation was sponsored by an unrestricted grant from Tourmaline Bio.

Presentation Content

1. Atherosclerotic Cardiovascular Disease (ASCVD)
2. Inflammation and Its Role in ASCVD
3. Inflammatory Biomarkers and How They Cause ASCVD
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5. Future Directions

Atherosclerotic Cardiovascular Disease (ASCVD)

ASCVD

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide.

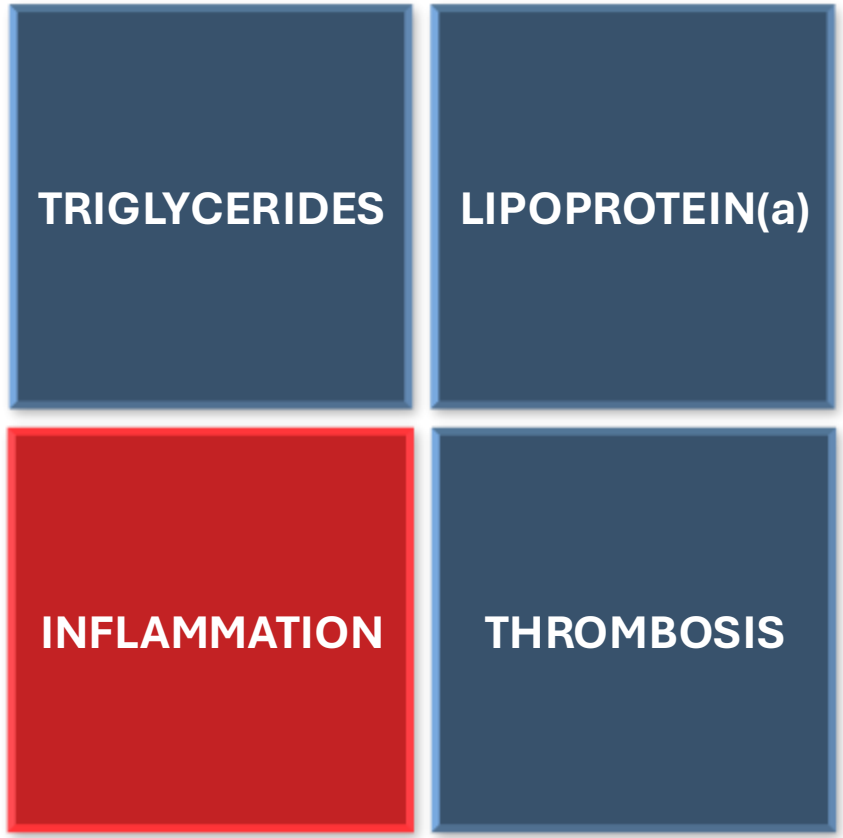
ASCVD is caused by plaque buildup in arterial walls and refers to conditions that include:

- Coronary Heart Disease (CHD), Cerebrovascular disease, Peripheral artery disease (PAD), Aortic atherosclerotic disease, such as abdominal aortic aneurysm (AAA) and thoracic aortic aneurysm.
- Despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapy, **people with ASCVD still face a 30% risk of a major adverse cardiovascular event over 10 years.**

Kaasenbrood L, et al. *Circulation* 2016;134:1419–29.

ASCVD: Risk Pathways Beyond LDL Cholesterol

- Although lipid-lowering therapy has been a mainstay of ASCVD prevention (both primary and secondary), 'residual risk' persists.
- Multiple contributors have been implicated, including elevated Lp(a), hypertriglyceridemia, excess thrombotic risk, and **systemic inflammation**.



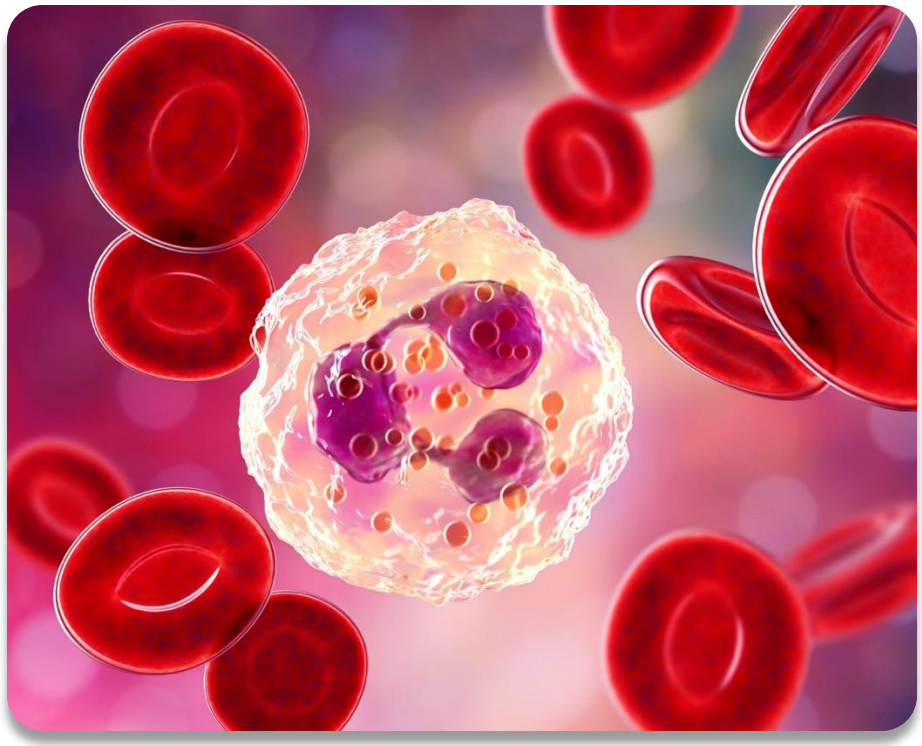
Mehta A, et al. *US Cardiology Review.* 2025;19:e06.

What is Inflammation?

Atherosclerosis is widely recognized as a chronic inflammatory disease of the blood vessels caused by the accumulation of low-density lipoprotein cholesterol.

Chronic inflammation is:

- A low-grade, non-infectious, systemic inflammatory state that is associated with age, psychology, environment, lifestyle, and the resolution of acute inflammation.
- Associated with endothelial dysfunction, leukocyte recruitment, transformation of monocytes into macrophages and eventually into foam cells, smooth muscle cell migration and other processes.
- Involved in the whole process of the occurrence and development of atherosclerosis and is the core of atherosclerosis.



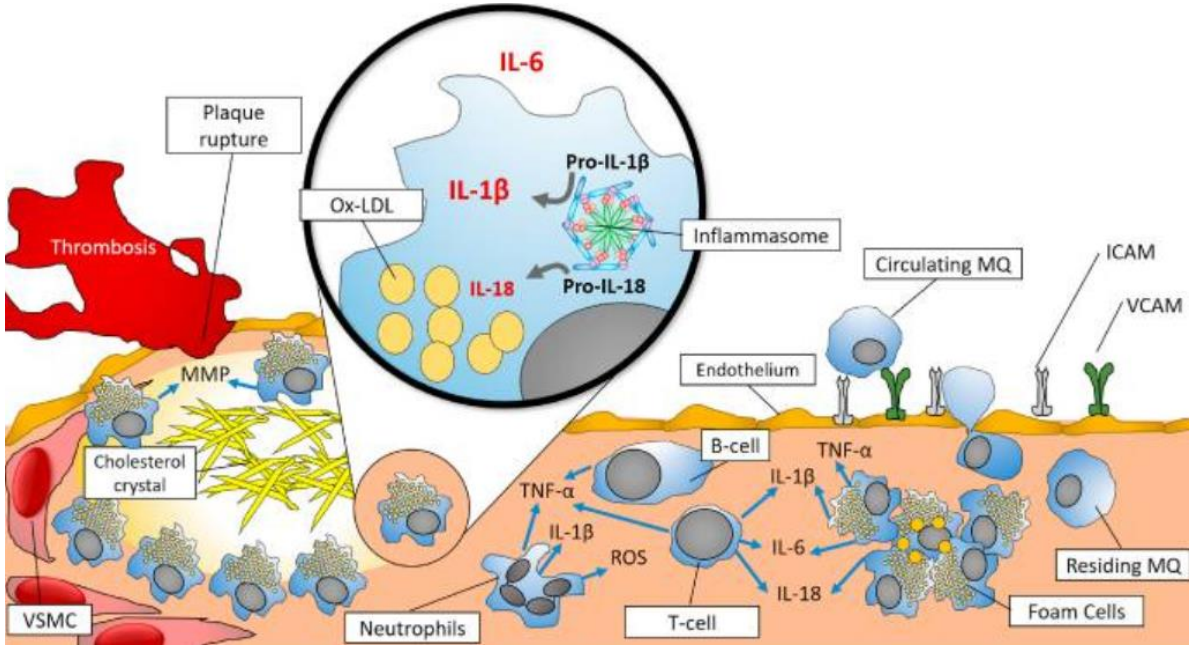
Liao M, et al. *PLoS ONE*. 2024;19(5):e0303869.

