Therapeutic Modulation of Lipoprotein-associated Phospholipase A2 (Lp-PLA2)

Alexandros D. Tselepis*, Manfredi Rizzo1,2 and Ioannis A. Goudevenos3

Laboratory of Biochemistry, Department of Chemistry and 3Department of Cardiology, University of Ioannina, 45110 Ioannina, Greece; 1Department of Internal Medicine and Medical Specialities, University of Palermo, Italy; 3Euro-Mediterranean Institute of Science and Technology, Italy

Abstract: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a calcium-independent phospholipase A2 that circulates in plasma in association with lipoprotein particles, whereas in atherosclerotic plaques it is co-localized with macrophages. Lp-PLA2 generates two proinflammatory mediators, lysophosphatidylcholine and oxidized nonesterified fatty acids, which play a role in the development of atherosclerotic lesions and formation of a necrotic core, leading to more vulnerable plaques. Epidemiologic studies demonstrate that increased circulating levels of Lp-PLA2 predict an increased risk of myocardial infarction, stroke and cardiovascular mortality. Furthermore, histologic examination of diseased human coronary arteries reveals intense presence of the enzyme in atherosclerotic plaques that are prone to rupture. These considerations suggest Lp-PLA2 as a promising therapeutic target in cardiovascular disease. Plasma levels of Lp-PLA2 are increased in various types of hyperlipidemias, while hypolipidemic drugs reduce plasma Lp-PLA2 activity and mass along with the improvement of plasma lipid profile. A selective inhibitor of Lp-PLA2 activity, darapladib, has been developed and studies in animal models and humans have shown that it effectively and safely reduces Lp-PLA2 activity in plasma and in atherosclerotic plaques. Furthermore, in animal models darapladib decreases plaque area and necrotic core area whereas in humans it prevents the expansion of necrotic core volume. Whether the results obtained from the use of darapladib in studies in vitro, as well as in preclinical and clinical studies would translate into benefits on cardiovascular event outcomes, awaits to be proved in 2 ongoing phase 3 trials.

Keywords: Atherosclerosis, Cardiovascular disease, Darapladib, Inflammation, Lipoproteins, Lp-PLA2.

1. INTRODUCTION

Atherosclerosis is a leading cause of death, myocardial infarction and stroke in the US and Western countries and low-density lipoprotein cholesterol (LDL-C) concentrations remain the main treatment target for effective cardiovascular prevention in most guidelines [1-3]. However, current approaches for the treatment of hypercholesterolemia are associated with residual cardiovascular risk despite aggressive use of lipid-lowering agents. This residual risk has been linked to the presence of atherogenic lipoproteins, beyond LDL-C.

Indeed, evidence suggest that both “quality” and “quantity” of plasma lipids and lipoproteins influences cardiovascular risk [4]. For example, LDL and high density lipoprotein (HDL) particles do not comprise homogenous populations, but multiple subclasses with discrete size and density, different physicochemical composition, metabolic behaviour and atherogenicity [5,6]. The presence of small, dense LDL has been associated with cardiovascular risk beyond plasma lipid levels (reviewed in [7,8]). This has led to research on novel agents that will achieve comprehensive lipid management and, ultimately, more effective cardiovascular prevention [9].

One of the potential targets of novel lipid-lowering strategies is lipoprotein-associated phospholipase A2 (Lp-PLA2), a calcium-independent phospholipase A2 whose products have pro-inflammatory properties [10]. This is directly linked to the role of inflammation in atherosclerosis, which has become a promising therapeutic target. In this view, a 2008 consensus panel on Lp-PLA2 has recommended its use as a diagnostic test for vascular inflammation to better identify patients at high or very high risk who will benefit from intensification of lipid-modifying therapies [11]. The aim of the present article is therefore to discuss the role of selective inhibition of Lp-PLA2 as a potential novel therapeutic target, reviewing the most recent data with Lp-PLA2 inhibitors.

2. THE ROLE OF Lp-PLA2 ON CARDIOVASCULAR RISK

A very large amount of Lp-PLA2 (approximately 70 to 80%) circulates bound to LDL and the remainder is bound to HDL, lipoprotein (a) [Lp(a)], and very low-density lipoproteins (VLDL) [12]. Lp-PLA2 was initially discovered in vitro as platelet activating factor acetylhydrolase (PAF-AH), degrading the inflammatory mediator platelet activating factor (PAF) [13]. This already suggested an atheroprotective role of Lp-PLA2. However, more recent evidence highlighted the role of Lp-PLA2 for atherosclerosis development and progression.

