Role of Lipoprotein-Associated Phospholipase A\textsubscript{2} in Atherosclerosis
Biology, Epidemiology, and Possible Therapeutic Target

Andrew Zalewski, Colin Macphee

Abstract—The development of atherosclerotic vascular disease is invariably linked to the formation of bioactive lipid mediators and accompanying vascular inflammation. Lipoprotein-associated phospholipase A\textsubscript{2} (Lp-PLA\textsubscript{2}) is an enzyme that is produced by inflammatory cells, co-travels with circulating low-density lipoprotein (LDL), and hydrolyzes oxidized phospholipids in LDL. Its biological role has been controversial with initial reports purporting atheroprotective effects of Lp-PLA\textsubscript{2} thought to be a consequence of degrading platelet-activating factor and removing polar phospholipids in modified LDL. Recent studies, however, focused on pro-inflammatory role of Lp-PLA\textsubscript{2} mediated by products of the Lp-PLA\textsubscript{2} reaction (lysophosphatidylcholine and oxidized nonesterified fatty acids). These bioactive lipid mediators, which are generated in lesion-prone vasculature and to a lesser extent in the circulation (e.g., in electronegative LDL), are known to elicit several inflammatory responses. The proinflammatory action of Lp-PLA\textsubscript{2} is also supported by a number of epidemiology studies suggesting that the circulating level of the enzyme is an independent predictor of cardiovascular events, despite some attenuation of the effect by inclusion of LDL, the primary carrier of Lp-PLA\textsubscript{2}, in the analysis. These observations provide a rationale to explore whether inhibiting Lp-PLA\textsubscript{2} activity and consequent interference with the formation of bioactive lipid mediators will abrogate inflammation associated with atherosclerosis, produce favorable changes in intermediate cardiovascular end points (e.g., biomarkers, imaging, and endothelial function), and ultimately reduce cardiovascular events in high-risk patients. (Arterioscler Thromb Vasc Biol. 2005;25:923-931.)

Key Words: atherosclerosis ■ inflammation ■ lipoprotein-associated phospholipase A\textsubscript{2}

Despite considerable progress in treating atherosclerotic vascular disease, patients at high risk continue to experience fatal and nonfatal cardiovascular events. Two complementary approaches to this problem have emerged. The first strategy focuses on aggressive control of modifiable risk factors (diabetes, hypertension, dyslipidemia, smoking). Efforts in this direction are justifiable because of the presence of at least 1 conventional risk factor in >80% patients presenting with acute myocardial infarction and the high societal cost of ineffective prevention.\textsuperscript{1–3} Clinical experience suggests no threshold values for implementing corrective therapies in regard to some risk factors in individuals at high risk.\textsuperscript{4,5} The second strategy seeks to identify novel treatments that target previously unrecognized mechanisms of atherosclerosis. Despite a wide range of clinical and pathological manifestations of atherosclerotic vascular disease, inflammation is common to all stages of the disease. Studies have linked circulating inflammatory biomarkers with cardiovascular risk, whereas mechanistic investigations have established a pivotal role of blood-borne inflammatory cells and their products in the...
initiation, progression, and destabilization of atheroma. This evidence notwithstanding, no current cardiovascular therapy is primarily used to mitigate low-grade inflammation commonly observed in individuals at risk for future events. Statins lower circulating inflammatory biomarkers, although the clinical relevance of so-called pleiotropic effects extending beyond concomitant low-density lipoprotein (LDL)-lowering remains unclear. In this context, the need to identify complementary approaches for patients at high risk is predicated by the continued accrual of clinical events despite contemporary therapies, including aggressive treatment with statins (Figure 1).9

