Lipoprotein-associated phospholipase A2 prognostic role in atherosclerotic complications

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Abstract

Atherosclerosis manifests itself clinically at advanced stages when plaques undergo hemorrhage and/or rupture with superimposed thrombosis, thus abruptly stopping blood supply. Identification of markers of plaque destabilization at a pre-clinical stage is, therefore, a major goal of cardiovascular research. Promising results along this line were provided by studies investigating the lipoprotein-associated phospholipase A2 (Lp-PLA2), a member of phospholipase A2 proteins family that plays a key role in the metabolism of pro-inflammatory phospholipids, as oxidized low-density lipoproteins, and in the generation of pro-atherogenic metabolites, including lysophosphatidylcholine and oxidized free fatty acids. We herein review the experimental and clinical studies supporting use of Lp-PLA2 activity for predicting cardiovascular events. To his end we considered not only Lp-PLA2 activity and mass, but also *Lp-PLA2* gene variations and their association with incident coronary artery disease, stroke, and cardiovascular mortality. Based on these evidences the major scientific societies have included in their guidelines the measurement of Lp-PLA2 activity among the biomarkers that are useful in risk stratification of adult asymptomatic patients at intermediate cardiovascular risk. The results of two recently published major clinical trials with the Lp-PLA2 inhibitor darapladib, which seem to challenge the pathogenic role of Lp-PLA2, will also be discussed.

Core tip: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a promising new marker of atherosclerotic plaque destabilization, which plays a key role in the metabolism of pro-inflammatory phospholipids and in the generation of pro-atherogenic metabolites. This review focuses on the experimental and clinical studies supporting use of Lp-PLA2 for predicting cardiovascular events considering not only Lp-PLA2 activity and mass, but also *Lp-PLA2* gene variations. Based on current evidences the major scientific

societies have included Lp-PLA2 activity measurement in their guidelines among the biomarkers that are useful in risk stratification of adult asymptomatic patients at intermediate cardiovascular risk.

INTRODUCTION

Exposure of endothelial cells to damaging stimuli, as smoking, arterial hypertension, diabetes mellitus, dyslipidemia can induce qualitative changes that are collectively defined as "endothelial activation", and are currently postulated regarded as one of the earliest events in atherogenesis[1]. An "activated" endothelium expresses adhesion molecules and chemotactic substances, increases its permeability to macromolecules with ensuing variation of the sub-endothelial extracellular matrix composition. As a result, low-density lipoproteins (LDLs), particularly those that are smaller and denser and therefore more pro-atherogenic, penetrate the vessel wall and remain trapped in the sub-intimal space, where they undergo oxidative changes. Oxidized LDLs induce recruitment of monocytes by vascular cells and promote their differentiation into macrophages[2]. The latter internalize oxidized LDLs and become foam cells[3], the distinctive feature of the atherosclerotic lesions.

Atherosclerosis manifests itself clinically either when the arterial vessel stenosis prevents the increase of blood flow and oxygen supply during augmented demand (*e.g.*, exercise or digestion) causing the onset of pain (angina pectoris, abdominis or claudicatio intermittens, depending on the segments involved), or when an unstable plaque undergoes hemorrhage and/or rupture with superimposed thrombosis.

Several studies showed that athero-thrombosis, which is responsible for acute ischemic events, does not correlate strictly with the degree of atherosclerotic plaque narrowing[4,5], but rather with the plaque features, and, more specifically, with the extent of inflammation, thinning of the fibrous cap, and expression of inflammatory cytokines and metalloproteinases that degrade the fibrous cap[6,7]. This explains why the atherosclerotic disease might manifest clinically with acute catastrophic events even in patients with apparently mild lesions.

Identification of circulating markers that can be useful to improve the prediction of cardiovascular events is akin the current frontiers of Cardiology. C-reactive protein and cholesterol levels, despite being among the most studied biomarkers[8,9], bear a rather small predictive value: for example, in the Framingham Heart Study most of the patients who developed ischemic heart disease during twenty-six years follow-up had "normal" total cholesterol levels comparable to those not developing any cardiovascular disease[10].

In the Get with the Guidelines study database[11], which included 231896 patients admitted to 541 United States hospitals with a diagnosis of acute coronary syndrome, 136905 (59%) subjects had the lipid levels determined at admission and 21.1% of them were treated with cholesterol-lowering drugs. The average lipid profile was: LDL cholesterol 104.9 mg/dL (2.17 mmol/L), high-density lipoprotein (HDL) cholesterol 39.7 mg/dL (1.03 mmol/L), and triglycerides 161 mg/dL (1.82 mmol/L). According to this study about half of the patients admitted to the hospital with an acute coronary syndrome had LDL cholesterol levels in the normal range (Figure 1)[11]. These data provide compelling evidence for the urgent need to perform clinical and laboratory research to identify new biomarkers of imminent plaque destabilization. Along this line, encouraging results were provided by studies investigating the lipoprotein-associated phospholipase A2 (Lp-PLA2), a member of phospholipase A2 proteins family that plays a crucial role in the metabolism of pro-inflammatory phospholipids, such as oxidized LDLs, and in the generation of pro-atherogenic metabolites, such as lysophosphatidylcholine and oxidized free fatty acids (Figure 2).