Lp-PLA2 rapidly degrades polar phospholipids present in oxidized LDL, resulting in the production of lysophosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids (ox-NEFAs), which exhibit a wide range of pro-inflammatory and pro-apoptotic effects (reviewed in [14,15]). There is evidence proposing a regulatory role of these pro-inflammatory lipids in promoting atherosclerotic plaque development, which can lead to formation of a necrotic core, involving the recruitment and activation of leucocytes [16], induction of apoptosis [17,18], impaired removal of dead cells [19,20], as well as active recruitment of macrophages and monocytes to atherosclerotic plaque [21]. Inflammatory cells in the atherosclerotic plaque subsequently produce more Lp-PLA2, resulting in a self-enhancing cycle of upregulation of Lp-PLA2 and progression of the atheroma; indeed, Lp-PLA2 products (lysoPC and ox-NEFAs) may be crucial in determining plaque instability [22]. All this evidence suggests that Lp-PLA2 is a link between lipid metabolism and the inflammatory response [23].

Several studies have highlighted the role of Lp-PLA2 as an independent predictor for cardiovascular disease (CVD), for both primary and secondary events (reviewed in [24,25]). Overall, these studies consistently demonstrated a correlation between elevated Lp-PLA2 levels and the increased risk for cardiovascular events, even after multivariable adjustment for traditional risk factors, with roughly a doubling of risk associated with upper quartile levels [26]. When primary prevention was considered, it still demonstrated an association between Lp-PLA2 and risk of future coronary events, stroke and transient ischaemic events in patients without prior history of CVD [24]. Also, in secondary prevention studies

*Address correspondence to this author at the Professor of Biochemistry-Clinical Chemistry Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece; Tel: (+30) 26510-08365; Fax: (+30) 26510-08785; E-mail: atselep@uoi.gr
Lp-PLA2 helped to identify which high-risk persons are at very-high-risk for coronary events; notably, several studies suggested that low Lp-PLA2 may have a particularly useful role as a negative predictor [24,25]. These findings were also highlighted by the recent meta-analysis from 32 prospective studies performed by the Lp-PLA2 Studies Collaboration group [26].

3. SELECTIVE Lp-PLA2 INHIBITORS

The persistent residual risk of recurrent adverse cardiovascular events despite the continuous improvement of evidence-based standard-of-care therapies has prompted intense research into novel approaches aiming to further reduce the CVD risk. These efforts have established the key role that inflammation plays in atherogenesis. In this regard, accumulated data provided by epidemiological studies have demonstrated that increased plasma Lp-PLA2 activity and mass are associated with an increased risk of CVD. Furthermore, data provided by histologic examination of atherosclerotic human coronary arteries have indicated the presence of the enzyme in plaques that are prone to rupture [22]. Consequently, Lp-PLA2 is currently considered as a promising therapeutic target. In this regard, a series of novel and potent azetidinone inhibitors of Lp-PLA2 were initially described [27,28]. This class of selective Lp-PLA2 inhibitors target the active-site serine residue of Lp-PLA2 [27]. In experiments in vitro, selective Lp-PLA2 inhibition by the most potent of these azetidinone inhibitors, SB-222657, reduced the generation of lysoPC and ox-NEFA during LDL oxidation, i.e. the bioactive products of Lp-PLA2 activity that are mostly responsible for the proatherogenic activities of this enzyme [28,29]. Furthermore, Lp-PLA2 inhibition with SB-222657 inhibited monocyte chemotaxis [28] and protected against cell death of monocyte/macrophages induced by oxidized LDL [29]. Subsequently, a series of substituted pyrimidones that selectively inhibit Lp-PLA2 activity in vitro at nanomolar concentrations, were developed [30-32]. Modification of the pyrimidine 5-substituent in Lp-PLA2 inhibitor SB-435495 has given a series of enzyme inhibitors with sub-nanomolar potency. Among them, SB-480848 showed enhanced in vitro and in vivo inhibitory profile vs SB-435495 [32]. Mechanistic studies using steady state and transient kinetics indicated SB-480848 to be a freely reversible, non-covalently bound, inhibitor of recombinant Lp-PLA2 with a Ki value of 110 nM. SB-480848 potently inhibited Lp-PLA2 in whole human plasma with an IC50 value of 5 ± 2 nM. Furthermore, SB-480848 prevented the production of lyso-PC during LDL oxidation (IC50 = 4 ± 3 nM) and subsequent monocyte chemotaxis (IC50 = 4 ± 1 nM). In vivo studies with SB-480848 indicated an oral bioavailability of 11 ± 2% in the fed rat and 28 ± 4% in the dog. Oral administration of 10 mg/kg SB-480848 in hyperlipidemic rabbits reduced plasma Lp-PLA2 activity by >60%, which was maintained for more than 24 h. Furthermore, 2h after oral administration of 30 mg/kg SB-480848 in these animals, inhibited Lp-PLA2 activity by 95% within atherosclerotic plaques [32]. Other favorable characteristics of SB-480848 among the original family of candidate compounds included its relatively straightforward chemical synthesis and minimal interactions with liver cytochrome P450 isozymes [32]. Importantly, SB-480848 at a concentration of 1 μM exhibits minimal inhibition on other secretory PLA2s implicated in atherogenesis, 0% inhibition for sPLA2-IIa and sPLA2-V and 8% inhibition for sPLA2-X [reviewed in 33]. This weak activity of SB-480848 against other sPLA2s is expected, given that they have very different catalytic motifs and requirements for catalysis compared to Lp-PLA2 [34]. Due to the above favorable characteristics, SB-480848 named as darapladib (GlaxoSmithKline, Philadelphia, PA), became the leading compound among all substituted pyrimidines and was selected for further evaluation in man.