“Atherosclerosis-Specific” Inflammatory Pathways

From the therapeutic standpoint, the challenge has been to identify an inflammatory pathway that is “atherosclerosis-specific,” whereby therapeutic intervention would result in vascular benefit without affecting the patient’s ability to mount host defense (eg, during infection). In this context, the hydrolysis of oxidized phospholipids in LDL that is mediated by lipoprotein-associated phospholipase A2 (Lp-PLA2) may represent an appropriate pathway for testing the inflammation hypothesis. LDL oxidation results in a range of modifications affecting phospholipid and apolipoprotein B (apoB) components that render this molecule distinct from its native form. These reactions include formation of lipid hydroperoxides and aldehydes (eg, malondialdehyde, 4-hydroxynonenal) that react with lysine residues of apoB, altering the physicochemical properties of LDL. Elevated levels of circulating oxidized LDL are associated with morphological evidence of plaque vulnerability, endothelial dysfunction, and are higher in patients presenting with acute coronary syndromes. Several pro-inflammatory phospholipids that display wide differences in the structure of the modified polyunsaturated fatty acids at the sn-2 position, increase in minimally oxidized LDL analyzed in vitro, stimulate leukocyte–endothelial cell interactions, and accumulate in aortas of cholesterol-fed rabbits. Until recently, oxidative modification of LDL was assumed to yield a final product responsible for several reactions involved in atherogenesis. However, oxidative modification of polyunsaturated fatty acids in the sn-2 position of phospholipids within LDL molecules renders them susceptible to hydrolysis by Lp-PLA2, yielding 2 additional products: lysophosphatidylcholine (lysoPC) and oxidized non-esterified fatty acids (NEFA) (Figure 2). The process of oxidative modification also yields other biologically active phospholipids, including 1-palmitoyl-2-(5,6-epoxyisoprostane E2)-sn-glycero-3-phosphorylcholine, that lack oxidative truncation of the polyunsaturated fatty acids at the sn-2 position. Individual phospholipids differ in their pro-inflammatory effects in vitro. The accumulation of several oxidized phospholipids and lysoPC has been reported in experimental models of atherosclerosis, further raising the prospect of their involvement in pro-inflammatory processes in vivo. Research in this field has been confounded by the complexity of phospholipid biochem-

Figure 1. Kaplan–Meier estimates of the incidence of primary end point (all-cause mortality or a major cardiovascular event) in PROVE IT-TIMI 22 trial. Patients presenting with acute coronary syndrome experience a high rate of events despite aggressive management, including coronary revascularization (~70%), lipid-lowering therapy (100%), antiplatelet drugs (~90%), β-blockers (85%), and other guideline-mandated treatments. Even those allocated to treatment with a high dose of atorvastatin continued to experience a 22% event rate at 24 months after the index event (adapted with permission from Cannon et al. N Engl J Med. 2004).3

Figure 2. Schematic representation of the proposed pro-atherogenic mechanism of Lp-PLA2 in the vessel wall. Lp-PLA2 binds to apoB on LDL, its primary carrier, which delivers Lp-PLA2 to lesion-prone segments of the arterial wall. Subsequent LDL oxidation leads to formation of truncated phospholipid in the sn-2 position, which is susceptible to enzymatic hydrolysis by Lp-PLA2. This results in generation of 2 bioactive lipid mediators, lysophosphatidylcholine (lysoPC) and oxidized non-esterified fatty acids (NEFA), that are proposed to play an important role in homing of inflammatory cells into lesion-prone areas and local increases in inflammatory mediators. The influx of inflammatory cells that express Lp-PLA2 increases its concentration in the vessel wall. Bioactive lipid mediators generated by Lp-PLA2 are also cytotoxic to macrophages, which may facilitate the formation of a necrotic lipid core in advanced atherosclerotic lesions.
TABLE 1. Biological Effects of Putative Inflammatory and Proatherogenic Products Derived From Enzymatic Hydrolysis of LDL-Associated Oxidized Phospholipids34–53