ROLE OF LP-PLA2 IN ATHEROSCLEROSIS

Lp-PLA2 is a calcium-independent lipase mainly produced by monocytes and macrophages[12], which catalyze the hydrolysis of the sn-2 acyl chain of the phospholipid substrate[13] on the surface of LDLs[14], releasing lysophosphatidylcholine and oxidized fatty acids. The latter are well-established triggers of the inflammatory cascade[14-16], *via* stimulation of endothelial cells expression of adhesion molecules and cytokines, induction of chemotaxis of monocytes and leucocytes, and promotion of their entry in the sub-intimal space of the arterial walls.

The accumulation of lysophosphatidylcholine and oxidized fatty acids in the sub-intimal space contributes to the development of the plaque lipid "core". Moreover, these substrates once taken up by macrophages promote their conversion into foam cells[17]. In addition, lysophosphatidylcholine induces the production of reactive oxygen species, such as superoxide, by activating the endothelial nicotinamide adenine dinucleotide phosphate oxidase and by inducing the endothelial nitric oxide synthase (eNOS) "uncoupling"[18,19]. Through the latter mechanism the enzyme becomes a superoxide and peroxynitrite producer, thus contributing to atherogenesis and plaque destabilization, as corroborated by the increased cardiovascular mortality found in coronary artery disease patients carrying an *eNOS* gene polymorphism that implies enhanced eNOS
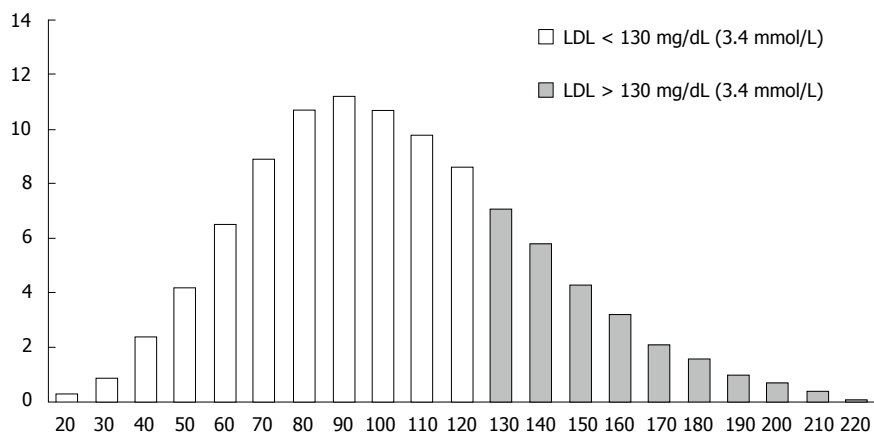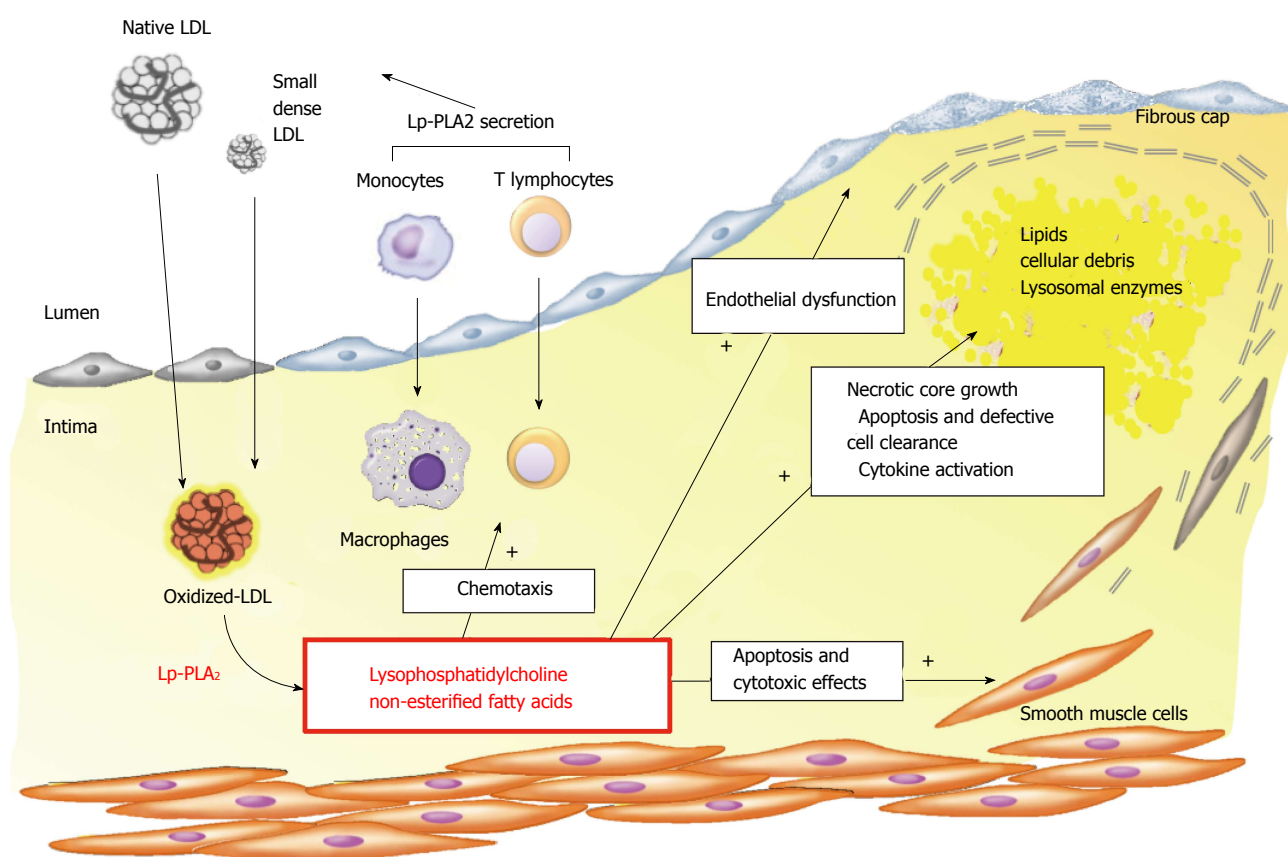
Figure 1 Low-density lipoprotein cholesterol levels on admission in patients with acute coronary syndrome[74]. LDL: Low-density lipoprotein.