Darapladib Preclinical Evaluation

The first preclinical studies with darapladib (SB-480848) were performed in hyperlipidemic rabbits [32]. However, rabbits as well as mice may not be the most appropriate models to study darapladib effects on Lp-PLA2 since these animals have different plasma lipoprotein profile compared with humans (predominance of HDL over apoB-containing lipoproteins) and in these animals Lp-PLA2 is primarily associated with HDL [35]. Thus, in a more recent study the effect of darapladib on Lp-PLA2 was investigated in a diabetic/hypercholesterolemic porcine model (DM-HC), which has a lipoprotein profile similar to humans (predominance of apoB-containing lipoproteins over HDL). Furthermore, plasma Lp-PLA2 in these pigs is mainly associated with LDL thus making these animals more appropriate for studying the effects of darapladib on Lp-PLA2, inflammation and atherosclerosis. One month after DM-HC induction, animals were randomly assigned into either a control (n = 17) or treatment groups (n = 20) receiving oral darapladib (10 mg/kg per day). Three pigs that did not undergo DM-HC induction acted as age-matched controls. DM-HC animals exhibited an increase in plasma apoB-containing lipoproteins that carry the bulk of Lp-PLA2, relative to control animals along with an elevation in plasma glucose (~380 mg/dl) and cholesterol (~700 mg/dl) levels. Average increase of Lp-PLA2 activity in these animals was 230% [36]. Specimens were harvested 24 weeks after initiation of treatment. In animals treated with darapladib, a significant reduction in Lp-PLA2 activity both in plasma and in artery wall (by 89 and 84%, respectively) was observed compared with placebo treatment of DM-HC animals. Plasma and tissue Lp-PLA2 activity levels were reduced compared with those observed in control non-DM-HC animals. Importantly, the reduction in enzyme activity in darapladib-treated animals was associated with a reduction in elevated arterial lyso-PC levels, a major Lp-PLA2 product. Histological examination of the coronary arteries revealed that the median plaque area was smaller in darapladib-treated DM-HC animals compared with the untreated ones. Atherosclerotic coronary lesions similar to advanced human fibrous cap or thin fibrous cap atheroma were detected in 7 of 17 (41%) untreated DM-HC animals but in only 2 of 20 (10%) darapladib-treated DM-HC animals. The mean necrotic core area was significantly smaller in the darapladib-treatment group compared with the control group. Immunohistochemical staining showed macrophage predominance in the plaques of untreated DM-HC pigs with predominance of smooth muscle cells in lesions from darapladib-treated DM-HC pigs. The macrophage content present in combined intimal and medial areas of coronary lesions was also reduced by 59% in darapladib-treated DM-HC animals compared with untreated ones. Using quantitative polymerase chain reaction analysis it was found that coronary artery expression of 87 genes implicated in inflammation, leukocyte function and atherogenesis was increased in DM-HC pigs. Darapladib treatment was associated with significant reduction in expression of 24 of these genes, including 8 of 14 that were most increased by DM-HC induction. In particular, there was a substantial reduction in expression of several genes associated with monocyte and T-lymphocyte recruitment and activation [36]. The above results suggest that oral administration of darapladib to animals exhibiting similar to human’s plasma lipoprotein profile and Lp-PLA2 distribution among lipoprotein subspecies, reduces circulating and tissue Lp-PLA2 activity and attenuates the development of coronary lesions resembling human atherosclerosis thus leading to more stable and less vulnerable atherosclerotic lesions. Importantly it restores various qualitative measures of plaque progression in levels seen in control non-DM-HC animals [36]. As the above darapladib effects were independent of cholesterol levels or the severity of hyperglycaemia, these results demonstrate the independent role for vascular inflammation in the development of coronary heart disease (CHD) and further support the hypothesis that Lp-PLA2 is causally involved in the development of coronary atherosclerosis and formation of an unstable lesion phenotype [36].
Darapladib Clinical Studies

