Lp-PLA$_2$ ¿Why does it matter?

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Despite continued progress in the field of coronary artery disease (CAD), cardiovascular events remain high, and heart disease is still the leading cause of death among Americans[1]. The *PROVE IT-TIMI 22* trial found that despite high dose statin therapy, patients had a 22.4% residual risk for death or major adverse cardiovascular events in the two years after an acute coronary syndrome[2]. In the Treating to New Targets trial, patients with stable coronary artery disease treated with intense statin therapy still had an 8.7% residual risk of a major adverse cardiovascular event within 4 years[3,4]. Consequently, new therapies are needed to augment the current standard of care if progress is to be made.

Lp-PLA$_2$

Lipoprotein-associated Phospholipase A$_2$ (Lp-PLA$_2$) is an enzyme produced and secreted by many cells of the immune system (monocytes, macrophages, T-lymphocytes and mast cells)[5]. In humans, 80% of Lp-PLA$_2$ in plasma circulates bound to the c-terminus of ApoB in low density lipoprotein (LDL) fragments. The remaining fraction circulates bound to high density lipoprotein (HDL) or is produced locally at the site of inflammation[6]. After LDL is oxidized at a site of inflammation such as a neointimal plaque, Lp-PLA$_2$ cleaves it into two inflammatory mediators, lysophosphatidylcholine (Lyso-PC) and oxidized nonesterified fatty acids (oxNEFAs)[5]. It has a particular affinity for small, dense LDL fragments that are believed to be more highly pathogenic[7].

Lp-PLA$_2$ AND VULNERABLE PLAQUES

Lp-PLA$_2$ has been shown to be highly upregulated in vulnerable and ruptured plaques, with significantly lower levels of expression in stable plaques[8,9]. Lp-PLA$_2$ may contribute to as well as be a marker for plaque instability[10]. Both of its products, Lyso-PC and oxNEFAs, are chemoattractants for macrophages, and Lyso-PC has been shown to induce the apoptosis of macrophages in a plaque[9]. The Lp-PLA$_2$ on LDL particles that enter a developing plaque produce Lyso-PC, which recruits macrophages to the site. These migrating macrophages then produce and secrete additional Lp-PLA$_2$ before being induced to apoptose by Lyso-PC. The resultant positive feedback loop may drive the progression and expansion of the necrotic core and thinning of the fibrous cap (**Figure 1**)[11].

Lp-PLA$_2$ and Lyso-PC also contribute to atherosclerosis through the induction of endothelial dysfunction. Lyso-PC causes an increase in oxidative stress, downregulation of endothelial nitric oxide synthase, and decreased endothelial cell migration to sites of damage[12].

Lp-PLA$_2$ AND CARDIOVASCULAR DISEASE

Lp-PLA$_2$ has been shown to be a reliable marker of increased risk for cardiovascular events. A meta-analysis of 32 studies showed that Lp-PLA$_2$ mass and activity were associated with increased risk of coronary heart disease, ischemic stroke, and vascular mortality independent of conventional risk factors and hs-CRP[13]. The West of Scotland Coronary Prevention Study (*WOSCOPS*) found plasma Lp-PLA$_2$ mass to be independently associated with a doubling of risk of nonfatal MI, death from coronary heart disease, or need for revascularization in patients with established coronary heart disease[14]. In patients with LDL levels <130 mg/dL in the Atherosclerosis Risk in Communities (ARIC) study, elevated plasma Lp-PLA$_2$ mass was associated with a higher incidence of cardiovascular events[15]. The *PROVE-IT* study showed that Lp-PLA$_2$ activity at 30 days after ACS is associated with an increased risk of cardiovascular events independent of hs-CRP and LDL[16]. Lp-PLA$_2$ expression above median in carotid plaques was linked to a three-fold increase in risk for cardiovascular events (**Figure 2**)[17].