Modified from Steen DL and O'Donoghue ML, *Cardiol Ther* 2013.

Figure 2 Pathogenic role of lipoprotein-associated phospholipase A2 in atherosclerosis development. LDL: Low-density lipoprotein; Lp-PLA2: Lipoprotein-associated phospholipase A2.

expression and reactive oxygen species generation[20].

In summary, experimental evidences indicate that due to its pro-inflammatory and pro-oxidative effects Lp-PLA2 plays a key role in the pathogenesis of atherosclerosis.

LP-PLA2 SECRETION AND CIRCULATION IN THE BLOOD-STREAM

Hematopoietic (monocytes, macrophages, lymphocytes, mastocytes, and platelets) and hepatic cells (Kupffer's cells)

produce Lp-PLA2; however, its synthesis and release in the circulation occur with monocytes maturation into macrophages[21] alongside activation by inflammatory mediators[22].

In the bloodstream Lp-PLA2 circulates by two-thirds bound to the LDLs and by one third to HDLs[23,24]. It is, however, worth highlighting that with normal LDL-levels the total plasma Lp-PLA2 activity associated with HDL accounts for only 4.9% of the total enzyme activity[25].

Plasma ultracentrifugation leads to partial separation

of Lp-PLA2 from the lipoproteins, thus indicating that there is a dissociable and a non-dissociable form of the enzyme[26]. The transition between them might be one of the mechanisms regulating the activity of Lp-PLA2 *in vivo*. The association with HDL and LDL is controlled by post-translational chemical modifications: Glycosylation of specific residues decreases the association of Lp-PLA2 and lipoproteins, even though these changes do not seem to influence the enzyme secretion by the cells[27].

As regards the relationship of Lp-PLA2 with apolipoproteins, B100 plays a key role in the association of Lp-PLA2 with LDLs, especially its carboxyl terminus, which interacts with the Lp-PLA2 residues Tyr-205, Trp-115, and Leu-116 and, to lesser extent, with the Met-117[28]. In spite of the fact that Lp-PLA2 preferentially associates with the most dense and electronegative LDLs fractions, even among the latters only 1% of the particles contain Lp-PLA2[29-31]. As mentioned, only one third of Lp-PLA2 circulates in plasma with HDLs. Multiple amino-acid residues, as well as the carbohydrate content of the enzyme, appear to play a crucial role for its association with HDL apolipoprotein A-I[27,32].

Finally, when plasma lipoprotein(a) concentrations are $\geq$ 30 mg/dL detectable amounts of Lp-PLA2 are associated with this lipoprotein. A major role for its attachment is played by apolipoprotein B-100[33].