Inflammation and Its Role in ASCVD

The Role of Inflammation in ASCVD

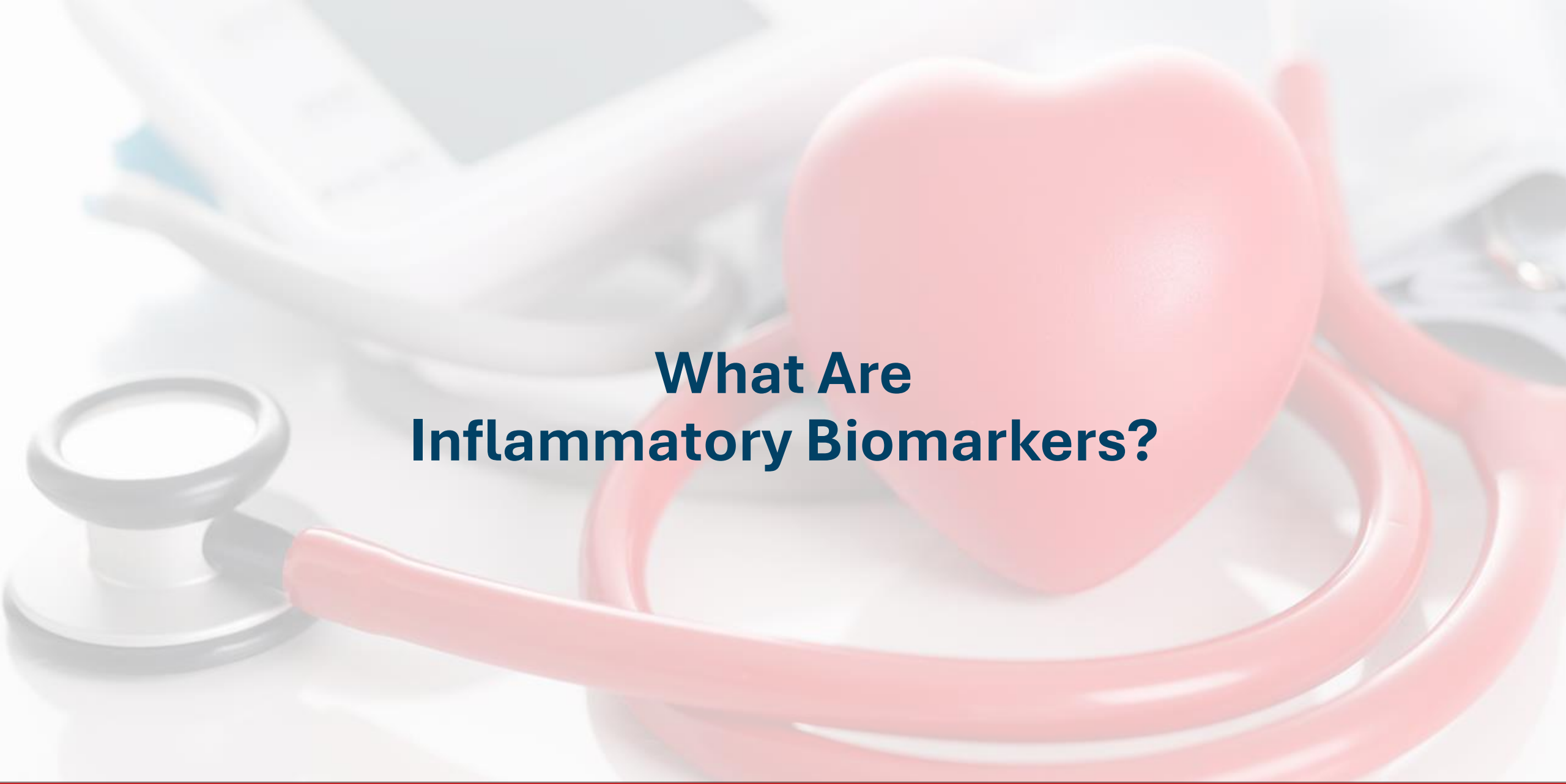
Inflammation is a key driver of all the steps involved in atherothrombosis.

- At the inception of atherosclerotic lesions, endothelial dysfunction and subintimal cholesterol accumulation ignite a subintimal inflammatory response.
- Cytokines are released to activate a variety of inflammatory cells and produce interleukin 6 (IL-6).
- IL-6 stimulates the production of C-reactive protein (CRP) from the liver and amplifies the inflammatory cascade within the vessel wall.



ICAM=Intercellular adhesion molecule; VCAM=Vascular cell adhesion molecule; IL=interleukin; MQ=macrophage; MMP=metalloproteinases; VSMC=vascular smooth muscle cell; Ox-LDL=oxidized low-density lipoprotein.

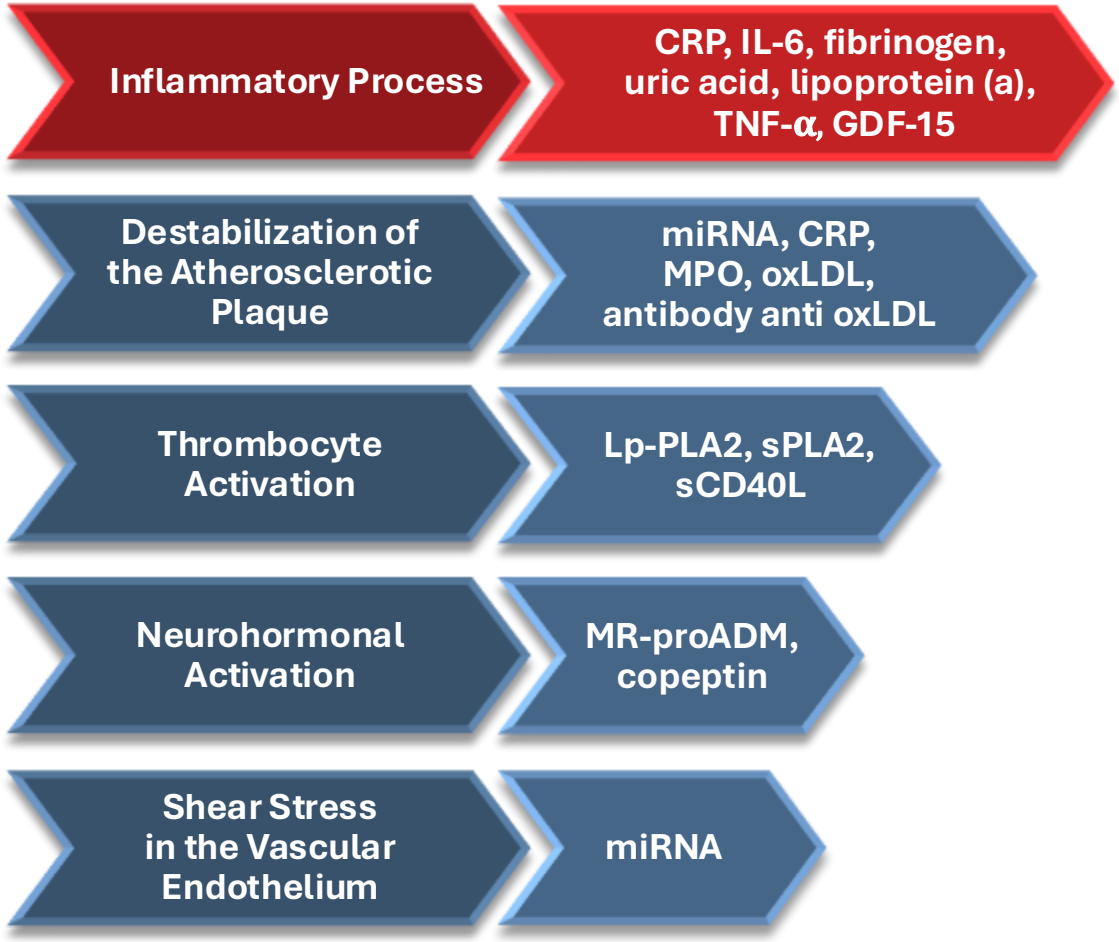
Alfaddagh A, et al. *American Journal of Preventive Cardiology*. 2020;4:100130.



What Are Inflammatory Biomarkers?

Biomarkers Involved in the Development and Progression of the Atherosclerotic Process

- Atherosclerosis is known to be a chronic inflammatory process in which IL-6, CRP, myeloperoxidase (MPO), and matrix metalloproteinase 9 (MMP-9) are used as biomarkers
- IL-6 and tumor necrosis factor α (TNF-α) are two proinflammatory cytokines associated with increased cardiovascular risk and atherosclerotic plaque formation



CRP=C reactive protein; TNF=tumor necrosis factor; GDF-15=growth/differentiation factor-15; MPO=myeloperoxidase; oxLDL=oxidized low-density lipoprotein; Lp-PLA2=lipoprotein-associated phospholipase A2; Spla2=phospholipase A2; sCD40L=soluble CD40-ligand; MR-proADM=midregional pro-adrenomedullin).

