Inflammatory markers in cardiovascular health: a quick overview

It has been more than 40 years since Dr. Russell Ross and Dr. John Glomset published their groundbreaking "response-to-injury" hypothesis, bringing to light the role of inflammation in atherosclerosis and cardiovascular disease (CVD).[1] Their work revealed that atherosclerosis is initiated through injury and propagated through inflammation. **Several studies have since supported the hypothesis that inflammation is a driver of atherosclerosis.**[2]

1 out of every 3 deaths is caused by coronary heart disease. It is the leading cause of death in the U.S.[3]

Despite these findings, the medical community has generally continued to rely on lipid testing to monitor elevated levels of low-density lipoprotein cholesterol (LDL-C).[2] **Yet, roughly 50% of heart attacks and strokes occur in patients with "normal" cholesterol levels.**[4,5] Injury, or the infiltration of LDL particles into the arterial wall, is only part of the CVD story—and as the statistic to the right indicates, assessing only lipids may fail to fully identify a patient's risk for adverse cardiac events.

>800,000
deaths caused by coronary heart disease[3]

In addition to lipids, measuring inflammatory biomarkers in patients being treated for elevated LDL-C levels is essential. Doing so can help physicians see the complete picture—uncovering a patient's hidden risk for cardiac events and enabling them to take the right actions to address both injury *and* inflammation for better outcomes.

This paper reviews:

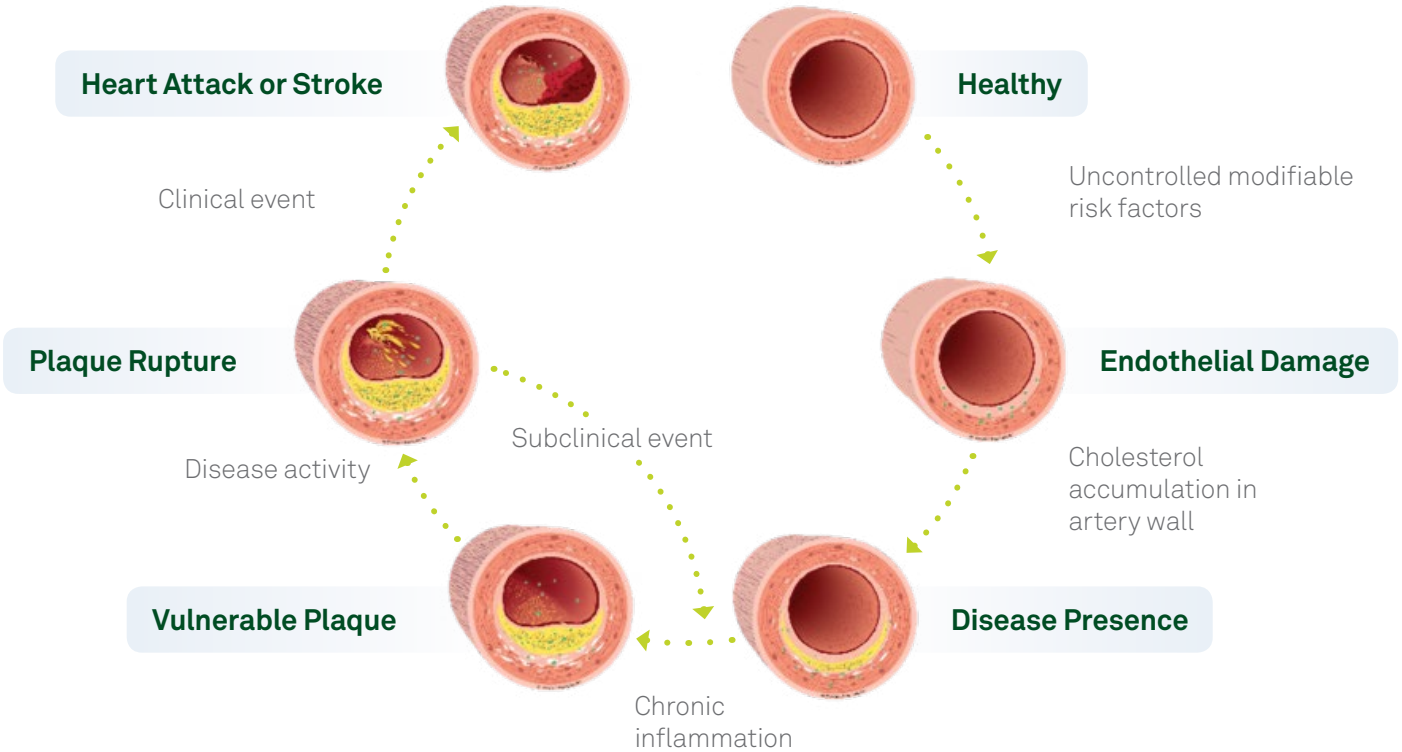
- **The role of inflammation in CVD**
- **The markers that help accurately assess injury response, or inflammation**—and which markers indicate risk for disease, disease presence, and disease activity
- **What can be done to address inflammation in at-risk patients**