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Cellular Target</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LysoPC</td>
<td>Endothelial cells</td>
<td>Homing of inflammatory cells: upregulation of adhesive molecules (VCAM-1/ICAM-1) and MCP-141,42 Functional responses: impaired proliferation/migration and reduced NO-dependent vasodilation47–50 Cytotoxicity: apoptosis51</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Homing of inflammatory cells: upregulation of MCP-142 Oxidative stress: NADPH oxidase activation and ROS-dependent ERK1/2 phosphorylation43 Functional responses: increased growth factor gene expression, proliferation, and migration44,45 LDL retention: upregulation of biglycan core protein and elongation of GAG chains46 Cytotoxicity: apoptosis47</td>
<td></td>
</tr>
<tr>
<td>Monocytes/macrophages</td>
<td>Formation of inflammatory mediators: upregulation of cytokines (IL-1β), Ca2+⋅dependent PLA2 enzymes, and arachidonic acid release44,46 Functional responses: increased chemotaxis48,49 Cytotoxicity: increased cellular permeability and apoptosis50</td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>Functional responses: increased chemotaxis51 Immune response: interferon-γ upregulation52,53</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Oxidative stress: NADPH oxidase activation and myeloperoxidase release51 Functional responses: increased chemotaxis, elastase release51</td>
<td></td>
</tr>
<tr>
<td>oxNEFA Monocytes/macrophages</td>
<td>Cytotoxicity: increased cellular permeability and apoptosis52</td>
<td></td>
</tr>
</tbody>
</table>

GAG indicates glycosaminoglycan; ICAM-1, intercellular adhesive molecule-1; IL-1β, interleukin-1β; LysoPC, lysophosphatidylcholine; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; oxNEFA, oxidized nonesterified fatty acids; PLA2, phospholipase A2; ROS, reactive oxygen species; VCAM-1, vascular cell adhesive molecule-1.

istry, the paucity of animal models of human atherosclerotic vascular disease that would display rupture-prone plaques, and the difficulty in establishing a causal link between specific lipid mediators within the vessel wall and clinical events.

Lp-PLA2: Functional Characteristics

Lp-PLA2 belongs to the expanding superfamily of structurally diverse phospholipase A2 enzymes described elsewhere in detail.21 First cloned in 1995, Lp-PLA2 is a 45-kDa protein with 441 amino acids that is distinct from other members of the phospholipase A2 family in that it is calcium-independent.22 The secreted isoform was first identified on the basis of its ability to degrade platelet-activating factor (PAF), hence it is also known as PAF-acetylhydrolase.23 In contrast to other phospholipase A2 enzymes, Lp-PLA2 acts preferentially on water-soluble polar phospholipids with oxidatively truncated sn-2 chains, lacking enzymatic activity on naturally occurring long-chain fatty acids in phospholipids found in cellular membranes.24

The biological role of Lp-PLA2 has been controversial with seemingly contradictory anti- or pro-atherogenic functions being proposed. The anti-atherogenic properties of Lp-PLA2 were suggested because of the enzymatic catabolism of biologically active oxidized phospholipids in LDL and degradation of the unrelated polar phospholipid, PAF.25,26 To this end, Lp-PLA2 was reported to alter biological properties of minimally modified LDL by abrogating the ability of LDL to promote endothelial cell binding of monocytes.26 In addition, a number of studies have shown that minimally modified LDL containing oxidized phospholipids induce chemotaxis and monocyte adhesion to endothelial cells.15,16 Recent findings, however, have ascribed several anti-inflammatory properties to oxidized phospholipids, which illustrates the complexity of this field.27,28 In addition, the assertion that Lp-PLA2 degrades PAF in vivo remains unproven. This is an important consideration because PAF has been implicated in prothrombotic, allergic, and inflammatory responses, suggesting that blocking its degradation in cardiovascular patients would be detrimental. However, administration of a potent reversible Lp-PLA2 inhibitor to experimental animals did not influence plasma concentrations of PAF (G.M. Benson, PhD: unpublished data). Furthermore, intravenous administration of recombinant human Lp-PLA2 (≈10-fold plasma increase) failed to alter PAF-mediated responses in patients with asthma or those with septic shock.29,30 These seemingly contradictory observations between the susceptibility of PAF to Lp-PLA2 in vitro, and the aforementioned observations in vivo, could be explained by the presence of other enzymatic systems, such as high-density lipoprotein (HDL)-associated paraoxonase, lecithin-cholesterol acyltransferase, or other PAF-acetylhydrolases (eg, PLA2 group VIIb) that degrade PAF, although this view is not shared by all.21,31–33