Adam CA, et al. *Int J Mol Sci.* 2022;23:4998.

C-Reactive Protein (CRP)

What Is CRP?

- CRP is an acute-phase protein primarily synthesized in liver hepatocytes and plays a critical role in inflammation response.[1-2]
- Elevated CRP levels are directly proportional to CVD risk and are an independent risk factor for cardiac death.[1]
- Mild, 2-to 5-fold increases in baseline plasma CRP levels in asymptomatic individuals are associated with an increased risk of cardiovascular events such as stroke and myocardial infarction.[3-4]
- The use of mildly elevated CRP levels to guide primary prevention has led to a significant reduction in major cardiovascular events in apparently healthy persons.[5]

1. Zhou HH, et al. *Front Immunol*. 2024;15:1425168; 2. Mouliou DS.. *Diseases*. 2023;11:132; 3. Ridker PM, et al. *New Engl J Med*. (2002) 347:1557–65; 4. Eisenhardt SU, et al. *Circ Res*. (2009) 105:128–37; 5. Ridker PM, et al. *New Engl J Med*. (2008) 359:2195–207.

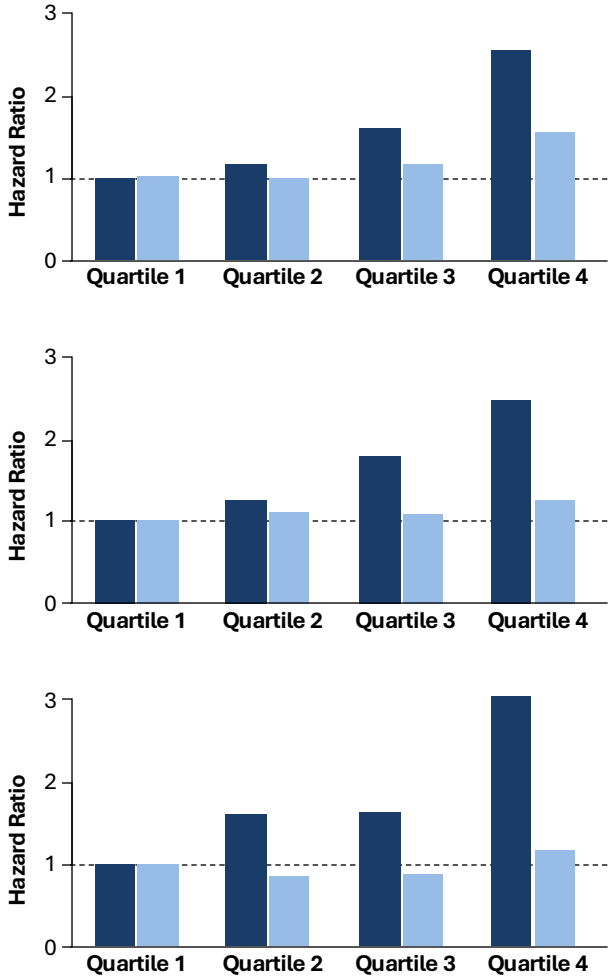
hs-CRP vs LDL-C

■ hs-CRP ■ LDLC

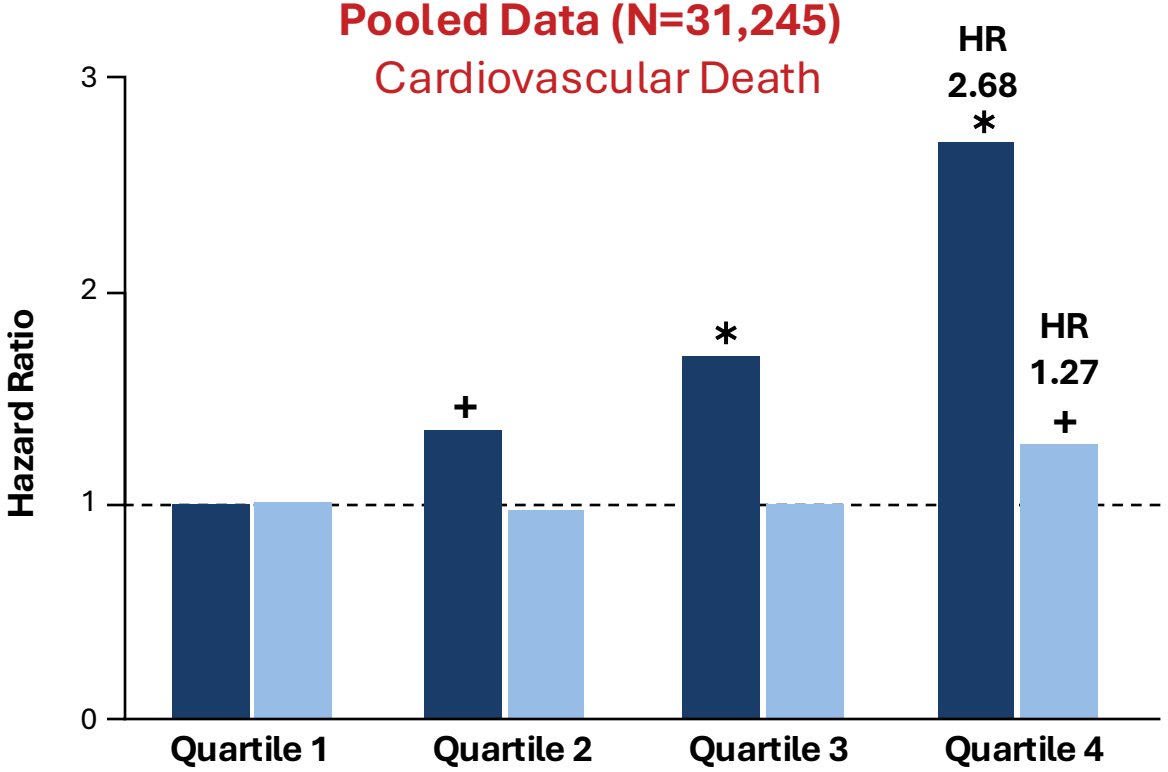
PROMINENT
(N = 9,988)

REDUCE-IT
(N = 8,179)

STRENGTH
(N = 13,078)



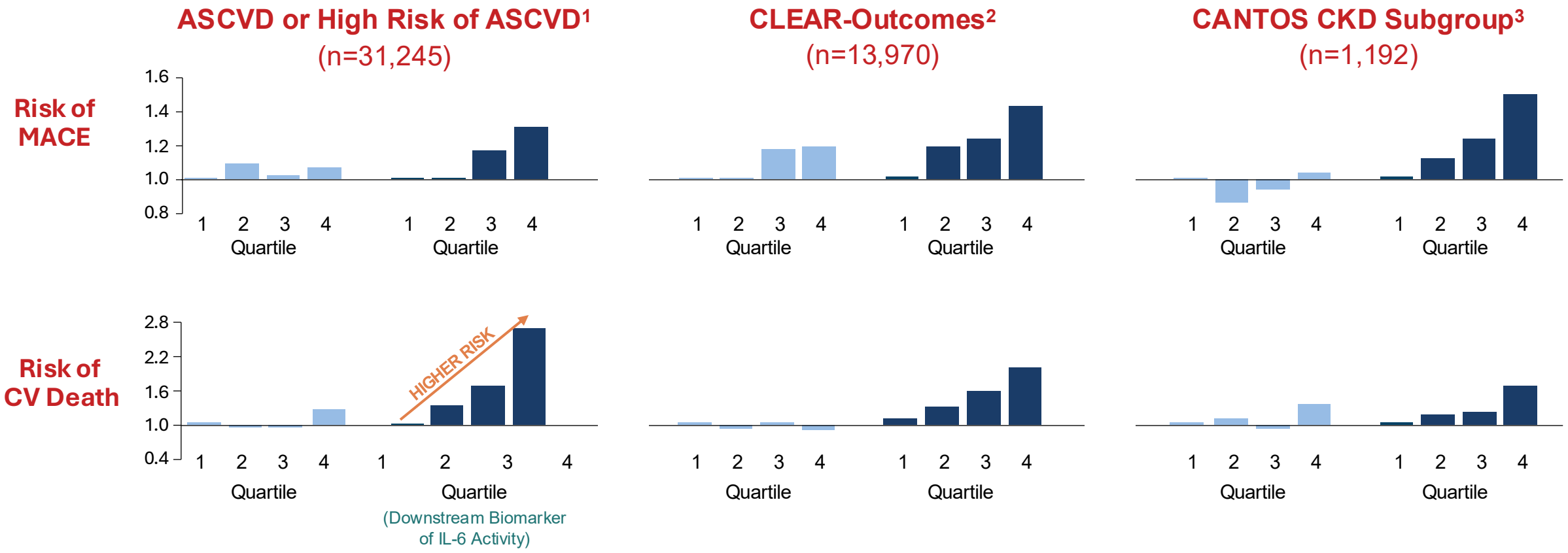
Pooled Data (N=31,245)
Cardiovascular Death



* P<0.0001
\+ P<0.05
Among statin treated patients, residual inflammatory risk is a more powerful predictor of CV death than LDL cholesterol.
Ridker, et al. *Lancet*. 2023;401:1293-1301.