The role of inflammation in CVD

Recognized as a chronic inflammatory disease, atherosclerosis begins with risk factors. Its progression includes a "crucial interplay among lipid accumulation, lipid oxidation, and inflammation."[6]

1. **It starts with risk factors**—like smoking, obesity, and diabetes. These risk factors can damage the endothelial wall, making it more susceptible to further damage.
2. **Dyslipidemia plays a role as well.** When a patient has dyslipidemia, or abnormal blood lipids, the excess cholesterol in circulation enters and deposits in arterial walls, and cholesterol accumulates.
3. **Inflammatory lipids are released**, stimulated by a series of modifications of the LDL particles, initiating the inflammatory response and further amplifying it.
4. **Plaque continues to grow and a fibrous cap forms over it**. Collagen provides stability to the fibrous cap.
5. **Collagen is compromised.** An amplified inflammatory response compromises the collagen, destabilizing the plaque and making it more prone to rupture.
6. **Plaque's lipid core is released upon rupture, leading to blockage of the artery** and subsequent lack of blood flow to the heart muscles.
7. **A heart attack results.**

CVD progression



Inflammatory markers and what they tell you

The JUPITER Trial, published in 2008, was the first landmark trial to provide evidence that elevated inflammation can indicate risk for adverse cardiovascular events, no matter what a patient's cholesterol levels.[4] Prior to the results of this publication, most research focused solely on monitoring LDL-C to determine cardiovascular risk.[7]

Understanding a patient's levels of various inflammatory markers can help physicians better identify risk and take action to reduce inflammation.

The following inflammatory markers have been identified as relevant risk markers for CVD.

Patients with high levels of:

- F_2-IsoPs are 2.6x more likely to develop coronary artery disease[8]
- Oxidized LaDL are 3.5x more likely to develop metabolic syndrome[9]
- MPO are >2x more likely to experience cardiovascular mortality[10]

Low risk: risk of disease

F_2-Isoprostanes (F_2-IsoPs)—prostaglandin-like compounds formed from free radical-mediated oxidation of arachidonic acid. F_2-IsoPs measure oxidative stress induced by lifestyle risk factors for CVD, including smoking, poor diet, high red meat intake, and a sedentary lifestyle. F_2-IsoPs contribute to CVD progression through increased vasoconstriction via thromboxane production, platelet aggregation, and thrombus formation. Elevated levels of F_2-IsoPs indicate an increased risk for coronary artery disease (CAD) and CVD mortality.[11,12]

Oxidized LDL (OxLDL)—measures damage of the ApoB protein subunit on the surface of LDL due to oxidative modification. Oxidation of ApoB is an initiating factor in macrophage recruitment, foam cell formation, and vascular inflammation within the arterial wall. Elevated OxLDL levels indicate an increased risk of having a coronary heart disease (CHD) event and developing metabolic syndrome.[9]

Moderate risk: presence of disease

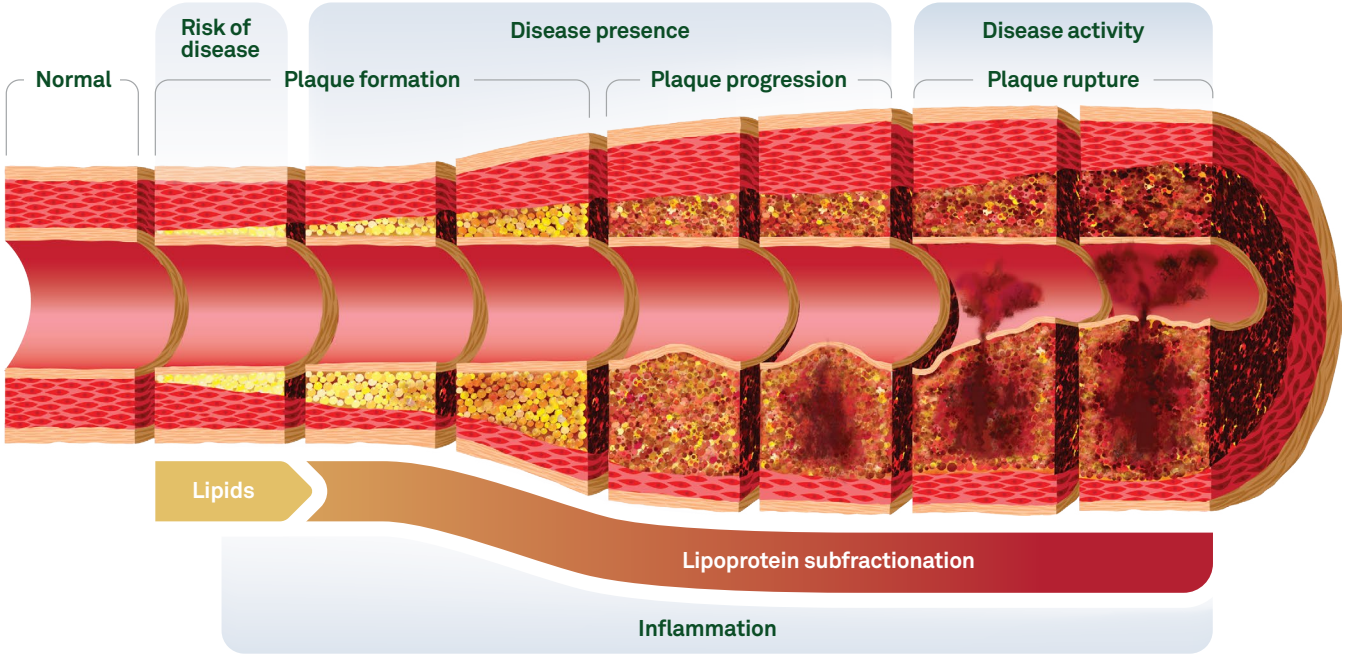
Asymmetric dimethylarginine (ADMA)/ symmetric dimethylarginine (SDMA)—derivatives of the amino acid L-arginine, produced via protein degradation. ADMA is a competitive inhibitor of nitric oxide synthase and can reduce the production of nitric oxide. Nitric oxide deficiency is an early manifestation of endothelial dysfunction and atherosclerotic disease. Elevated ADMA indicates an increased risk of CVD, CHD, and stroke. SDMA is primarily excreted in the urine and strongly correlates with reduced renal function.[13]