In contrast, the pro-atherogenic function of Lp-PLA2 is thought to arise from the formation of downstream inflammatory mediators derived from oxidized phospholipids. This view is supported by experimental evidence suggesting that the products of Lp-PLA2 activity on oxidized phospholipids (lysoPC and oxidized NEFA) elicit several potentially proatherogenic effects (Table 1).34–53 The link between Lp-PLA2
and putative toxicity of downstream lipid mediators is strengthened by the observations that selective inhibition of this enzyme prevented lysoPC and NEFA generation in oxidized LDL, resulting in inhibition of monocyte chemotaxis and protection of macrophages against apoptotic death.\(^{50,52}\) The recent discovery of a high-affinity G2A receptor for lysoPC in macrophages, lymphocytes, and lipiderich human atherosclerotic lesions has provided additional evidence for the mechanism by which the molecules derived from hydrolysis of oxidized LDL exert their biological activity.\(^{54,55}\) In particular, Lp-PLA\(_2\)–derived lysoPC species (16:0/18:0/18:1) compete for binding with the G2A receptor. The interaction of this receptor with lysoPC activates an intracellular signal transduction cascade (extracellular signal regulated kinase mitogen-activated protein kinase) and induces inflammatory cell migration.\(^{54}\)

**Medical Genetics of Lp-PLA\(_2\)**

The gene for Lp-PLA\(_2\) (PLA2G7) has 12 exons and is located on chromosome 6p21.2 to 12. Several missense polymorphisms within the coding regions of PLA2G7 have been described with some variants noted mainly in certain ethnic groups (eg, Val279Phe variant is common in Japanese, Turks, and Kyrgyzes but absent in whites). Studies of functional polymorphisms (“the experiment of nature”) could provide insights into the biological role of this enzyme, although the reports to date are contradictory. The Val279Phe variant is associated with reduced levels of Lp-PLA\(_2\) in 27% of heterozygous Japanese and complete absence of Lp-PLA\(_2\) in 4% of homozygous individuals caused by a defect in enzyme secretion.\(^{56,57}\) Several studies suggest a higher prevalence of cardiovascular disease in Japanese carriers of this variant, although some of these investigations were underpowered and showed no differential effect between heterozygotes and homozygotes (ie, no gene dose effect).\(^{58–61}\) In fact, the largest study of genetic polymorphisms failed to identify an association between the Val279Phe variant and the risk of myocardial infarction in 4152 Japanese subjects.\(^{62}\) Another caveat to consider is that because misfolded and nonsecreted Val279Phe protein is not secreted, this, in itself, could cause adverse effects.\(^{63,64}\) In whites, different functional polymorphism affecting PLA2G7 has been identified in which the Ala379Val variant results in reduced affinity of Lp-PLA\(_2\) for exogenous PAF.\(^{65}\) Homozygotes for Val379 (~5% population) appear to have reduced risk of myocardial infarction.\(^{66}\) These contradictory findings, arguing against (Val279Phe) or supporting (Ala379Val) the concept of therapeutic inhibition of Lp-PLA\(_2\), reinforce the need for comprehensive and larger investigations of genetic variants, as highlighted in the recent analysis of paraoxonase polymorphisms that share some similarities with Lp-PLA\(_2\).\(^{67}\)