Multiple Observational Studies Show hs-CRP Levels Predict Future MACE Even Better Than Cholesterol in High-risk Populations

■ hs-CRP ■ LDLC



CKD=chronic kidney disease. hs-CRP=high-sensitivity C-reactive protein. LDL=low-density lipoprotein cholesterol

Hazard ratios shown. Major adverse cardiovascular events (MACE) include myocardial infarction, stroke, coronary revascularization, cardiovascular (CV) death. Certain data in this presentation are based on a cross-trial comparison and are not based on head-to-head clinical trials. Cross trial comparisons are inherently limited and may suggest misleading similarities or differences in outcomes. Results of head-to-head comparisons may differ significantly from those set forth herein.

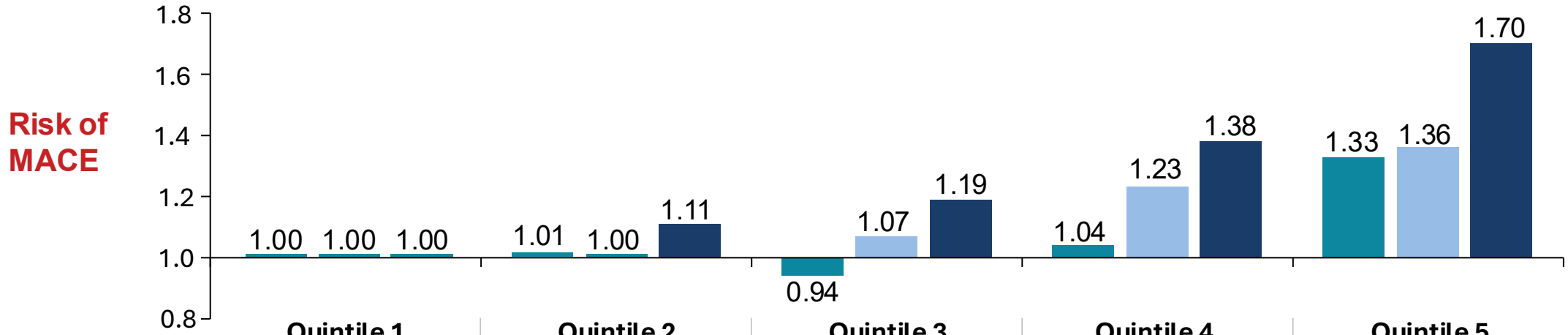
1. Ridker, et al. *Lancet*. 2023; 2. Ridker, et al. *Circulation*. 2023; 3. Ridker, et al. *Eur Heart J*. 2022.

Emerging Evidence Suggests That hs-CRP Is More Strongly Associated with MACE Than Both LDL and Lp(a)

Late breaking data presented at European Society of Cardiology 2024 Congress and simultaneously published in the New England Journal of Medicine

30-Year Longitudinal Data from the Women's Health Study

(n=27,929)



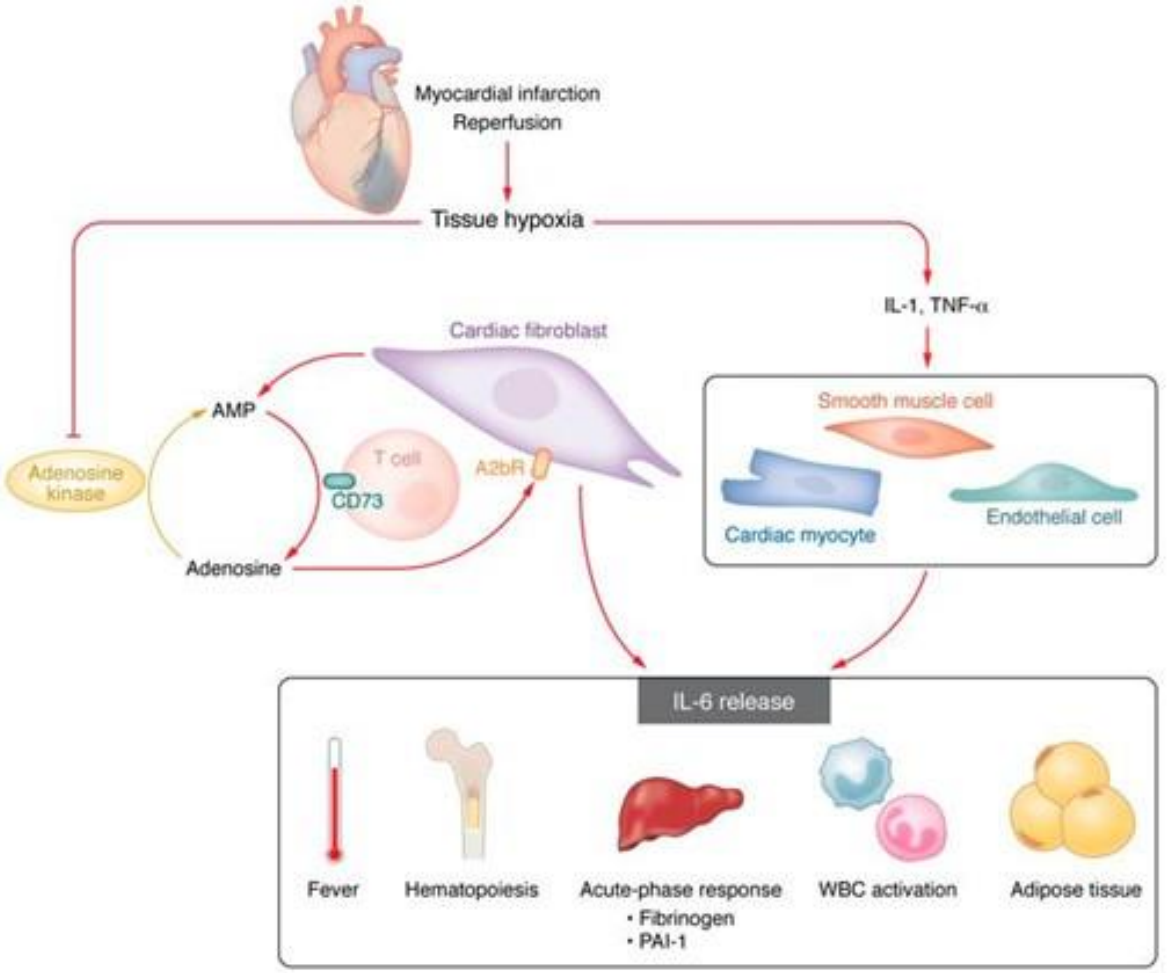
	Quintile 1 (Reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5
hs-CRP mg/L baseline	<0.65	0.65 to <1.47	1.47 to <2.75	2.75 to <5.18	≥5.18
LDL-C mg/dL baseline	<96.1	96.1 to <113.5	113.5 to <129.7	129.7 to <150.7	≥150.7
Lp(a) mg/dL baseline	<3.6	3.6 to <7.6	7.6 to <15.5	15.5 to <44.1	≥44.1

Ridker, et al. *NEJM*. 2024.

Interleukin 6 (IL-6)

What Is IL-6?

- Interleukin (IL)-6 is an immune-mediated, pro-inflammatory cytokine that
  is elevated in systemic inflammatory states.[1]
- IL-6 plays a direct role in activating endothelial monocytes and macrophages, thereby accelerating plaque accumulation and atherosclerosis.