PLASMA LP-PLA2 DETERMINATION

Originally specific tests were developed to determine the Lp-PLA2 plasma concentration (mass) and enzymatic activity. The plasma mass assays were thereafter abandoned due to lack of significant advantages and lower accuracy in patients' risk stratification than enzymatic activity assays. The assessment of Lp-PLA2 activity exploits enzymatic substrates, such as 2 Tio-PAF, whose degradation releases free thiol groups, which are detectable by spectrophotometric reading.

GENETIC DETERMINANTS OF LP-PLA2 ACTIVITY

The prognostic relevance of Lp-PLA2 measurement raised the question whether the enzyme levels and activity are genetically determined ("nature") or influenced by environmental factors ("nurture"). According to one study and a recent meta-analysis Caucasians carry higher Lp-PLA2 activity levels than Hispanics and African-Americans, suggesting that Lp-PLA2 is genetically influenced[34,35]. Moreover, Lp-PLA2 activity was reported to be 10% lower in females compared to males, possibly due to higher estrogen levels in the former, which down-regulate Lp-PLA2 activity and decrease LDL-cholesterol[34,35]. A conclusive demonstration of hereditability was provided by twins' studies. In fact, genetically identical monozygotic twins showed differences in their plasma levels of Lp-PLA2 much smaller than dizygotic twins, who share only

half of their genes, thus showing that about 62% of the variance of Lp-PLA2 activity levels is under genetic control[36].

The *Lp-PLA*2 gene (*PLA2G7*) is located in chromosome 6p21.2 to 12 and entails 12 exons. Its cDNA was cloned in 1995[37] and comprises an open reading frame codifying a precursor of 441 amino acids that is cleaved into a 45.4 kDa mature protein[38]. The *PLA2G7* gene is characterized by non-synonymous polymorphisms that could cause reduction or loss of the enzymatic activity.

The first evidence of the functional relevance of these mutations dates back to the identification of five Japanese families with absent circulating Lp-PLA2, an autosomal recessive trait[39] linked to a Val279Phe polymorphism on the exon 9[40]. This variant causes the absence of Lp-PLA2 enzymatic activity because of an amino acid change in proximity of Ser-273 and Asp-296 that is responsible of folding and, thus, functioning of the mature protein.

The Val279Phe polymorphism was associated to atherosclerosis[41,42], stroke[43], and dilated cardiomyopathy[44]. However, these early evidences, which have been produced when Lp-PLA2 was believed to be anti-atherogenic, were not confirmed by subsequent studies that, in fact, showed just opposite results[45]. Thus, it remains unclear whether the lack of Lp-PLA2 activity is pro- or anti-atherogenic and if carriers of this genetic variant, who are exclusively Asian, could have inherited compensatory mechanisms that change unpredictably the final clinical phenotype.

Other polymorphisms were thereafter identified in Caucasians[46,47]: Arg92His (exon 4), Ile198Thr (exon 7), Ala379Val (exon 11). In particular, the Ile198Thr variation is located near the Tyr205 residue, a binding site for LDLs, in a position that might decrease the affinity for the substrate, thus explaining the observed reduction of enzymatic activity[46]. Another polymorphism, the Ala379Val, is located near the residue belonging to the catalytic triad of lipase (Hys-351), suggesting that it could influence the enzymatic activity[48].

Ala379Val and Arg92His variants have been associated with coronary artery disease (CAD)[49], but only the former correlated with the severity of atherosclerosis in a Taiwanese population[50] and to acute myocardial infarction in two case-control studies[49,50]. In other studies this association was neither confirmed[51] nor denied[52,53]. Two recent meta-analyses[54,55], which included more than 10000 patients of European ancestry, failed to demonstrate any association between the *PLA2G7* gene polymorphisms and CAD risk. These studies, as well as the meta-analyses that included them, were biased and affected by confounding factors, in that: (1) only a minority of studies used a prospective cohort study design, which is more reliable compared to case-control studies; and (2) the adjustment for potential confounders by multivariate analysis was not consistently performed. Therefore, likely their results
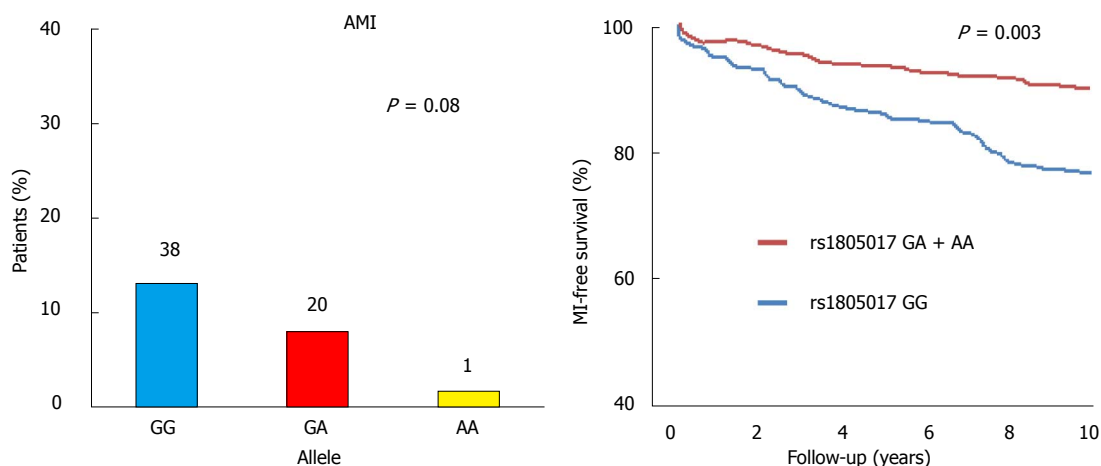
Figure 3 Increased number of acute myocardial infarction depending on the variant gene Arg92His. A: The patients with variant gene GG (Arg92) have a greater number of infarcts compared to the other two variants; B: The Kaplan-Meyer curve shows a lower survival free from acute myocardial infarction in patients with variant GG (Arg92). AMI: Acute myocardial infarction.