High-sensitivity C-reactive protein (hsCRP)—an acute-phase reactant protein that increases in response to inflammation. In large epidemiologic studies, elevated levels of CRP have been shown to be a strong indicator of CVD. It's also been demonstrated that lowering hsCRP, independent of lipid levels, results in a risk reduction of recurrent cardiovascular events.[14-16]

High risk: disease activity

Myeloperoxidase (MPO)—an inflammatory enzyme released within the vascular lumen during white blood cell activation in response to fissures, erosions, or degradation of the fibrous cap. MPO is a specific marker of vascular inflammation and is a measure of vulnerable plaque. Elevated levels of MPO independently predict an increased risk of future cardiovascular events (myocardial infarction, coronary revascularization, or CVD-related death).[17-20]

Lp-PLA_2 (lipoprotein-associated phospholipase A_2) Activity—an enzyme produced by macrophages and foam cells within the necrotic core of arterial plaque. Lp-PLA_2 Activity measures the disease activity within the arterial wall under the calcified cap of the plaque. Elevated Lp-PLA_2 Activity has been associated with an increased risk for developing CHD independent of non-HDL cholesterol levels. Elevated Lp-PLA_2 Activity levels also indicate an increased risk of having a CHD event (myocardial infarction, coronary revascularization, or CHD-related death).[21]



Taking action against the risk for CVD—by addressing inflammation

Measuring inflammatory biomarkers in addition to lipid levels can point to a range of treatments, depending on the inflammation panel results.

A test result showing elevated F_2-IsoPs and OxLDL levels, for example, could better motivate a patient to change his behavior and make healthier choices (e.g., quit smoking, start exercising, change his diet), increasing patient engagement.

Other inflammatory markers may indicate more effective prescription or nonprescription drugs or supplements. Studies have demonstrated, for instance, that statin therapy is associated with a reduction in hsCRP,[2] and elevated ADMA/SDMA levels may be helped by antihypertensive therapy, if blood pressure is a concern. Lp-PLA_2 and MPO testing can help identify patients who are at greater risk for an adverse event, prompting more urgent action. This range of inflammatory marker testing enables physicians to assess risk more completely, identify those patients most at risk for an adverse event, and determine a treatment plan that's more individualized to each patient.

More accurately assessing patient risk for CVD can also help practices improve their scores as part of the Merit-based Incentive Payment System under MACRA (the Medicare Access and CHIP Reauthorization Act), in both the Quality and Clinical Practice Improvement Categories (e.g., screening for tobacco use and providing cessation intervention; prescribing statin therapy to prevent and treat CVD; collecting and following up on patient experience and satisfaction data; etc.).

Ultimately, examining inflammatory markers and taking the necessary and appropriate steps to identify root causes and make corrections can help improve health and practice outcomes.

A lab that's committed to helping physicians uncover risk

With the acquisition of Cleveland HeartLab, Quest Diagnostics is furthering its commitment to helping physicians deliver the best care to patients at risk for CVD. Quest offers an enhanced menu of advanced cardiovascular tests, including a full complement of inflammatory markers, to help physicians improve patient outcomes.

Interested in learning more? Visit **QuestDiagnostics.com/Inflammation**.

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