Role of Lipoprotein-Associated Phospholipase A2 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 A2 (Lp-PLA2) 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-PLA2 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-PLA2 mediated by products of the Lp-PLA2 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 (eg, in electronegative LDL), are known to elicit several inflammatory responses. The proinflammatory action of Lp-PLA2 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-PLA2, in the analysis. These observations provide a rationale to explore whether inhibiting Lp-PLA2 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 (eg, 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 A2

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.1–3 Clinical experience suggests no threshold values for implementing corrective therapies in regard to some risk factors in individuals at high risk.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
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

initiation, progression, and destabilization of atheroma.5 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 extends beyond concomitant low-density lipoprotein (LDL)-lowering remains unclear.7,8 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 A_{2} (Lp-PLA_{2}) 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.10 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.11–14 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.15,16 Until recently, oxidative modification of LDL was assumed to yield a final product responsible for several reactions involved in atherogenesis.17 However, oxidative modification of polyunsaturated fatty acids in the sn-2 position of phospholipids within LDL molecules renders them susceptible to hydrolysis by Lp-PLA_{2}, 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-glycerol-3-phosphorylcholine, that lack oxidative truncation of the polyunsaturated fatty acids at the sn-2 position.18 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.19,20 Research in this field has been confounded by the complexity of phospholipid biochem-

Figure 2. Schematic representation of the proposed pro-atherogenic mechanism of Lp-PLA_{2} in the vessel wall. Lp-PLA_{2} binds to apoB on LDL, its primary carrier, which delivers Lp-PLA_{2} 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-PLA_{2}. 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-PLA_{2} increases its concentration in the vessel wall. Bioactive lipid mediators generated by Lp-PLA_{2} 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 Phospholipids

<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-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Formation of inflammatory mediators: activation of Ca\textsuperscript{2+}-dependent PLA\textsubscript{2} enzymes and arachidonic acid release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional responses: impaired proliferation/migration and reduced NO-dependent vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytotoxicity: apoptosis</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Homing of inflammatory cells: upregulation of MCP-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxidative stress: NADPH oxidase activation and ROS-dependent ERK1/2 phosphorylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional responses: increased growth factor gene expression, proliferation, and migration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDL retention: upregulation of biglycan core protein and elongation of GAG chains</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytotoxicity: apoptosis</td>
</tr>
<tr>
<td>Monocytes/macrophages</td>
<td>Formation of inflammatory mediators: upregulation of cytokines (IL-1\beta), Ca\textsuperscript{2+}-dependent PLA\textsubscript{2} enzymes, and arachidonic acid release</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional responses: increased chemotaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytotoxicity: increased cellular permeability and apoptosis</td>
</tr>
<tr>
<td>T cells</td>
<td></td>
<td>Functional responses: increased chemotaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immune response: interferon-\gamma upregulation</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>Oxidative stress: NADPH oxidase activation and myeloperoxidase release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional responses: increased chemotaxis, elastase release</td>
</tr>
<tr>
<td>oxNEFA</td>
<td>Monocytes/macrophages</td>
<td>Cytotoxicity: increased cellular permeability and apoptosis</td>
</tr>
</tbody>
</table>

GAG indicates glycosaminoglycan; ICAM-1, intercellular adhesive molecule-1; IL-1\beta, interleukin-1\beta; LysoPC, lysophosphatidylcholine; MCP-1, monocyte chemotactic protein-1; NO, nitric oxide; oxNEFA, oxidized nonesterified fatty acids; PLA\textsubscript{2}, phospholipase A\textsubscript{2}; ROS, reactive oxygen species; VCAM-1, vascular cell adhesive molecule-1.

The biological role of Lp-PLA\textsubscript{2} has been controversial with the difficulty in establishing a causal link between specific lipid mediators within the vessel wall and clinical events.

Lp-PLA\textsubscript{2}: Functional Characteristics

Lp-PLA\textsubscript{2} belongs to the expanding superfamily of structurally diverse phospholipase A\textsubscript{2} enzymes described elsewhere in detail.\textsuperscript{21} First cloned in 1995, Lp-PLA\textsubscript{2} is a 45-kDa protein with 441 amino acids that is distinct from other members of the phospholipase A\textsubscript{2} family in that it is calcium-independent.\textsuperscript{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.\textsuperscript{23} In contrast to other phospholipase A\textsubscript{2} enzymes, Lp-PLA\textsubscript{2} 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.\textsuperscript{24}