could not be considered conclusive even despite the large number of patients analyzed.

A recently published prospective cohort study performed with an appropriate prospective cohort design and an utmost care to the role of potential confounders, showed that Arg92His is associated to both high levels of Lp-PLA2 activity, and a 1.75-fold increase of relative risk of acute myocardial infarction (Figure 3)[56]. Hence, it would appear that genetic predisposition to high Lp-PLA2 activity translates into increased susceptibility to acute coronary events.

LP-PLA2 ACTIVITY AND CARDIOVASCULAR DISEASE

The first study showing an association between elevated Lp-PLA2 plasma levels and cardiovascular events was the West of Scotland Coronary Prevention Study (WOSCOPS)[57]. Other studies thereafter confirmed Lp-PLA2 to be a predictor of cardiovascular events in different cohorts[58-66], but the large Women Health Study[67], which enrolled a healthy female population, found just an opposite association. In apparently healthy populations, three trials demonstrated the Lp-PLA2 prognostic role. In the ARIC study, which enrolled a large cohort of healthy subjects of both genders, those with low LDL cholesterol (< 130 mg/dL) and high Lp-PLA2 levels had an increased relative risk of ischemic heart disease [HR 2.08, 95% confidence interval (CI): 1.20-3.62] compared to those with low levels of Lp-PLA2[68]. The JUPITER trial also showed that patients with high Lp-PLA2 activity (fourth quartile) had a more than two-fold increased relative risk (HR 2.15, 95%CI: 1.13-4.08) of developing cardiovascular events than those with low activity (first quartile)[69]. Finally, the Bruneck study also reported that the population in the third tertile of Lp-PLA2 activity had a higher relative risk of incident cardiovascular events (HR 2.2, 95%CI:

1.1-4.8) compared to those in the first tertile[70].

Lp-PLA2 activity might predict the occurrence of events also in patients at high cardiovascular risk: in the MDCS study, which enrolled healthy subjects, those with metabolic syndrome and high Lp-PLA2 activity had a 1.97 (95%CI: 1.34-2.90) relative risk of cardiovascular events[71]. The combined analysis of two studies, HPFS and NHS, including patients with diabetes mellitus, showed that those with a high Lp-PLA2 activity had a 1.75 (95%CI: 1.05-2.92) relative risk of cardiovascular mortality and AMI[72].

The ability of Lp-PLA2 to predict cardiovascular events was also confirmed in subjects with cardio-vascular disease. The VA-HIT study, which included patients with ischemic heart disease, the increase of Lp-PLA2 activity levels was associated with a higher relative risk of cardiovascular events (HR 1.17, 95%CI: 1.04-1.32) and death (HR 1.23, 95%CI: 1.01-1.50)[73]. Similar results were obtained in the LIPID trial that entailed subjects with history of acute coronary syndrome in whom Lp-PLA2 activity was associated to a higher risk of cardiovascular mortality (HR 1.32, 95%CI: 1.00-1.75)[74]. Another study that included 1051 patients affected by CAD showed that Lp-PLA2 activity predicted the risk of cardiovascular events (HR 2.40, 95%CI: 1.35-4.29)[63]. Finally, in a large cohort of subjects with CAD of the GENICA Study, we demonstrated that a high Lp-PLA2 activity level predicted both cardiovascular mortality (HR 1.01, 95%CI: 1.00-1.02) and acute myocardial infarction (HR 1.01, 95%CI: 1.00-1.02) (Figure 4)[75].

