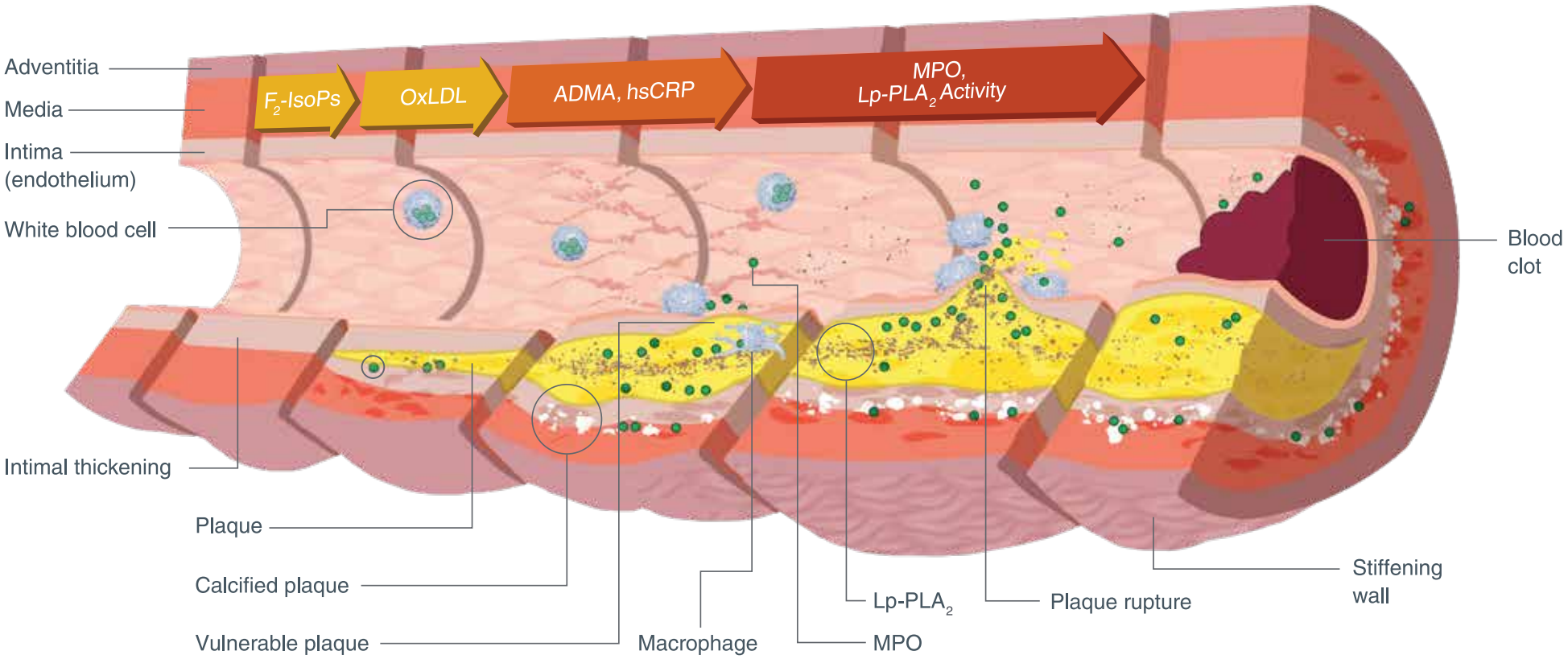
Inflammatory biomarkers and their association with atherosclerosis

Progression of atherosclerosis is associated with specific inflammatory biomarkers that can be assessed to improve cardiometabolic risk stratification.



Approximately 50% of patients hospitalized with CAD have normal LDL cholesterol levels.[1]

Improve risk stratification using a multimarker assessment of lipids, inflammation, and metabolic dysfunction

The risk of developing cardiovascular disease has traditionally been assessed by measuring LDL cholesterol and HDL cholesterol.

Although it is essential to assess cholesterol levels, adverse events (such as a heart attack, stroke, or death) have been associated with inflammation,[2] specifically vulnerable plaque related to increased white blood cell activation. Both the CANTOS trial in 2017 (canakinumab)[3] and the COLCOT trial in 2019 (colchicine)[4] demonstrate reduced CV event rates with inflammation inhibition, characterizing inflammation as a critical component of atherosclerotic disease and cardiovascular risk, independent of lipids.

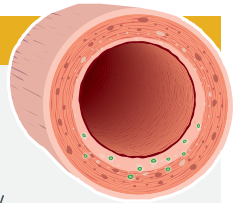
Metabolic dysfunction is a root cause of many chronic conditions, including CVD. A multimarker assessment that acknowledges the interaction of dyslipidemia, inflammation, and metabolic dysfunction is important for CV risk stratification.

The impact of inflammation on the progression of cardiovascular disease

In 1976, renowned vascular biologist Dr Russell Ross proposed the "response to injury" hypothesis, providing insight into the initiation and subsequent progression of cardiovascular disease.[2] Risk factors such as smoking, hypertension, and diabetes can damage the vessel wall, making it more susceptible to penetration and accumulation of atherogenic cholesterol. The body responds to the injury with an inflammatory response designed to remove cholesterol from the artery wall. This process becomes dysregulated and ultimately potentiates the progression of cholesterol deposition and vulnerable plaque formation, placing an individual at increased risk of plaque rupture and subsequent heart attack or stroke.