DARAPLADIB

Darapladib is a selective, reversible, potent, competitive inhibitor of Lp-PLA$_2$ that has been shown to reduce Lp-PLA$_2$ activity up to 95% in a dose-dependent manner[18]. Darapladib also remains effective as an adjunct to current lipid lowering therapies. Even

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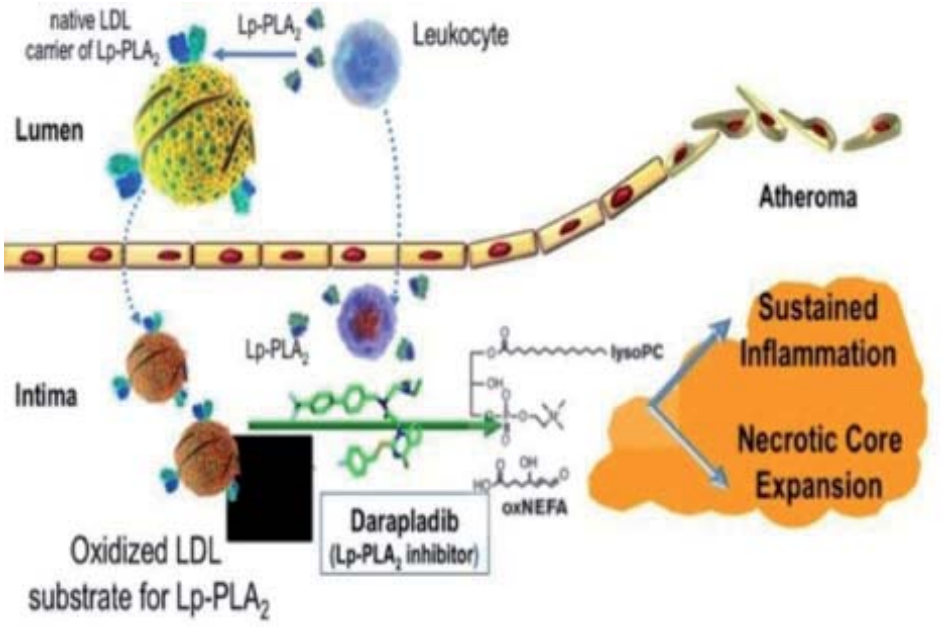

Figura 1. *Targeting Lp-PLA2, a hey player in atherosclerosis*. Progression and expansion of the necrotic core. Lp-PLA$_2$ is carried into plaques by LDL particles, where it breaks down LDL into Lyso-PC and oxNEFAs, which promote inflammation and apoptosis and contribute to the formation of the necrotic core and thinning of the fibrous cap. (Adapted from Zalewski and Macphee. ATVB.2005)

in the presence of intensive statin therapy, darapladib reduced Lp-PLA$_2$ activity by 66% at the 160 mg/day dose (**Figure 3**)[19].

Inhibition of Lp-PLA$_2$ has been shown to limit plaque development and improve patient outcomes. In diabetic, high cholesterol swine, darapladib reduced the progress of atherosclerosis[10]. The Integrated Biomarkers and Imaging Study (*IBIS-2*) showed that darapladib use resulted in a 50% reduction in Lp-PLA$_2$ activity and halted the expansion of the necrotic core. In the placebo group, the necrotic core continued to expand despite adherence to standard of care (**Figure 4**)[20].

Two ongoing trials have been designed to further investigate darapladib and its therapeutic potential. The Stabilization of Atherosclerotic Plaque by Inhibition of Darapladib Therapy Trial (*STABILITY*) is a phase III, multicenter, randomized, double-blind, placebo controlled study of darapladib vs. placebo in patients with chronic CAD. It is intended to test whether darapladib reduces the risk of death by cardiovascular event, nonfatal MI, or nonfatal stroke. *STABILITY* has a target enrollment of 15,500 patients and an expected follow-up of 3 years[21].

The Stabilization of Plaques Using Darapladib Trial

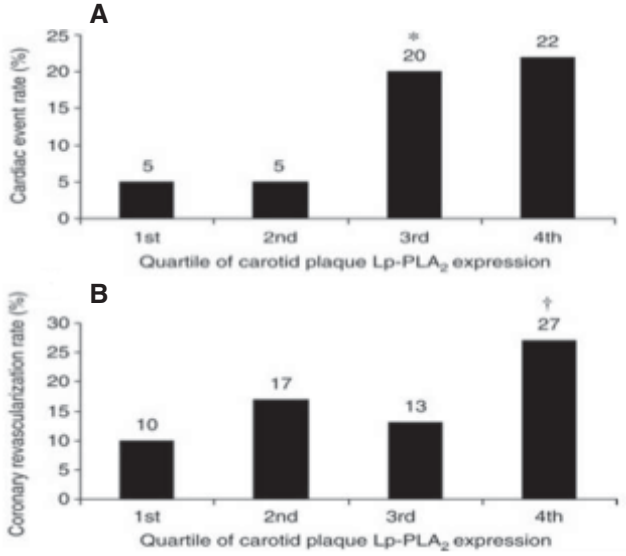

Figure 2. *Carotid Lp-PLA$_2$ expression and CV Outcomes*. Carotid plaque expression of Lp-PLA$_2$, above the median linked to 3-fold increase in cardiac event rate (A), and increased rate of revscularization (B). (Herrmann, J. et al. Eur Heart J 2009;30:2930)