**Lp-PLA\(_2\) as a Marker of Cardiovascular Risk**

An increased understanding of atherosclerosis and growing analytical capabilities have led to the discovery of associations between several soluble biomarkers and cardiovascular risk. In some instances, the upstream events culminate in the upregulation of the analyte (eg, C-reactive protein, serum amyloid A). In contrast, other biomarkers are thought to be directly implicated in disease development (eg, myeloperoxidase). To this end, serum levels of malondialdehyde, a marker of lipid oxidation, are also strongly predictive of cardiovascular events.\(^{68}\) This could reflect greater exposure of the vessel wall to oxidatively modified LDL, but it also indicates an increase in the substrate for Lp-PLA\(_2\) (Figure 2). Because plasma Lp-PLA\(_2\) can be measured, the association between this inducer of putative downstream lipid mediators and cardiovascular events adds to the supporting evidence that Lp-PLA\(_2\) plays a detrimental role in populations at risk. In general, Lp-PLA\(_2\) levels are lower in premenopausal women than in men, and Lp-PLA\(_2\) levels increase with age. Several studies to date have demonstrated that Lp-PLA\(_2\) levels (mass or activity) are higher in those in whom future cardiovascular events develop (univariate analysis). In most studies (Table 2), the risk estimates of death, coronary events, or stroke remain statistically significant even after full adjustment for several risk factors (multivariate analysis).\(^{69–74}\) Because circulating Lp-PLA\(_2\) levels are dependent on the level of its carrier, LDL cholesterol, a significant interaction between these measurements has been noted in some studies.\(^{71}\) The strength of association varies and is generally modest (hazard ratios <2), which is typical of common risk factors.\(^{75}\) Not surprisingly, C-reactive protein and Lp-PLA\(_2\) do not correlate with each other, because they likely reflect disparate inflammatory pathways. Nonetheless, they appear to have additive value in predicting cardiovascular risk, which highlights the importance of inflammation in atherogenesis and development of clinical events.\(^{71,74}\)

**Distribution of Circulating and Vascular Lp-PLA\(_2\)**

Although Lp-PLA\(_2\) is expressed in many tissues, the enzyme in circulation is derived from hematopoietic cells. A study of carriers of functional Val279Phe mutation of Lp-PLA\(_2\) who underwent allogeneic bone marrow transplantation established that plasma levels of Lp-PLA\(_2\) are determined by the genotype of the donors’ hematopoietic cells.\(^{76}\) In humans, ~70% to 80% of the enzyme is associated with LDL because of specific protein–protein interactions between the N-terminus of Lp-PLA\(_2\) and the C-terminus of apoB.\(^{77}\) The association of the remaining secreted enzyme with the phospholipid moiety of HDL is poorly understood, although posttranslational modifications of human Lp-PLA\(_2\) may be involved.\(^{78}\) Among different LDL particles, Lp-PLA\(_2\) preferentially associates with smaller and denser fractions that are believed to be more pro-atherogenic.\(^{79}\) Other researchers have focused on the electronegative subfraction of circulating LDL that exhibits signs of modifications, contains ~5-fold higher Lp-PLA\(_2\) activity, and is enriched in products of the Lp-PLA\(_2\) reaction (ie, lysoPC and NEFA).\(^{80,81}\) Electronegative LDL induces inflammatory gene expression and adhesion of monocytes to endothelial surface that is consistent with potential pro-atherogenic effects of Lp-PLA\(_2\).\(^{82,83}\) Species differences in amino acid sequences in both Lp-PLA\(_2\) and apoB are responsible for the predominant association of Lp-PLA\(_2\) with HDL in several animal species (eg, mouse, dog, and rabbit). This raises still-unanswered questions regarding the role of Lp-PLA\(_2\) in HDL particles, because
several preclinical studies suggest an atheroprotective role of HDL-associated enzyme.84,85 Both studies used adenovirus-mediated gene transfer of human enzyme in mice, resulting in ectopic expression (ie, in liver as opposed to natural leukocyte expression), with the majority of LP-PLA₂ presumably residing on HDL. Interestingly, a later study by the same group showed that in dyslipidemic obese, LDL receptor knockout, leptin-deficient, double-mutant mice with greatly accelerated disease, plasma LP-PLA₂ levels were elevated because of a much higher level of enzyme (in this instance naturally generated) associated with apoB-containing lipoproteins.86 A very similar observation was demonstrated in atherosclerosis-prone mice lacking both the LDL receptor and the ability to edit apoB mRNA (LDLR/APOBEC1) that also overexpressed human apoB100 (LDLR/APOBEC1/ERhB<sup>Δ</sup>).<sup>87</sup> In this case, the increase in apoB-associated LP-PLA₂ was associated with accelerated atherosclerosis. The situation in genetically engineered mice is clearly complex and requires better understanding. The paucity of simple models of atherosclerosis with a human-like lipoprotein profile and corresponding LP-PLA₂ distribution underscores the challenges in the testing of LP-PLA₂ inhibitors.