The effect of darapladib on plasma Lp-PLA2 activity was initially investigated in normal volunteers in several phase 1 trials. These studies demonstrated that daily administration of oral darapladib was acceptably tolerated, without effects on lipid plasma levels or platelet function. A proof of concept phase 2 trial was performed in 59 patients who were scheduled to undergo carotid endarterectomy [37]. Daily administration for 14 days before elective carotid endarterectomy of either 40 or 80 mg darapladib reduced plasma Lp-PLA2 activity by 57 and 82%, respectively and plaque Lp-PLA2 activity by 55 and 81%, respectively. Furthermore, IL-18 levels and activity of the pro-apoptotic caspase-3 and caspase-8 were attenuated compared with placebo [37]. Subsequently, the effect of darapladib on plasma Lp-PLA2 activity and cardiovascular biomarkers was investigated in a phase 2 multicenter, randomized, double-blind, parallel-groups study involving 959 stable CHD or CHD risk equivalent patients [38]. Eligible patients were randomized to double blind treatment with atorvastatin 20 or 80 mg daily. After 4 weeks of treatment, plasma LDL-C levels were determined and only patients with levels lower than 115 mg/dl were randomized to concomitant treatment with darapladib 40, 80, 160 mg or placebo for 12 weeks. Lp-PLA2 activity was reduced by 43, 55 and 66% among subjects randomised to darapladib 40, 80 and 160 mg, respectively. Lp-PLA2 mass measured in a subset of 228 subjects was reduced by 9.6, 12.9 and 9.3% by darapladib 40, 80 and 160 mg, respectively. Treatment with darapladib did not change plasma concentrations of total cholesterol, LDL-C, HDL-cholesterol (HDL-C) or triglycerides when compared with placebo. There was a significant reduction in interleukin-6 (IL-6) levels by 12.3% compared with placebo and by 21.5% within group, in the high-dose treatment group. High-sensitivity CRP (hsCRP) levels were not significantly reduced by 13.0% compared with placebo (p = 0.15) whereas within group comparison revealed a significant reduction of hsCRP by 20.2% (p = 0.003). No effects on platelet biomarkers associated with increased platelet activation (P-selectin, CD40 ligand, and urinary 11-dehydrothromboxane B2) were observed, suggesting that Lp-PLA2 inhibition does not adversely affect platelet reactivity. Finally, no major safety concerns were noted after 12 weeks of treatment [38].