The biological role of Lp-PLA\textsubscript{2} has been controversial with seemingly contradictory anti- or pro-atherogenic functions being proposed. The anti-atherogenic properties of Lp-PLA\textsubscript{2} were suggested because of the enzymatic catabolism of biologically active oxidized phospholipids in LDL and degradation of the unrelated polar phospholipid, PAF.\textsuperscript{25,26} To this end, Lp-PLA\textsubscript{2} was reported to alter biological properties of minimally modified LDL by abrogating the ability of LDL to promote endothelial cell binding of monocytes.\textsuperscript{26} In addition, a number of studies have shown that minimally modified LDL containing oxidized phospholipids induce chemotaxis and monocyte adhesion to endothelial cells.\textsuperscript{15,16} Recent findings, however, have ascribed several anti-inflammatory properties to oxidized phospholipids, which illustrates the complexity of this field.\textsuperscript{27,28} In addition, the assertion that Lp-PLA\textsubscript{2} 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-PLA\textsubscript{2} inhibitor to experimental animals did not influence plasma concentrations of PAF (G.M. Benson, PhD: unpublished data). Furthermore, intravenous administration of recombinant human Lp-PLA\textsubscript{2} (\(\sim10\)-fold plasma increase) failed to alter PAF-mediated responses in patients with asthma or those with septic shock.\textsuperscript{29,30} These seemingly contradictory observations between the susceptibility of PAF to Lp-PLA\textsubscript{2} 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-acylhydrolases (eg, PLA\textsubscript{2} group VIIb) that degrade PAF, although this view is not shared by all.\textsuperscript{21,31–33}

In contrast, the pro-atherogenic function of Lp-PLA\textsubscript{2} 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-PLA\textsubscript{2} activity on oxidized phospholipids (lysoPC and oxidized NEFA) elicit several potentially pro-atherogenic effects (Table 1).\textsuperscript{34–53} The link between Lp-PLA\textsubscript{2}
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 lipid-rich 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-PLA2−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-PLA2
The gene for Lp-PLA2 (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-PLA2 in 27% of heterozygous Japanese and complete absence of Lp-PLA2 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-PLA2 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-PLA2, 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-PLA2.67

Lp-PLA2 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-PLA2 (Figure 2). Because plasma Lp-PLA2 can be measured, the association between this inducer of putative downstream lipid mediators and cardiovascular events adds to the supporting evidence that Lp-PLA2 plays a detrimental role in populations at risk. In general, Lp-PLA2 levels are lower in premenopausal women than in men, and Lp-PLA2 levels increase with age. Several studies to date have demonstrated that Lp-PLA2 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-PLA2 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-PLA2 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-PLA2
Although Lp-PLA2 is expressed in many tissues, the enzyme in circulation is derived from hematopoietic cells. A study of carriers of functional Val279Phe mutation of Lp-PLA2 who underwent allogeneic bone marrow transplantation established that plasma levels of Lp-PLA2 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-PLA2 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-PLA2 may be involved.78 Among different LDL particles, Lp-PLA2 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-PLA2 activity, and is enriched in products of the Lp-PLA2 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-PLA2.82,83 Species differences in amino acid sequences in both Lp-PLA2 and apoB are responsible for the predominant association of Lp-PLA2 with HDL in several animal species (eg, mouse, dog, and rabbit). This raises still-unanswered questions regarding the role of Lp-PLA2 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 (Apobec1+/−) that also overexpressed human apoB100 (LDLR−/− Apobec1+/− ERhbB−/−).87 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).88 In coronary lesions, positive Lp-PLA2 immunostaining is particularly notable in macrophages within thin-cap fibroatheroma that is present in ~60% of victims of sudden cardiac death.89,90

### 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.91 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-PLA2.92 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.93,94 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 enrichment of a smaller pool of apoB100 particles with oxidized phospholipids has been noted.95 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.
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.

Acknowledgments

The authors thank Jeanenne J. Nelson, PhD, for critical review of epidemiologic results, G. M. Benson, PhD, for helpful comments and contributing unpublished data, Yi Shi, MD, PhD, and Shawn O’Brien, for sharing expression data in human atheroma, and Pat G. Iannuzzelli, PhD, for help with manuscript preparation.

References

Zalewski and Macphee The Role of Lp-PLA 2 in Atherosclerosis 929


13. By guest on October 23, 2017 http://atvb.ahajournals.org/ Downloaded from
46. Chang MY, Tsai C, Wight TN, Chait A. Lysophosphatidylcholine reg- 
ulates synthesis of biglycan and the proteoglycan form of macrhophe 
colony stimulating factor. Arterioscler Thromb Vasc Biol. 2003;23: 
809–815.

47. Hsieh CC, Yen MH, Liu HW, Lau YT. Lysophosphatidylcholine induces 
apoptotic and non-apoptotic death in vascular smooth muscle cells; in 

48. Liu-Wu Y, Hurt-Camejo E, Wiklund O. Lysophosphatidylcholine induces 
the production of IL-1beta by human monocytes. Atherosclerosis. 1998; 
137:351–357.

