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The role of lipoprotein-associated phospholipase A2 on cardiovascular disease risk assessment and plaque rupture: a clinical review

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Abstract: During the last several last decades, reduction in lipids has been the main focus to decrease the risk of coronary heart disease (CHD). Several lines of evidence, however, have indicated that lipids account only for the <50% of variability in cardiovascular risk in the United States. Therefore, for better identification of people at high cardiovascular risk, a more effective and complete approach is required. Our understanding of atherosclerosis has shifted from a focal disease resulting in symptoms caused by severe stenosis to a systemic disease distinguished by plaque inflammation with a potential to rupture and thrombosis, turning a substenotic atherosclerotic lesion into a complete occlusive lesion. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a novel inflammatory biomarker that can provide much needed information about plaque inflammation and plaque stability. Lp-PLA_2 is among the multiple biomarkers that have been associated with increased CHD risk. In this present work, we review the evidence from previous studies addressing the effect of different therapies on decreasing Lp-PLA_2 and the role of direct Lp-PLA_2 inhibitors. This work also briefly reviews the evidence of Lp-PLA_2 clinical utility as a potential marker of vascular inflammation and formation of rupture prone plaques. Additionally, we also discuss the implication of available evidence in context of current cardiovascular inflammatory biomarkers recommendations and the evidence from epidemiologic studies addressing the relationship of Lp-PLA_2 and risk of cardiovascular disease.

During the past several decades, substantial efforts have been directed toward reducing average blood lipids, specifically, the low-density lipoprotein (LDL) cholesterol levels of the American population. Although the level of success in the fight against the cardiovascular disease is appreciable, it has not been able to stem the tide of heart disease completely. Our present understanding of cardiovascular risk assessment is not enough and is just an oversimplification of the complex issue of cardiovascular disease. With the advent of new technology and better understanding of plaque structure and pathophysiology, many new biomarkers that play an essential role in assessing cardiovascular risk have been recognized. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is one such inflammatory biomarker that may possibly help health care workers recognize rupture-prone plaque and the degree of inflammation present in the walls of coronary arteries.

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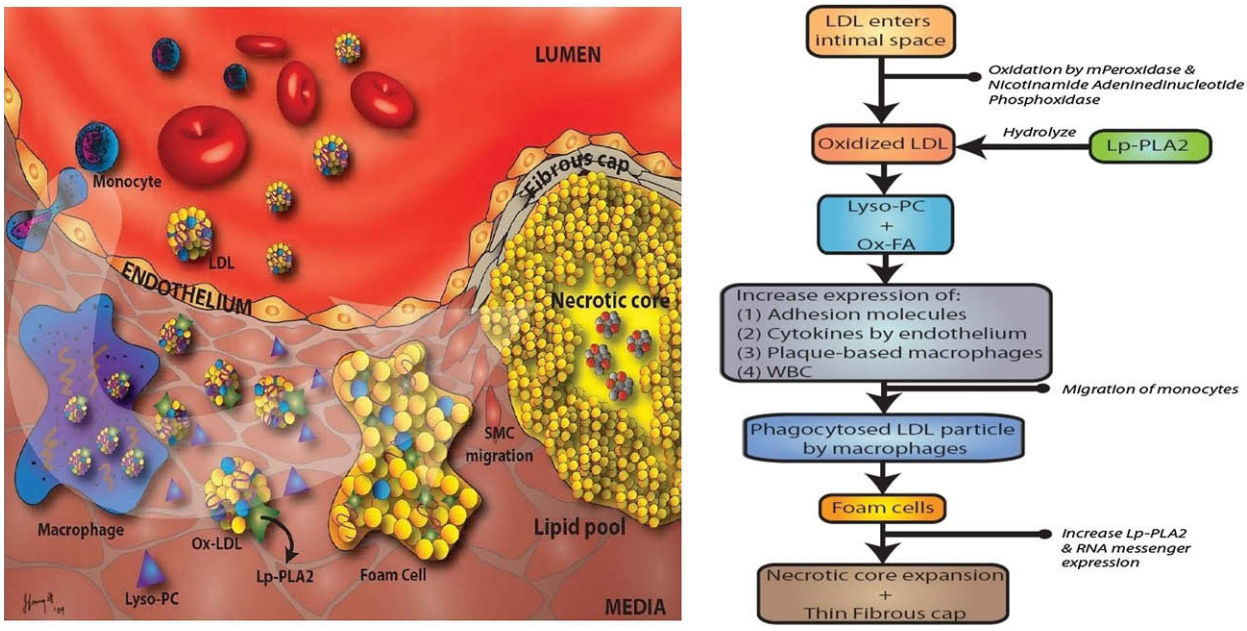

Figure 1 Schematic presentation of the lipoprotein-associated phospholipase A_2 (Lp-PLA_2) role in vascular inflammation.

The purpose of this work is to review the evidence from previous studies addressing the effect of different therapies on decreasing Lp-PLA_2 and the role of a direct Lp-PLA_2 inhibitor, as well as a brief review of the evidence of Lp-PLA_2 clinical utility as a potential marker of vascular inflammation and of formation of rupture-prone plaques. Additionally, we also discuss the implication of available evidence in the context of current cardiovascular inflammatory biomarker recommendations and the evidence from epidemiologic studies addressing the relationship of Lp-PLA_2 and the risk of cardiovascular disease.

Biomarker concept, definition and current available biomarkers

A biomarker is an indicator of a particular disease state or a particular state of organism. A National Institutes of Health working group defined biomarkers as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1] Ideally, an effective biomarker would be an indicator of disease etiology, independently predict the risk of developing disease, have prognostic value, be easily measured, and be a cost-effective therapeutic intervention target. Much effort, time, and available resources have been invested in this area of research in finding an ideal biomarker. As a result, numbers of emerging biomarkers have shown potential benefits.

High-sensitive C-reactive protein (hs-CRP) is by far the best tested proposed cardiovascular disease inflammatory biomarker. Numerous available prospective data suggests a twofold increase of events in individuals with high hs-CRP levels. However, this effect was attenuated with adjustment of classical risk factors. hs-CRP levels are confounded by other systemic inflammatory diseases and risk factors, eg, smoking, body mass index, overt hyperlipidemia, insulin resistance, obesity, and high blood pressure. Aside from clinical utility debate, the causal role of CRP in cardiovascular disease still remains uncertain. Mendelian randomization trials have failed to provide firm evidence that CRP is a causal factor in cardiovascular disease.[2,3] Recently, the Justification for the use of statin in prevention: An intervention trial Evaluating Rosuvastatin (JUPITER)[4] trial studied 17,802 apparently healthy men and women with LDL cholesterol levels of <130 mg/dL (3.4 mmol/L) and hs-CRP levels of 2.0 mg/L or higher who received rosuvastatin 20 mg/day or placebo. They were followed for the occurrence of the combined primary end points of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Rosuvastatin decreased the relative risk of the primary end point by 44% (hazard ratio [HR] for rosuvastatin compared with placebo, 0.56; 95% confidence interval [CI], 0.46–0.69). Those with a family history of premature coronary heart disease (CHD) had an even greater relative risk reduction in the primary end point of about 65%. The study observed similar reduction in the events rates in participants who had elevated hs-CRP, irrespective of their lower or higher risk. JUPITER did not include a control group with low levels hs-CRP. Moreover, it is now apparent that statins reduce cardiovascular risk even in those who do not have high blood cholesterol, and that reduction in LDL explains almost entirely the statin-induced reductions in events, and, interestingly, also reduction in CRP.[5] Its highly likely that the reduction achieved in JUPITER is one of the pleotropic effect of statins on hs-CRP,[6] and