Circulating Lp-PLA2 activity levels could be an index of systemic inflammation as suggested by the finding of a direct link between Lp-PLA2 enzymatic activity and activation of lympho-monocytic cells[76]. These data were confirmed by studies on CAD patients (Rotterdam Study and Ludwigshafen Risk and Cardiovascular Health Study) that demonstrated an association
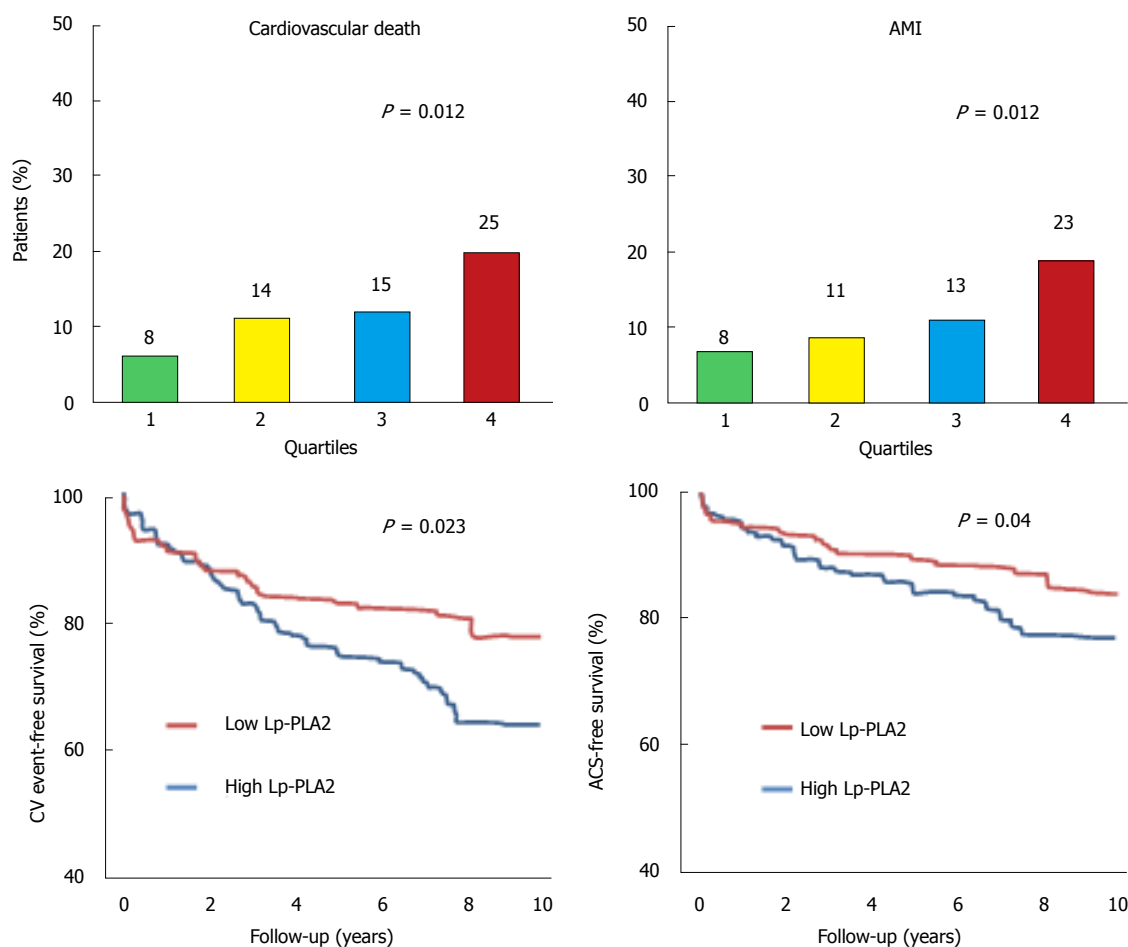
Figure 4 The Kaplan-Meyer curves underline a greater survival free from cardiovascular events (death, acute myocardial infarction) in patients with lower lipoprotein-associated phospholipase A2 activity. AMI: Acute myocardial infarction; ACS: Acute coronary syndrome; CV: Cardiovascular.

between Lp-PLA2 enzymatic activity and CAD risk[77,78].

A meta-analysis that included all prospective studies conducted on Lp-PLA2 including a total of 79036 patients showed a relationship between Lp-PLA2 activity and mass and incidence of CAD, stroke, and cardiovascular mortality[79].

LP-PLA2 AND GUIDELINES

Based on these evidences, the guidelines of four major international societies, including the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the American Society of Endocrinology, included the Lp-PLA2 activity measurement among the biomarkers that are useful for risk stratification of asymptomatic adult patients. The use of this marker is particularly advantageous in patients at moderate cardiovascular risk (> 2 risk factors) and in those at high-risk in whom an increase of Lp-PLA2 activity levels should guide the lipid-lowering treatment to reach a target LDL-cholesterol lower than, respectively, 130 mg/dL (< 3.3 mmol/L) or 100 mg/dL (< 2.5 mmol/L) in primary prevention[80] (Figure 5).