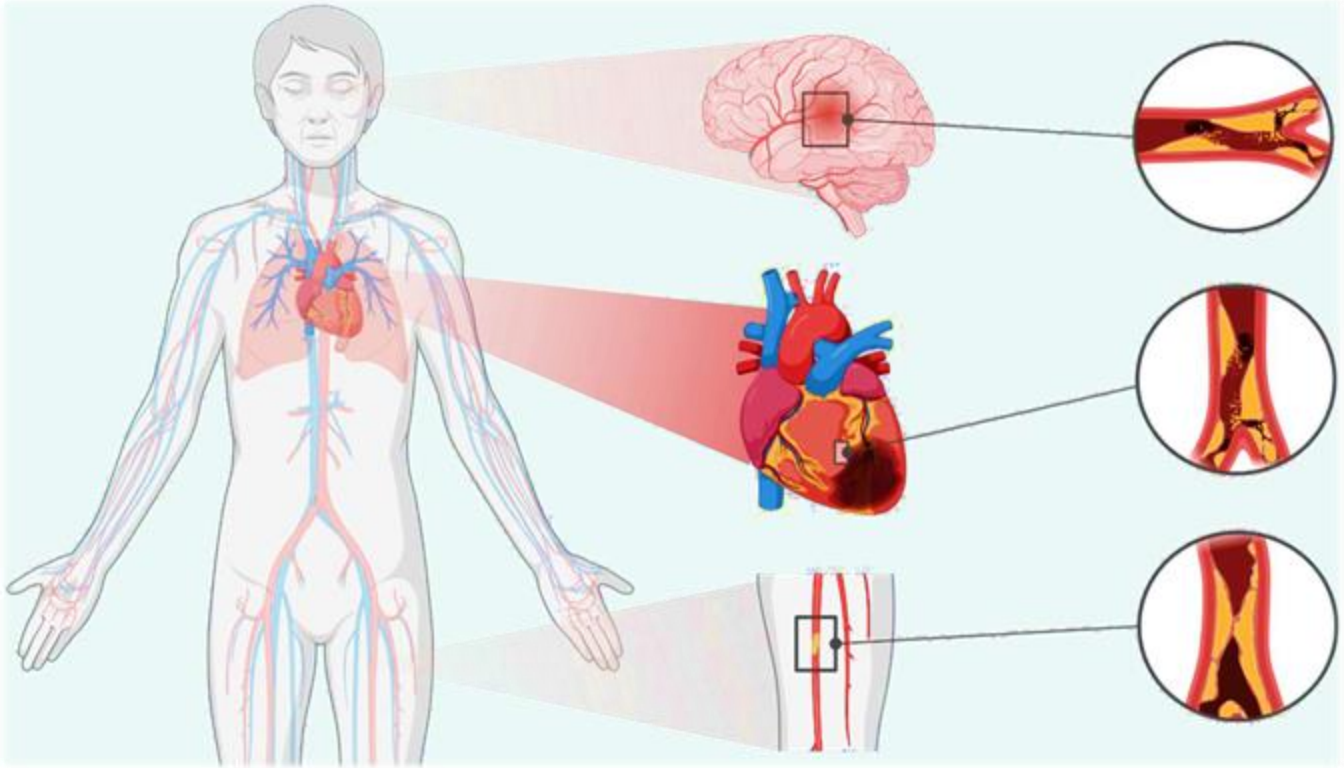
Adapted from: J Clin Invest. 2023;133(11):e167670.

Khan MS, et al. *JACC Adv*. 2024 Aug;3(8):101063.

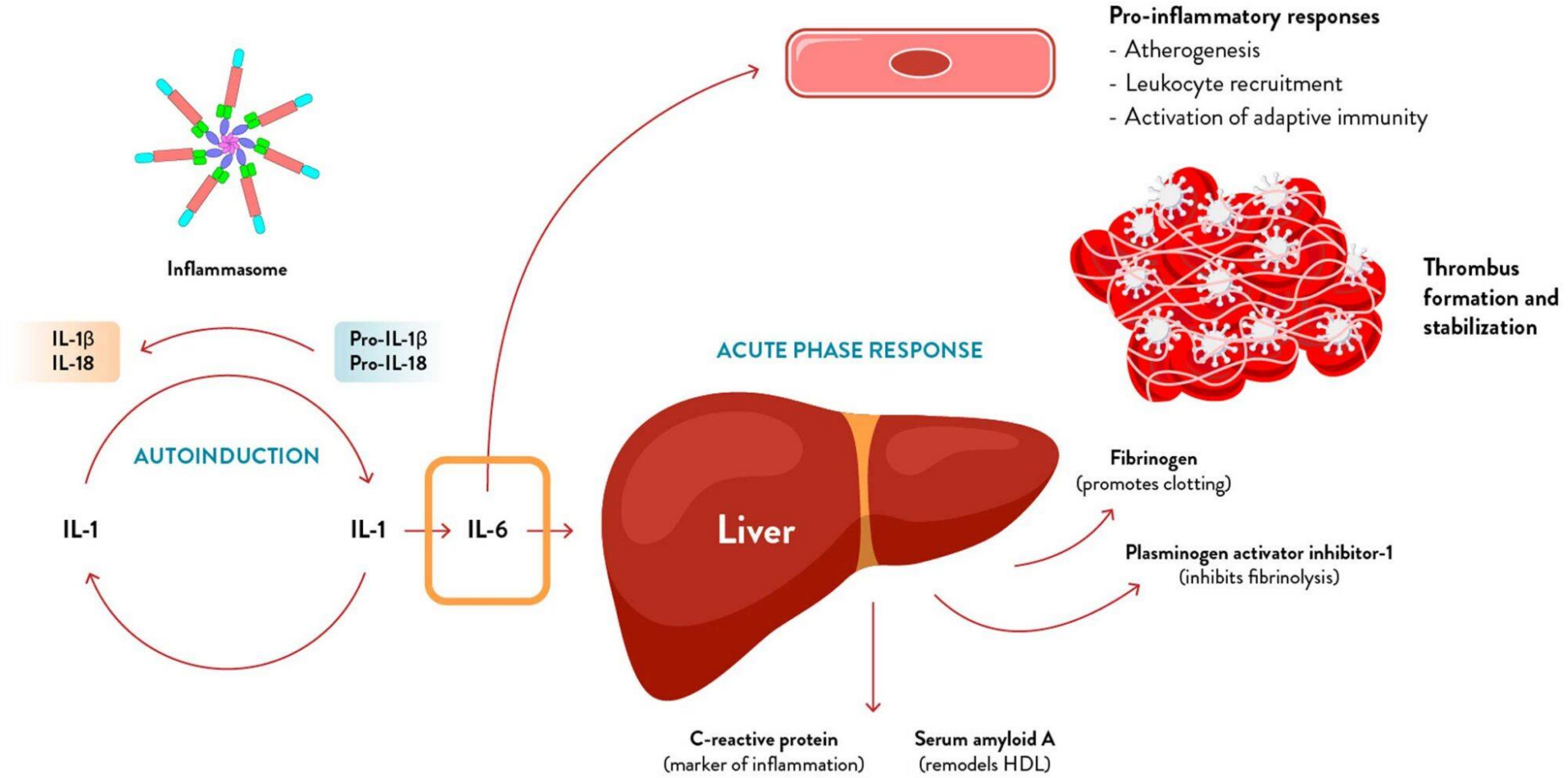
Convergence of Human Evidence Supports Therapeutic Potential of IL-6 Inhibition for ASCVD

- Human Genetic Evidence
- Epidemiological Evidence
- Clinical Trial Evidence

Evidence Suggests IL-6 May Drive ASCVD Risk



Role of IL-6 in ASCVD



Adapted from: Libby, et al. *Cells*. 2021 and Libby, et al. *Int J Cardiol*. 2018.

Landmark CANTOS Study Validated Therapeutic Potential of Addressing Inflammation in ASCVD

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) Trial Design

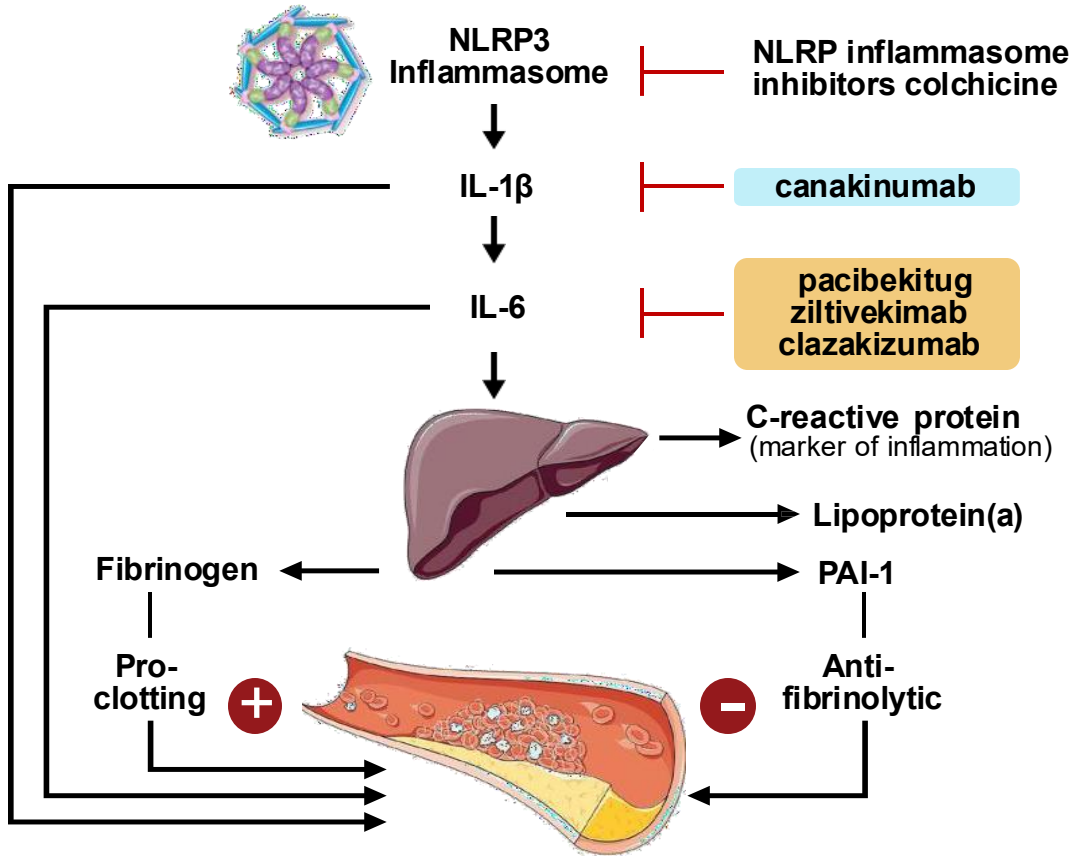
10,061 Patients

- Stable CAD (post MI)
- On Statin, ACE/ARB, BB, ASA
- hs-CRP ≥2 mg/L

- Canakinumab 50 mg Q3M n=2,170
- Canakinumab 150 mg Q3M n=2,284
- Canakinumab 300 mg Q3M n=2,263
- Placebo Q3M n=3,344