The effects of darapladib on coronary plaque deformability, composition and volume as well as on several plasma biomarkers were investigated in the International Biomarkers and Imaging Study (IBIS-2), a phase 2 randomized, double-blind, placebo-controlled trial [39]. The study involved 330 patients with angiographically documented CHD who were treated with either 160 mg daily of darapladib (n = 175) or placebo (n = 155) for 12 months. The primary end points of the study were coronary plaque deformability determined by intravascular ultrasound (IVUS)-based palpography and plasma hsCRP levels, whereas secondary end points included several plasma biomarkers (LDL-C, Lp-PLA2 activity, markers of platelet activation), necrotic core size (by IVUS-based radiofrequency analysis), atheroma volume (by IVUS-angiography) as well as clinical safety parameters. Consistent with the results described in the above study by Mohler ER, et al [38], darapladib did not influence plasma levels of LDL-C, HDL-C, hsCRP and platelet activation biomarkers, whereas it significantly reduced plasma Lp-PLA2 activity by 59% compared with placebo group [39]. Concerning hsCRP it should be noted that a significantly higher percentage of patients treated with darapladib (62%) achieved very low levels of hsCRP (<1 mg/l) compared with placebo (45%) (p < 0.008). No significant difference in the primary end point of coronary plaque deformability was observed between the 2 groups, however expansion of necrotic core volume was halted in darapladib-treated patients whereas it significantly increased in placebo-treated patients, resulting in a significant treatment difference of -5.2 mm³ (p = 0.012). These intraplaque compositional changes were not accompanied by a difference in total plaque volume or calcification (p = 0.95). Finally, darapladib exhibited a favorable safety profile [39]. Since necrotic core size is a primary component of vulnerable plaques that are associated with increased risk of sudden luminal thrombosis [40], the results of the IBIS-2 trial suggest that darapladib may be a potentially useful therapeutic agent, especially in patients with an acute coronary syndrome.

Consistent results from the above studies, suggest that the effect of darapladib on inflammatory markers, other than Lp-PLA2, is modest and limited to the highest dose. This suggests that the use of darapladib may be limited to treat atherosclerotic diseases and not any inflammatory condition. However, in cases that an inflammatory disease is associated with a greater risk of vascular events such as rheumatoid arthritis the use of darapladib could provide an additional clinical benefit. Indeed, rheumatoid arthritis is considered as a CHD equivalent, and cardiovascular events are the most important cause of mortality and morbidity, due to a number of proatherogenic alterations found in rheumatoid arthritis patients, even in the early stages of the disease [41-44]. Thus, management of rheumatoid arthritis-related CHD is likely to require both aggressive control of inflammation and systematic screening and management of CHD risk factors such as Lp-PLA2. Therefore, the use of darapladib in rheumatoid arthritis patients should be explored in future studies.

Whether the results obtained from the use of darapladib in studies in vitro, as well as in preclinical and clinical studies would translate into benefits on cardiovascular event outcomes, awaits to be proved in 2 ongoing phase 3 trials. The STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial (ClinicalTrials.gov identifier NCT00799903) and the SOLID-TIMI 52 (the Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52) trial (ClinicalTrials.gov identifier NCT01000727).

STABILITY is a randomized, placebo-controlled, double-blind, parallel-assign, multicenter, clinical outcome trial sponsored by GlaxoSmithKline. The study has randomized 15,828 patients with chronic CHD receiving standard of care to darapladib entericoated tablets, 160 mg or placebo. STABILITY will assess whether direct inhibition of Lp-PLA2 with darapladib added to the standard of care confers clinical benefit to patients with CHD. The primary end point is the composite of major adverse cardiovascular events (MACE), i.e. cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The key secondary end points will include major coronary events, total coronary events, individual components of MACE, and all-cause mortality. Prespecified substudies include 24-h ambulatory blood pressure monitoring, albuminuria progression, changes in cognitive function, and pharmacokinetic and biomarker analyses. Health economic outcomes and characterization of baseline lifestyle risk factors also will be assessed. The study began in December 2008 and is expected to be completed in October 2012 or until 1,500 primary end points have occurred to achieve 90% power to detect a 15.5% reduction in the primary end point. The median treatment duration is anticipated to be 2.75 years [45].

The SOLID-TIMI 52 trial will include 11,500 patients with an acute coronary syndrome. This study is currently recruiting participants and will test whether darapladib (160 mg per day) can safely lower the chances of having a cardiovascular event (such as a heart attack or stroke) when treatment is started within 30 days after an acute coronary syndrome. The primary outcome measures of the study are time to the first occurrence of any component of the composite of MACE, i.e. cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. The study began in December 2009 and is expected to be completed in April 2014 [46].
4. NON-SELECTIVE REDUCTION OF LP-PLA2 LEVELS BY CARDIOVASCULAR DRUGS