THERAPEUTIC STRATEGY TO REDUCE LP-PLA2 LEVELS

As the majority of plasma Lp-PLA2 is linked to LDLs, a therapeutic strategy aimed at decreasing LDL cholesterol levels could be expected to reduce Lp-PLA2 activity. Accordingly, several cholesterol-lowering treatments, such as statins[66,74,81,82], fibrates[81,83], ezetimibe[81], and omega-3 fatty acids[84], were found to reduce plasma Lp-PLA2 activity. However, it remained unclear whether the reduction of Lp-PLA2 activity with a lipid-lowering treatment translates into a lower mortality and cardiovascular event rate, and if these benefits could be explained by the reduction of plasma lipids, of Lp-PLA2 activity levels, or of both. This hypothesis has been tested in the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) study, a double blind multicenter trial that randomized to placebo or pravastatin 9014 patients with CAD[74]. The levels of many biomarkers, such as cholesterol fractions and Lp-PLA2 activity were determined at "baseline" and after one year of treatment. The study showed that after one-year follow-up, the statins group
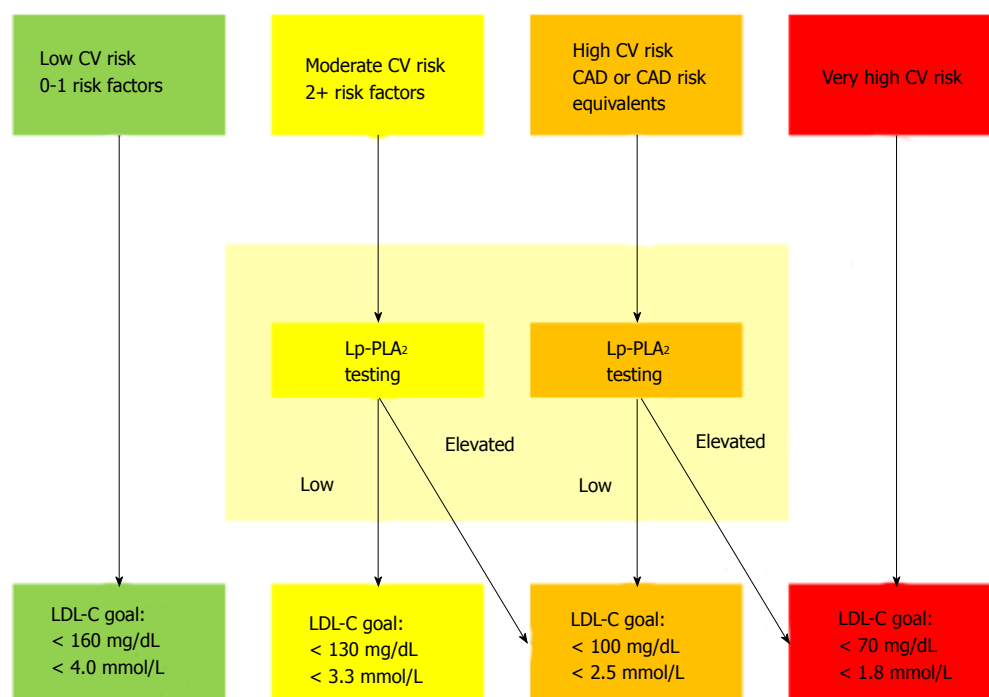
Figure 5 Relevance of measuring of lipoprotein-associated phospholipase A2 activity for risk stratification in adult patients with moderate cardiovascular risk (> 2 risk factors) or higher[80]. Lp-PLA2: Lipoprotein-associated phospholipase A2; LDL: Low-density lipoprotein; CAD: Coronary artery disease; CV: Cardiovascular.

had a reduction Lp-PLA2 activity (50 nmol/min per milliliter, $P < 0.001$) compared to both baseline values and to the placebo group. Similarly to previous studies, the "baseline" values of Lp-PLA2 activity predicted the risk of cardiovascular events, including CAD mortality and acute myocardial infarction, and total mortality; after adjustment at multivariate analysis, the baseline values of Lp-PLA2 activity predicted only CAD mortality. The key finding was that after one year of treatment low Lp-PLA2 levels predicted less major CAD events (HR 0.65, 95%CI: 0.50-0.86, $P = 0.002$), less major cardiovascular events (cardiovascular death, less non fatal acute myocardial infarction or stroke, HR 0.70, 95%CI: 0.55-0.89, $P = 0.003$), and less cumulative cardiovascular events (major cardiovascular events, unstable angina, revascularization, HR 0.70, 95%CI: 0.59-0.83; $P < 0.001$), comparing the first with the fourth quartile of Lp-PLA2 levels. These prognostic value persisted unaltered after adjustment for twenty-three risk factors at enrolling, which led the authors to conclude that the reduction of Lp-PLA2 during treatment with statin was as predictive, or even more predictive, than the decrease of LDL cholesterol[74]: about 59% of the beneficial effects of pravastatin were explained by a decrease of Lp-PLA2 values. This study could not, however, verify whether the reduction of circulating Lp-PLA2 was associated with a decrease of the enzyme activity into the atherosclerotic plaque, a data that, if confirmed, could explain the observed decrease of events.