Primary Endpoint:
Time to the first occurrence of MACE
(CV death, non-fatal MI, or non-fatal stroke)

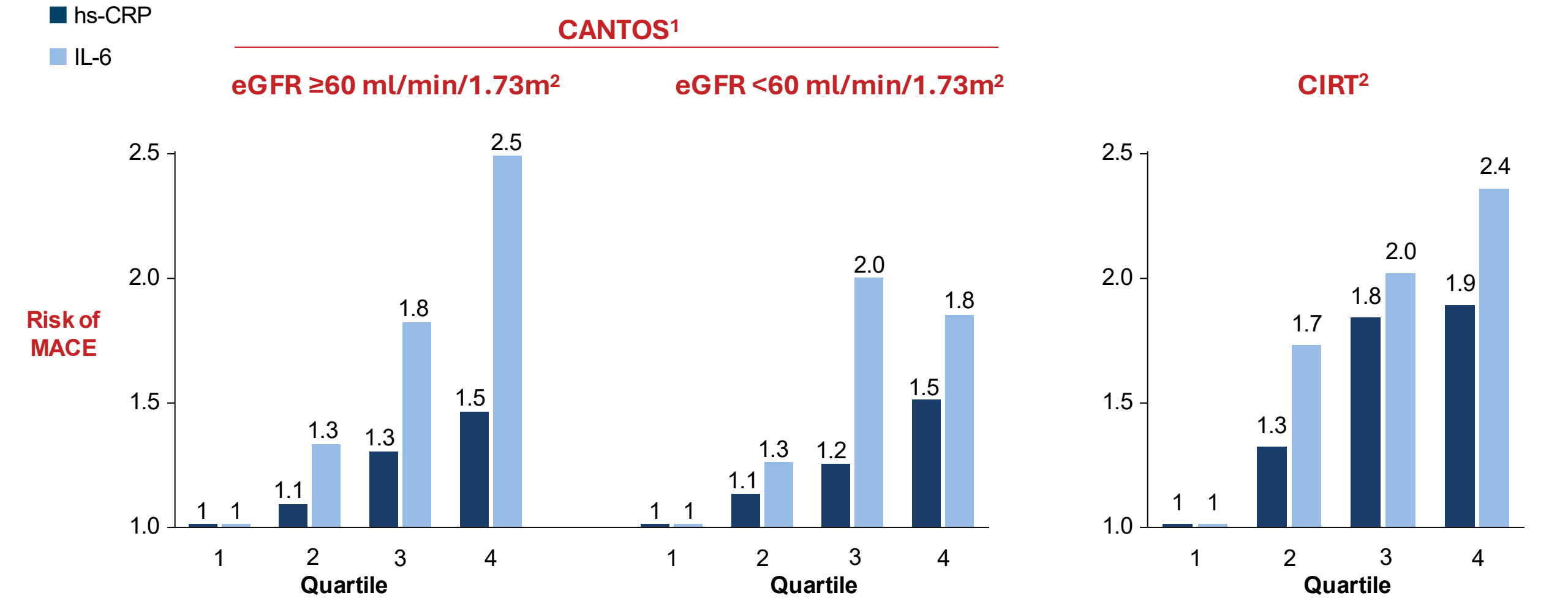
IL-1β Is Upstream of IL-6



Ridker, et al. *NEJM*. 2017; 2. Adapted from Ridker, et al. *Circ Res*. 2016.

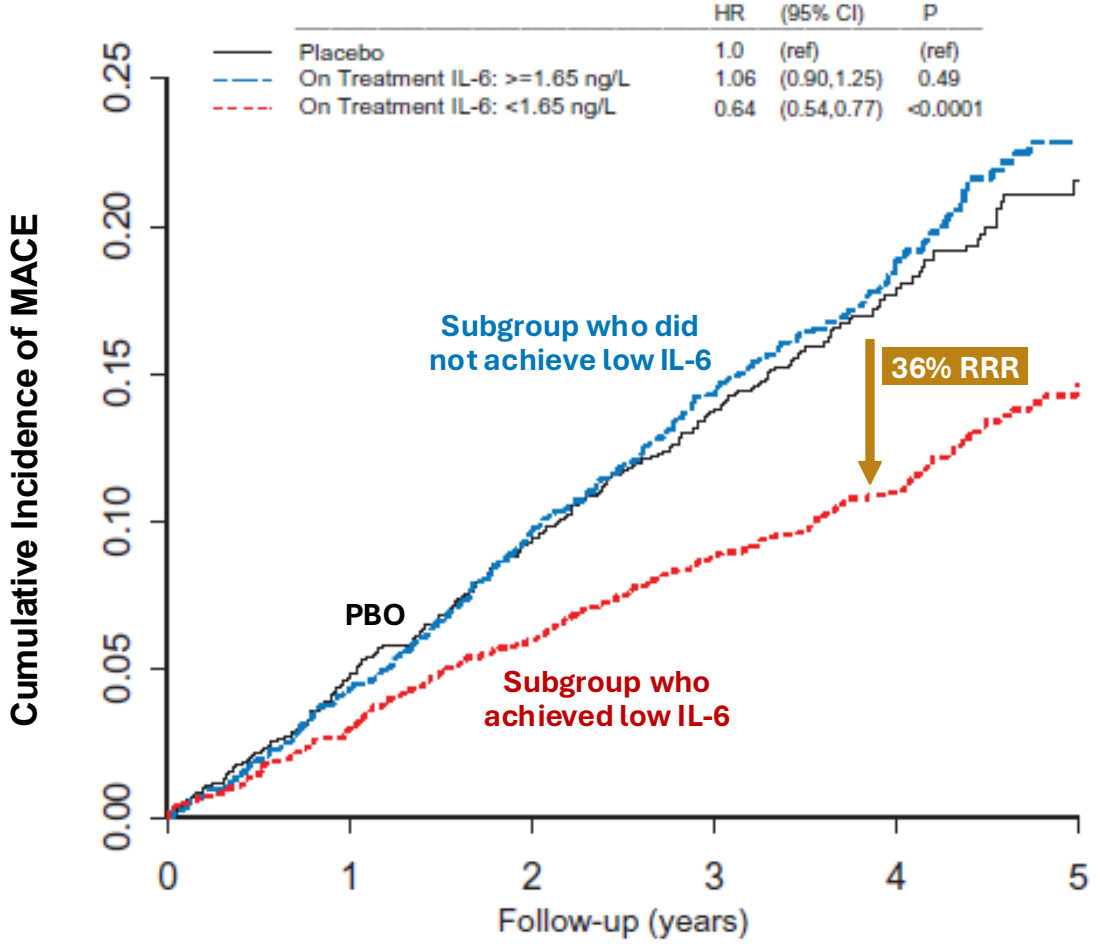
Adapted from: . Arnold, et al. *Eur J Cardiol*. 2021 and Muller, et al. *J Lipid Res*. 2015.