49. Oestvang J, Anthonsen MW, Johansen B. Role of secretory and cytosolic 
phospholipase A2 enzymes in lysophosphatidylcholine-stimulated 

50. Carpenter KL, Dennis IF, Challis IR, Osborn DP, Macphee CH, Leake 
DS, Arends MJ, Mitchinson MJ. Inhibition of lipoprotein-associated 
phospholipase A2 diminishes the death-inducing effects of oxidised LDL 

51. McMurray HF, Parthasarathy S, Steinberg D. Oxidatively modified low 
density lipoprotein is a chemotaxtractant for human T lymphocytes. J Clin 

52. Macphee CH, Moores KE, Boyd HF, Dhanak D, Ibe RJ, Leach CA, Leake 
DS, Milliner KJ, Patterson RA, Suckling KE, Tew DG, Hickey DM. 

53. Macphee CH. Lipoprotein-associated phospholipase A2: a potential new 
risk factor for coronary artery disease and a therapeutic target. Curr Opin 

54. Kabarovski JH, Zhu K, Le LJ, Witte ON, Xu Y. Lysophosphatidylcholine as a 
ligand for the immunoregulatory receptor G2A. Science. 2002;293:702–705.

M, Ejiri J, Shiomi M, Inoue N, Kawashima S, Yokokawa M. Expression 
of G2A, a receptor for lysophosphatidylcholine, by macrophages in 
murine, rabbit, and human atherosclerotic plaques. Arterioscler Thromb 

56. Stafforini DM, Satoh K, Atkinson DL, Tjoelker LW, Vaitkus D, McIntyre TM, 
Blum J, Dada N, Fox JC, Manson JE, Ridker PM. A prospective evaluation of 
lipoprotein-associated phospholipase A2(2) levels and the risk of future 

Sharrett AR. Lipoprotein-associated phospholipase A2, high-sensitivity 

AR, Wu KK, Myerson M, Chambless LE, Boerwinkle E. Lipoprotein- 
associated phospholipase A2, high-sensitivity C-reactive protein, and risk for 
ischemic stroke in middle-aged men and women in the Atheroscle-

59. Koenig W, Khuseyinova N, Lowel H, Trischler G, Meisinger C. 
Lipoprotein-associated phospholipase A2 adds to risk prediction of 

60. Oei H-HS, van der Meer I, Hofman A, Koudstaal P, Breteler M, 
Wittenberg J. Lipoprotein-associated phospholipase A2 is associated with 
2005;111:570–575.


62. Asano K, Okamoto S, Fukunaga K, Shiomi T, Mori T, Iwata M, Ikeda 
Y, Yamaguchi K. Cellular source(s) of platelet-activating-factor acetylhy-
drolase activity in plasma. Biochem Biophys Res Commun. 1999;261: 
511–514.

63. Stafforini DM, Tjoelker LW, McCormick SP, Vainikus D, McIntyre TM, 
Gray PW, Prescott SM. Platelet-activating factor acetylhydrolase defi-

64. Unno N, Nakamura T, Igarashi T, Yamanoto T, Sugatai J, Miwa M, 
Nakamura S. Plasma platelet-activating factor acetylhydrolase deficiency 
and induction of chemokine release from human endothelial cells. 

T, Futamatsu T, Hara K, Chiba Y. Oxidized LDL-induced expression 

66. Sanchez-Quesada JL, Caslave ML, Mcmahon AD, Ford I, Cooney J, 
Mackeeth C, Suckling KE, Krishna M, Wilkinson FE, Rumley A, Lowe 
GD. Lipoprotein-associated phospholipase A2 as an independent pre-
dicator of coronary heart disease. West of Scotland Coronary Prevention 

67. Blake GI, Dada N, Fox JC, Manson JE, Ridker PM. A prospective eva-

68. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Heiss G, 
Sharrett AR. Lipoprotein-associated phospholipase A2, high-sensitivity 
C-reactive protein, and risk for ischemic stroke in middle-aged men and women in the Atheroscle-

Lipoprotein-associated phospholipase A2 adds to risk prediction of 

70. Oei H-HS, van der Meer I, Hofman A, Koudstaal P, Breitler M, 
Wittenberg J. Lipoprotein-associated phospholipase A2 is associated with 
2005;111:570–575.


Role of Lipoprotein-Associated Phospholipase A2 in Atherosclerosis: Biology, Epidemiology, and Possible Therapeutic Target
Andrew Zalewski and Colin Macphee

Arterioscler Thromb Vasc Biol. 2005;25:923-931; originally published online February 24, 2005.
doi: 10.1161/01.ATV.0000160551.21962.a7

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/5/923

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/