The clinical evaluation of the efficacy of selective inhibitors of LP-PLA2, in reducing adverse cardiovascular events and death is currently in progress in 2 clinical trials and the first results are expected end of 2012. Currently, the knowledge of the effect on plasma LP-PLA2 levels of drugs commonly used in daily clinical practice for the prevention or treatment of CVD, may help clinicians to design the most effective therapeutic strategy for the prevention and treatment of atherosclerotic disease. In this regard, it should be noted that the main factors that affect the LP-PLA2 levels in plasma and alter the distribution of LP-PLA2 among plasma lipoproteins are abnormalities in lipoprotein metabolism such as those observed in various types of primary or secondary dyslipidemias [47,48]. Thus the main cardiovascular drugs that significantly reduce the plasma LP-PLA2 levels are those affecting lipid metabolism, primarily the various hypolipidemic drugs, i.e. statins (atorvastatin, rosuvastatin, fluvastatin), fenofibrate, ezetimibe, niacin or their combination [49-55]. All these drugs reduce LP-PLA2 in plasma mainly by decreasing the LP-PLA2 levels associated with apoB-containing lipoprotein particles, suggesting that the rate of LDL removal from the circulation may represent the main mechanism by which hypolipidemic drugs reduce plasma LP-PLA2 activity. This is also supported by the positive correlation observed between the reduction of plasma LDL-C levels and that of plasma LP-PLA2 activity or mass [48-51]. However, other mechanisms that may contribute to reduction in plasma LP-PLA2 induced by hypolipidemic drugs may not be excluded. Especially the effect of fibrates in patients with elevated triglyceride levels may also be mediated through reduction in triglyceride-rich lipoproteins (VLDL + IDL) as well as by inducing a shift from small, dense LDL particles to larger LDL particles [49,54]. In this regard it should be noted that fenofibrate therapy in Type IIB and Type IV patients significantly increased the HDL-associated LP-PLA2 due to the increase in enzyme activity associated with the HDL-3c subclass [49], an effect that is not observed in patients treated with statins [48,51]. In view of various studies showing that the HDL-associated LP-PLA2 may contribute to the antatherogenic and cardioprotective effects of HDL, the above fenofibrate effect may represent an important drug effect in improving the HDL functionality [49,51].

The non selective reduction of circulating LP-PLA2 activity by lipid lowering drugs can be further potentiated by darapladib which induces a dose-dependent inhibition in LP-PLA2 activity when added to intensive statin therapy [38]. This suggests that darapladib exerts a synergistic effect with lipid lowering drugs on circulating LP-PLA2 activity. The significance of this effect in the clinical practice remains to be established. In this regard, the clinical benefits of darapladib are postulated to be mainly related to inhibition of LP-PLA2 activity within atheroma. Thus it remains to be further established whether the combination of a lipid lowering drug with darapladib could have a synergistic effect in reducing LP-PLA2 activity within atherosclerotic plaque lesions.

5. CONCLUSIONS AND FUTURE PERSPECTIVES

The persistent residual risk of recurrent adverse cardiovascular events despite evidence-based standard-of-care therapies has prompted intense research into novel approaches aimed at reducing atherosclerotic burden, particularly vulnerable atherosclerotic plaques. Epidemiological studies support an association between plasma LP-PLA2 activity and mass levels and the risk of occlusive coronary and vascular events. A large body of research suggests that LP-PLA2 may increase the instability of atherosclerotic plaques by promoting inflammation and formation of a necrotic core. Although lipid-lowering agents non-specifically reduce circulating levels of LP-PLA2, this may not correlate with significant reductions in residual cardiovascular events.

As the main pool of LP-PLA2 is found within atherosclerotic plaque lesions, more direct targeting by pharmacologic agents may be necessary. The results of the phase 2 clinical studies are promising concerning the efficacy of the selective LP-PLA2 inhibitor darapladib in attenuating vascular inflammation and progression to high-risk lesions, which are the pathologic substrate for acute coronary syndromes, and ischemic stroke, without affecting plasma lipid levels. The phase 3 clinical trials STABILITY and SOLID-TIMI 52, which are currently in progress, will determine whether inhibition of LP-PLA2 activity with darapladib safely reduces adverse cardiovascular events and death.

CONFLICT OF INTEREST STATEMENT

The author has no conflicts of interest related to this publication.

FUNDING

This work received no specific grant support from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES


Rosenson RS. Fenofibrate reduces lipoprotein associated phospholipase A2 mass and oxidative lipids in hypertriglyceridemic subjects with the metabolic syndrome. Am Heart J 2008; 155: 499. e9-e16.