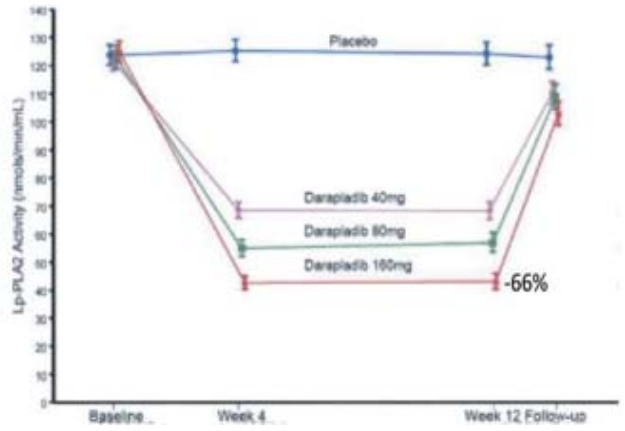

Figura 3. *Effect of Darapladib on Lp-PLA$_2$ activity in patients with stable coronary heart disease.* Darapladib significantly reduces Lp-PLA$_2$ activity as an adjunct to current intensive statin therapies. Darapladib 160 mg dose reduced Lp-PLA$_2$ activity by 66% when used in conjunction with statin therapy. (Mohler ER, et al. JACC 2008; 51: 1632-1641)

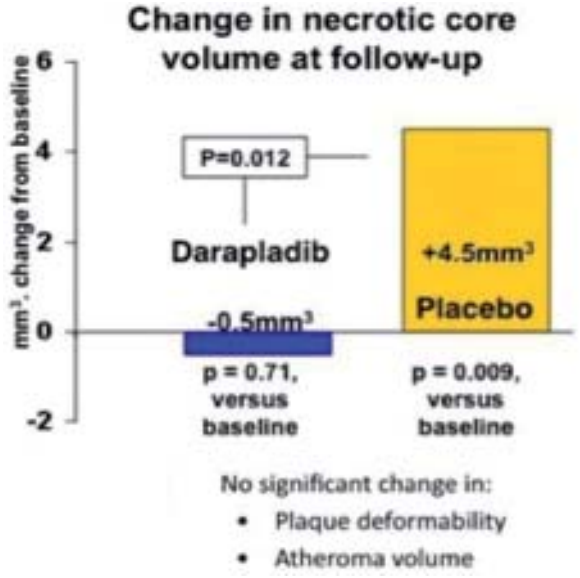

Figura 4. *IBIS-2 Results. Change in necrotic core volume at follow-up.* Results from the Integrated Biomarkers and Imaging Study (IBIS-2). IBIS-2 showed that darapladib halted the expansion of the necrotic core. In the lacebo group, necrotic core continued to expand. (Serruys PW, et al. Circulation 2008)

(*SOLID-TIMI 52*) is designed to investigate a higher risk group that STABILITY. Instead of patients with stable CAD, it is studying the therapeutic utility of darapladib when started within 30 days of an ACS. It is also a Phase III, multicenter, randomized, double-blind, placebo controlled study of darapladib vs placebo. SOLID has a target enrollment of 11,500 patients and a median follow-up of 3 years[22].

POSSIBLE ATHEROPROTECTIVE EFFECTS OF Lp-PLA$_2$

When first discovered, Lp-PLA$_2$ was described as an atheroprotective factor. Subsequent studies suggest that the pro-atherothrombotic effects outweigh any possibly atheroprotective abilities, but some controversy remains. Lp-PLA$_2$ was initially discovered and described as Platelet Activating Factor Acetylhydrolase (PAF-AH) because of its ability to degrade PAF *in vitro.* This effect, however, has not been shown to persist *in vivo*[20]. Initial studies of groups with missense mutations in the Lp-PLA$_2$ gene that result in reduced expression have yielded mixed results. The first two studies found a higher prevalence of cardiovascular disease in carriers of the mutation, but a larger, more recent study with greater power found no evidence of increased risk[18,23]. STABILITY and SOLID should provide more insight into the role of Lp-PLA$_2$ and the potential therapeutic benefit of its inhibition by darapladib.

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He swallowed a lot of wisdom, but it seemed as if all of it had gone down the wrong way. LICHTENBERG