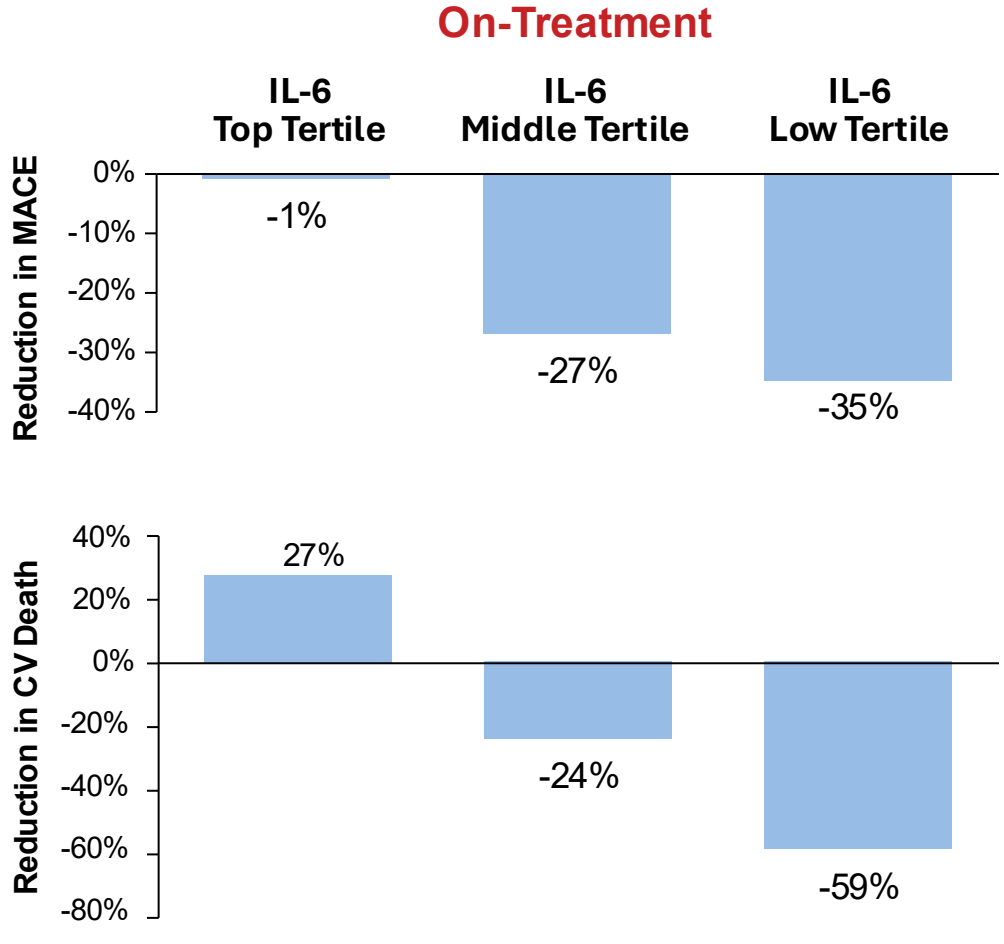
Higher Levels of IL-6, like hs-CRP, Strongly and Independently Predicted MACE in Large Prospective Studies



1. Ridker, et al. *Eur Heart J*. 2022, CANTOS; 2. Ridker. et al. *Eur Heart J*. 2020, CIRT; Myocardial infarction or multivessel coronary disease who additionally had diabetes or metabolic syndrome. Adjusted for age, gender, smoking status, body mass index, and blood pressure and stratified on diabetes and or metabolic syndrome.

Pre-specified Analysis Showed that Reductions in IL-6 Predicted CV benefit[1-3]



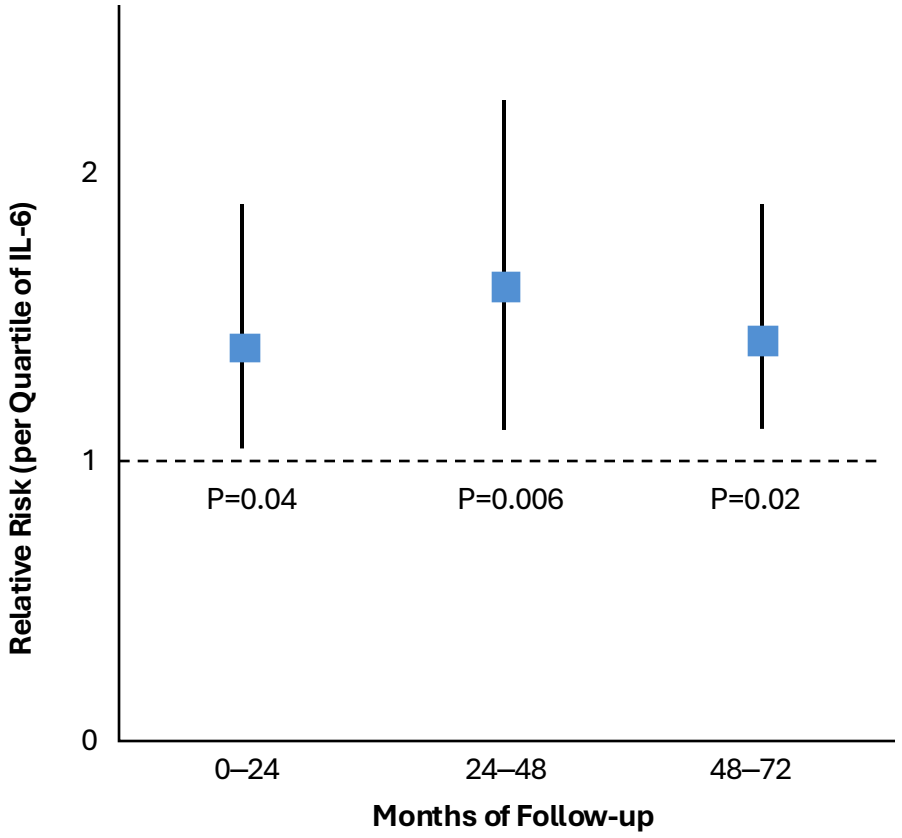


Reduction in MACE shown as 1-Hazard Ratio vs placebo. Covariates included in the adjusted multivariable model include age, gender, smoking status, hypertension, diabetes, body mass index, baseline level of IL-6, and baseline level of LDL cholesterol.

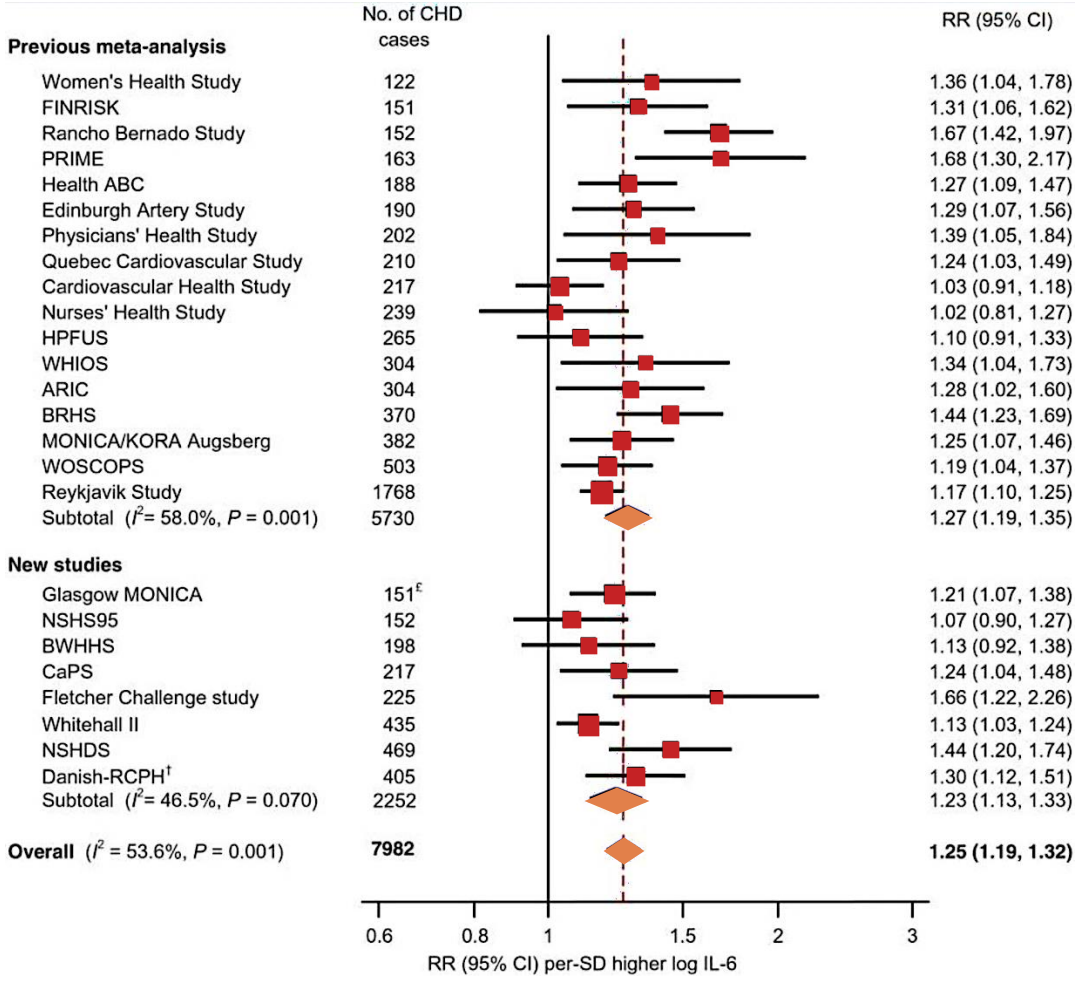
1. Ridker, et al. *Eur Heart J*. 2018; 2. Ridker, et al. *Circulation*. 2021; 3. Libby, et al. *Eur Heart J*. 2018.