The following inflammatory biomarkers may help identify atherosclerotic risk, presence, or disease activity

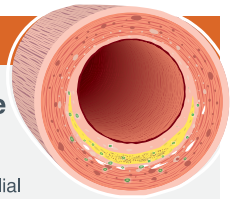
Risk for disease



F_2-isoprostanes (F_2-IsoPs) are prostaglandin-like compounds used for measuring oxidative stress.[5] An elevated level may be the result of reduced physical activity, smoking, or obesity and may indicate risk for atherosclerosis[5] and cancer.[6]

Oxidized LDL (OxLDL) is formed when the apolipoprotein B subunit on LDL particles becomes oxidized. Elevated levels may be the result of poor lifestyle choices and identify risk of metabolic syndrome.[7]

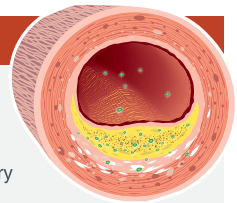
Presence of disease



Asymmetric dimethylarginine (ADMA) is a metabolite of L-arginine and can inhibit nitric oxide production. Elevated levels of ADMA are associated with endothelial dysfunction, insulin resistance, hypertension, and subclinical atherosclerosis.[8]

High-sensitivity C-reactive protein (hsCRP) is an acute-phase protein released into the blood by the liver during inflammation. Elevated levels are associated with the risk of adverse cardiovascular events in apparently healthy individuals[10] and individuals with stable coronary artery disease.[11]

Disease activity



Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity is a vascular-specific inflammatory enzyme that increases with the activation of macrophages in atherosclerotic lesions of the artery wall under the collagen cap. Increased Lp-PLA_2 activity is associated with risk of coronary heart disease or an acute coronary event.[12]

Myeloperoxidase (MPO) is a vascular-specific inflammatory enzyme released by white blood cells into the bloodstream in response to vulnerable plaque, erosion, or fissures in the artery wall. Elevated MPO levels are associated with risk of cardiac events in subgroups otherwise characterized as low risk and may improve cardiovascular risk stratification when used independently or alongside standard biomarker testing, such as hsCRP.[13]

Inflammatory biomarker test codes

Sonora Quest Test Codes	Biomarker
906899	F_2-Isoprostane/Creatinine
906898	Oxidized LDL (OXLDL)
906949	hs-CRP
906897	ADMA and SDMA
906961	Lp-PLA_2 Activity
906896	Myeloperoxidase (MPO)

References

1.Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. *Am Heart J.* 2009;157(1):111-117.e2. doi:10.1016/j.ahj.2008.08.010 2. Ross R, Glomset JA. The pathogenesis of atherosclerosis (first of two parts). *N Engl J Med.* 1976;295(7):369-377. doi:10.1056/NEJM197608122950707 3. Ridker PM, Macfadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018;391(10118):319-328. doi:10.1016/S0140-6736(17):32814-3 4. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med.* 2019;381(26):2497-2505. doi:10.1056/NEJMoa1912388 5. Morrow JD. Quantification of isoprostanes as indices of oxidant stress and the risk of atherosclerosis in humans. *Arterioscler Thromb Vasc Biol.* 2005;25(2):279-286. doi:10.1161/01.ATV.0000152605.64964.c0 6. Epplein M, Franke AA, Cooney RV, et al. Association of plasma micronutrient levels and urinary isoprostane with risk of lung cancer: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(7):1962-1970. doi:10.1158/1055-9965.EPI-09-0003 7. Holvoet P, Lee DH, Steffes M, Gross M, Jacobs DR Jr. Association between circulating oxidized low-density lipoprotein and incidence of the metabolic syndrome. *JAMA.* 2008;299(19):2287-2293. doi:10.1001/jama.299.19.2287 8. Dowsett L, Higgins E, Alanazi S, et al. ADMA: a key player in the relationship between vascular dysfunction and inflammation in atherosclerosis. *J Clin Med.* 2020;9(9):3026. doi:10.3390/jcm9093026 9. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001;286(4):421-426. doi:10.1001/jama.286.4.421 10. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336(14):973-979. doi:10.1056/NEJM199704033361401. Erratum in: *N Engl J Med* 1997;337(5):356. 11. Ndrepepa G, Kastrati A, Braun S, et al. N-terminal probrain natriuretic peptide and C-reactive protein in stable coronary heart disease. *Am J Med.* 2006;119(4):355.e1-8. doi:10.1016/j.amjmed.2005.10.060 12. Toth PP, McCullough PA, Wegner MS, Colley KJ. Lipoprotein-associated phospholipase A2: role in atherosclerosis and utility as a cardiovascular biomarker. *Expert Rev Cardiovasc Ther.* 2010;8(3):425-438. doi:10.1586/erc.10.18 13. Ndrepepa G. Myeloperoxi¬dase—a bridge linking inflammation and oxidative stress with cardiovascular disease. *Clin Chim Acta.* 2019;493:36-51. doi:10.1016/j.cca.2019.02.022

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