In human atherosclerotic lesions, 2 main sources of LP-PLA₂ can be identified, including that which is brought into the intima bound to LDL (from the circulation), and that which is synthesized de novo by plaque inflammatory cells (macrophages, T cells, mast cells). High levels of LP-PLA₂ mRNA (reverse-transcription polymerase chain reaction and microarrays) and protein (immunohistochemistry and activity assay) have been noted in carotid plaque (Figure 3).<sup>88</sup> In coronary lesions, positive LP-PLA₂ immunostaining is particularly notable in macrophages within thin-cap fibro-atheroma that is present in ≈60% of victims of sudden cardiac death.<sup>89,90</sup>

## Modulation of Circulating and Vascular LP-PLA₂

A rapid increase in plasma or tissue levels of LP-PLA₂ is observed in animals challenged with lipopolysaccharide to mimic the host response to infection.<sup>91</sup> Lipopolysaccharide-induced effects are mediated by toll-like receptor 4 on the surface of macrophages and the activation of p38MAPK pathway that ultimately results in transcriptional upregulation of LP-PLA₂.<sup>92</sup> Outside the acute phase response, smaller variations in plasma LP-PLA₂ levels are likely determined by chronic activation of peripheral blood mononuclear cells and circulating levels of LDL. Treatment with statins or fenofibrate lowers LP-PLA₂ activity by ≈20% to 30% (from concomitant reductions in LDL levels) without an effect on de novo synthesis and secretion of LP-PLA₂ by macrophages.<sup>93,94</sup> Lipoprotein fractionation studies suggest a predominant decrease in LP-PLA₂ associated with dense LDL. Not surprisingly, high doses of atorvastatin lower the total amount of oxidized phospholipids in plasma that are recognized by the murine monoclonal antibody E06. Interestingly, the enrichment of a smaller pool of apoB100 particles with the subsequent binding to apoB.<sup>95</sup> This may represent the efflux of oxidized phospholipid from the vessel wall with the subsequent binding to apoB.95 Although the clinical relevance of this finding remains unclear, it also illustrates a potential for synergy between statins and specific LP-PLA₂ inhibitors for further risk reduction.

The discovery of potent LP-PLA₂ inhibitors has allowed testing of their ability to lower enzyme activity in plasma and, more importantly, at vascular sites (Figure 2). Studies in healthy volunteers demonstrated that several orally bioavailable inhibitors of LP-PLA₂ reduce circulating enzyme activity in a dose-dependent manner up to >95%. In patients undergoing carotid endarterectomy, one of these compounds (480848) showed a dose-dependent inhibition of LP-PLA₂.