Landmark Epidemiological Studies of IL-6 Levels and Cardiovascular Outcomes

RIDKER, et al. 2000[1]



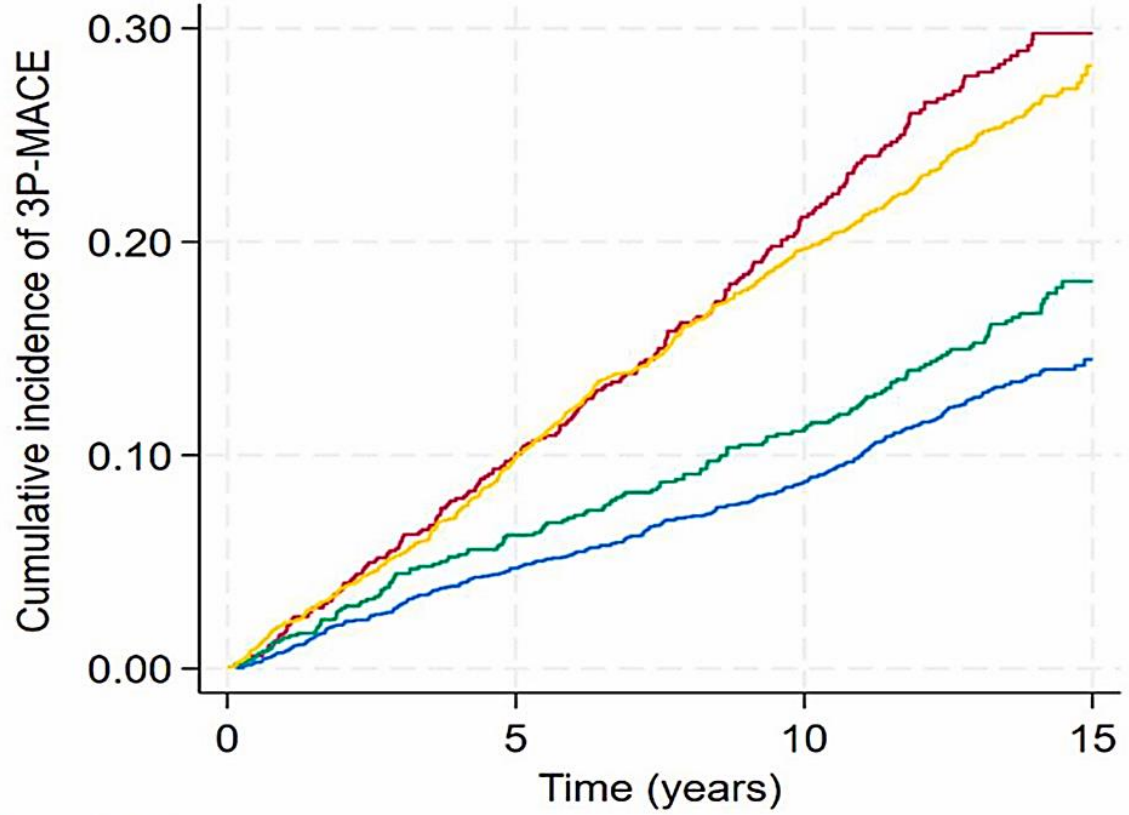
KAPTOGE, et al. 2014[2]



1. Ridker, P et al. *N Engl J Med* 2000;342:836-843; 2. S. Kaptoge, et al. *Eur Heart J*. 2014 Mar;35(9):578-89.

hs-CRP vs IL-6

Multi-Ethnic Study of Atherosclerosis (MESA): IL-6 or hs-CRP?



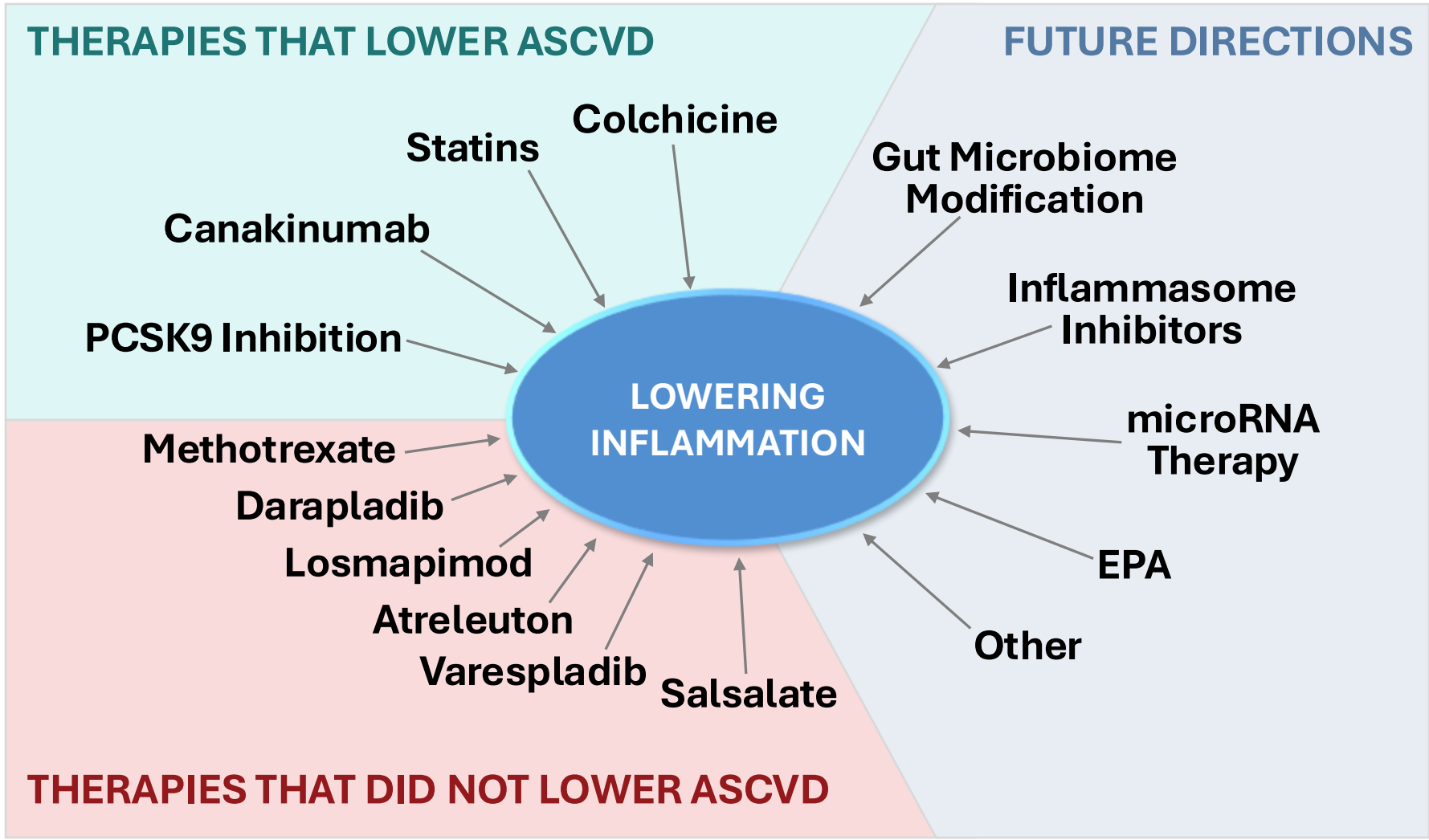
Number at risk				
Low IL6-Low hsCRP	2328	2104	1885	223
High IL6-Low hsCRP	1002	834	651	55
Low IL6-High hsCRP	975	867	760	101
High IL6-High hsCRP	2288	1880	1511	180

Patients with high IL6 (above median) experience higher risk of CV events, irrespective of hs-CRP levels.

Ferreira JP, et al. *Atherosclerosis*. 2024 Mar;390:117461.

Future Direction

Future Directions for Managing Inflammation



Alfaddagh A, et al. *American Journal of Preventive Cardiology*. 2020;4:100130.

Key Takeaways

Key Takeaways (1 of 2)

- Despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapy, people with ASCVD still face a 30% risk of a major adverse cardiovascular event over 10 years.
- Multiple contributors have been implicated, including elevated Lp(a), hypertriglyceridemia, excess thrombotic risk, and systemic inflammation.
- Atherosclerosis is known to be a chronic inflammatory process in which IL-6, CRP, myeloperoxidase (MPO), and matrix metalloproteinase 9 (MMP-9) are used as biomarkers responsible for “residual inflammatory risk”.
- Based on data of over 31,000 statin treated patients, residual inflammatory risk is a more powerful predictor of CV death than LDL cholesterol.

Key Takeaways (2 of 2)

- Elevated CRP levels are directly proportional to CVD risk and are an independent risk factor for cardiac death. In primary prevention, hsCRP predicts risk independent of other risk factors. In secondary prevention, hsCRP predicts recurrences despite the use of aggressive lipid-lowering drugs.
- Higher levels of IL-6, like hs-CRP, strongly and independently predicted MACE in large prospective studies.
- High IL-6 levels were associated with increased risk of MACE regardless of hs-CRP levels, but high hs-CRP levels were associated with higher risk only in conjunction with high IL-6 levels.
- Cardiovascular inflammation is largely unaddressed by existing treatments but future treatments have shown promise, including IL-6 pathway inhibition which could have transformative potential in ASCVD.