RANDOMIZED CONTROLLED CLINICAL TRIALS TESTING THE EFFICACY OF LP-PLA2 INHIBITORS

This piece of information was, however, obtained, in diabetic and dyslipidemic pigs: darapladib, a Lp-PLA2 inhibitor, reduced the lysophosphatidylcholine levels in coronary artery plaques and decreased macrophage infiltration and necrotic "core" in the plaques[85]. Moreover, in the IBIS-2 study in humans, darapladib decreased the Lp-PLA2 activity and the necrotic "core" in coronary plaques[85]. Two randomized trials were conducted to test whether pharmacological inhibition of Lp-PLA2 with darapladib reduces cardiovascular events in stable and unstable CAD and were recently published, the STABILITY[86] and the SOLID-TIMI 52[87].

The STABILITY trial randomized 15828 patients with stable CAD to receive darapladib or placebo for a median period of 3.7 years with a composite primary end-point of cardiovascular death, myocardial infarction, or stroke[86]. The trial fell short of proving its primary end-point and could not demonstrate any beneficial effect of darapladib on each individual component of the primary end-point, or on the overall mortality. However, it demonstrated a beneficial effect of Lp-PLA2 inhibition in that darapladib reduced the rate of major coronary events and total coronary events.

The SOLID-TIMI 52 trial enrolled 13026 patients with an acute coronary syndrome in the last 30 d

before randomization to darapladib or placebo for a median period of 2.5 years with a composite primary end-point of cardiovascular death, myocardial infarction or urgent coronary artery revascularization[87]. The results did not demonstrate any beneficial effect of darapladib on any of the either primary or secondary endpoints.

These disappointing results might seem to challenge the pathogenic role of Lp-PLA2 in atherosclerosis and plaque destabilization. However, considering the wealth of data demonstrating that Lp-PLA2 predicts cardiovascular events, one could argue that the plasma activity of Lp-PLA2 is only a prognostic marker and does not play a causative role. Another possibility is that the trials, due to the high rate of drug discontinuation (20% in the STABILITY trial and 17% in the SOLID TIMI 52), ultimately lacked the statistical power to challenge the hypothesis that darapladib is efficacious in reducing cardiovascular events. If this was the case the possibility that another, possibly better tolerated, antagonist could improve outcomes needs to be tested. Furthermore, the selection criteria did not include a threshold Lp-PLA2 level, whereas it is well known that the risk of cardiovascular events is dependent on the Lp-PLA2 levels. Moreover, the drug adherence assessment used, *e.g.*, pill count, is well known to underestimate the true therapeutic compliance[88]. The absence of any report of the Lp-PLA2 levels reached after darapladib administration, testing the therapy efficacy and the patients' compliance, is a missing crucial piece of information in these trials.

At present, from the available data it is possible to speculate that darapladib is not an efficacious therapy. Considering the extensive proof of the Lp-PLA2 prognostic value and the crucial information missing in the completed trials, it is possible to hypothesize that Lp-PLA2 is a marker of disease and does not have a pathogenic role, or that another more efficacious way to inhibit Lp-PLA2 activity by means of new drugs should be investigated.

CONCLUSION

In summary, compelling evidence indicate that high Lp-PLA2 activity levels predict an increased risk of cardiovascular events in the general population, as well as in patients with metabolic syndrome, diabetes, and coronary heart disease[63,68-75]. Many cholesterol-lowering medications besides decreasing LDL-cholesterol lower circulating Lp-PLA2 levels. Moreover, the Lp-PLA2 levels achieved with pravastatin treatment is a marker of cardiovascular risk and coronary events, even better than the LDL cholesterol level[74]. The available evidences support the usefulness of the measurement of plasma Lp-PLA2 activity in the clinical practice to stratify the cardiovascular risk, especially in patients at intermediate or high risk. In these subjects Lp-PLA2 activity levels should prompt the physician to pursue

two aims: (1) a more aggressive LDL-cholesterol treatment; and (2) the normalization of Lp-PLA2 levels (Figure 5). For this reason, the scientific societies guidelines introduced the measurement of Lp-PLA2 as a marker of risk in these categories of patients.

The role of Lp-PLA2 as a therapeutic target has been disproven by two large randomized clinical trials thus far. However, due to their intrinsic limitations, it remains unclear if these results depended on the Lp-PLA2 being only a marker of cardiovascular events devoid of a pathogenic role, or on the lack of efficacy of the drug tested in these trials. Further studies are needed to resolve this dilemma.

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