### TABLE 2. Plasma Levels of LP-PLA₂ and the Risk of Cardiovascular Events in Primary Prevention Population<sup>69–74</sup>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Cases/Noncases</th>
<th>End Point</th>
<th>Follow-Up, y</th>
<th>LP-PLA₂ Assay</th>
<th>LP-PLA₂ Cases vs Noncases</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Nested case-control</td>
<td>580/1160</td>
<td>CHD death, MI, revascularization</td>
<td>5</td>
<td>Mass</td>
<td>Higher</td>
<td>1.18 (1.05–1.33; P=0.005)*</td>
</tr>
<tr>
<td>WHS&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Nested case-control</td>
<td>123/123</td>
<td>CHD death, MI, stroke</td>
<td>3</td>
<td>Mass</td>
<td>Higher</td>
<td>1.17 (0.45–3.05; NS)†</td>
</tr>
<tr>
<td>ARIC&lt;sup&gt;71,72&lt;/sup&gt;</td>
<td>Case cohort</td>
<td>608/740</td>
<td>CHD death, MI, revascularization</td>
<td>6</td>
<td>Mass</td>
<td>Higher</td>
<td>1.15 (0.81–1.63; NS)‡</td>
</tr>
<tr>
<td>MONICA&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Cohort</td>
<td>97/837</td>
<td>Ischemic stroke</td>
<td>6</td>
<td>Mass</td>
<td>Higher</td>
<td>1.93 (1.14–3.27; P=0.015)‡</td>
</tr>
<tr>
<td>Rotterdam&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Case cohort</td>
<td>308/1822</td>
<td>CHD death, MI</td>
<td>7</td>
<td>Activity</td>
<td>Higher</td>
<td>1.96 (1.25–3.09; P=0.02)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110/1822</td>
<td>Ischemic stroke</td>
<td>6</td>
<td>Activity</td>
<td>Higher</td>
<td>1.95 (1.02–3.73; P=0.04)†</td>
</tr>
</tbody>
</table>

ARIC indicates the Atherosclerosis Risk In Communities study; CHD, coronary heart disease; CRP, C-reactive protein; HR, hazard ratio adjusted for age, smoking, diabetes mellitus, gender, systolic blood pressure, LDL cholesterol (or total cholesterol/HDL or non-HDL cholesterol), high-sensitivity CRP and other variables; MI, myocardial infarction; MONICA, the MONItoring of trends and determinants in CArdiovascular disease in men in Augsburg survey; WHS, the Women’s Health Study; WOSCOPS, the West Of Scotland Coronary Prevention Study.

*Increase of 1 SD.
†With the lowest quartile as the reference.
‡With the lowest tertile as the reference.
¶In population with baseline LDL<130 mg/dL.

<http://atvb.ahajournals.org/doi/10.1161/jaha.117.005733>
activity in plasma and atherosclerotic plaque, with a maximal dose resulting in an 80% inhibition of the enzyme activity after only 14 days of dosing. Unraveling the consequences of intraplaque reductions in the enzyme activity will require additional and longer studies; nevertheless, these early clinical findings provide the evidence that a potent inhibitor of Lp-PLA2 is able to penetrate the lesion and exert intravascular pharmacodynamic effects.

Conclusions

Ascribing a role for Lp-PLA2, an enzyme that is produced by inflammatory cells, is transported on circulating LDL and hydrolyzes oxidized phospholipids in LDL, has been controversial. Initial investigations focused on its presumed anti-inflammatory effects caused by degrading PAF and removing polar phospholipids in modified LDL. Functional evaluation of Lp-PLA2 in animals is hindered by the predominant association of Lp-PLA2 with HDL and the absence of rupture-prone vulnerable plaques in these models of atherosclerosis. More recent studies, however, propose a proinflammatory role of Lp-PLA2 that mediates formation of noxious bioactive lipid mediators (lysoPC and oxidized NEFA) in lesion-prone vasculature and to a lesser extent in the circulation (eg, in electronegative LDL). Additionally, a growing number of epidemiological studies suggest that Lp-PLA2 is an independent predictor of cardiovascular events, despite some attenuation of this relationship by LDL, the primary carrier of Lp-PLA2. These observations strengthen the rationale to explore causal links between Lp-PLA2 and plaque vulnerability. Selective Lp-PLA2 inhibition reduces enzyme activity in human lesions, thus providing a means of interfering with the production of bioactive lipid mediators. To this end, future mechanistic studies need to address whether this approach abrogates inflammation in atherosclerotic tissue and produces favorable changes in intermediate cardiovascular end points (eg, imaging and endothelial function). Only a careful and stepwise approach that builds evidence of causality between Lp-PLA2 and atherosclerosis and accumulates clinical safety information will provide the ultimate rationale for large-scale clinical investigations of selective Lp-PLA2 inhibitors for the purpose of reducing cardiovascular events in patients at high risk.

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