

## Editorial

# Is There a Role for Phospholipases in the Prevention of Cardiovascular Disease?

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Phospholipases, such as Secretary Phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) and Lipoprotein-associated Phospholipase A2 (Lp-PLA<sub>2</sub>), have been linked to atherosclerosis which plays an integral part in the pathophysiology of cardiovascular disease (CVD) [1]. Atherosclerosis, through its progress in the vessel wall, can lead to various clinical manifestations depending on the affected vessel, including acute coronary syndromes, stroke and peripheral artery disease. Lp-PLA<sub>2</sub> and sPLA<sub>2</sub> serve as markers of vascular inflammation, and seem to play an important role in the initiation and progression of cardiovascular diseases. Recent research has shown that direct pharmacological inhibition of Lp-PLA<sub>2</sub> activity exerts beneficiary effects on the atherosclerotic process, implying that a novel target for therapeutic intervention of CVD could be achieved.

Lp-PLA<sub>2</sub> and sPLA<sub>2</sub> belong to the same family of phospholipases, enzymes that catalyze the hydrolysis of phospholipids to produce free fatty acids and lysophospholipids. Lp-PLA<sub>2</sub>, formerly known as platelet-activating factor acetylhydrolase (PAF-AH), is produced by inflammatory cells that are involved in the process of atherogenesis [2-4]. Lp-PLA<sub>2</sub> resides mainly on LDL-cholesterol; it plays an active role in the oxidation of LDL [5] and reacts with oxidative modified phosphatidylcholine to generate oxidized fatty acids (OxFA) and lysophosphatidylcholine (Lyso-PC) that exert many pro inflammatory actions [6]. Lp-PLA<sub>2</sub> is found inside the atherosclerotic plaque and its concentration increases as the plaque grows in size [7-9]. Lp-PLA<sub>2</sub> mass or activity serve as vascular inflammation biomarkers and have been linked to increased cardiovascular risk [10]. Secretary Phospholipase A2 (sPLA<sub>2</sub>) is produced from macrophages and arterial wall smooth muscle cells, its levels being determined by other markers of inflammation, such as interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α). It has been shown to contribute to the pathogenesis of various inflammatory diseases [11], as well as coronary artery disease in correlation with increased CRP levels [12]. Patients with high levels of sPLA<sub>2</sub> have an increased probability of developing acute coronary events since sPLA<sub>2</sub> seems to play an important role in coronary artery spasm [13].

The enzymes of the phospholipase super family and their connection with CVD have been studied in many population-based studies. Serum levels of sPLA<sub>2</sub> have been found to be increased in cases of fatal or nonfatal CAD among 3,314 apparently healthy men and women [14]. Also, sPLA<sub>2</sub>-IIa levels have prognostic value in patients after an acute myocardial infarction, since a cut-off level of 360ng/dl for sPLA<sub>2</sub>-IIa is linked to a higher prevalence of death and readmission for heart failure [15]. LpPLA<sub>2</sub> levels have also been found to confer additive prognostic value in the prediction of future cardiovascular events in patients with hyperlipidemia [16] and in apparently healthy middle-aged individuals [17-21].

Estimation of cardiovascular risk is a challenging process and it has been shown that traditional risk factors are not enough to predict future adverse events [22]. Since several studies have demonstrated an additive prognostic value for LpPLA<sub>2</sub> to classic atherosclerotic risk estimation, there have been efforts to incorporate LpPLA<sub>2</sub> measurements in multi marker panels. In order to improve the prognostic value for cardiovascular events the combination of various biomarkers has been proposed, either in hospitalized patients with acute coronary syndrome [23] or in patients with stable coronary artery disease [24-26] in order to facilitate optimal management. The Adult Treatment Panel III (ATP III) scientific board proposes measurement of Lp-PLA<sub>2</sub> levels, not as a routine screening test, but as an additive test in patients with family history of coronary heart disease and relatively normal lipid values or patients that show a combination of risk factors that places them just below current guideline cut-off levels for treatment.

PLA<sub>2</sub> inhibitors are designed to target vascular inflammation. These medications have shown positive results in subclinical indices of atherosclerosis. Varespladib, an inhibitor of sPLA<sub>2</sub>, has been tested for its potential anti atherogenic properties [27]; in patients with coronary artery disease, Varespladib reduces LDL-cholesterol levels [28]. A study in progress, FRANCIS-ACS [29], is a phase III trial designed to test the use of Varespladib in patients with acute coronary syndrome and the results will enlighten our knowledge regarding this potential useful medication.

Lp-PLA<sub>2</sub> levels can be reduced with the use of hypolipidemic drugs, such as statins and fibrates [30,31]. Darapladib is a novel medication that acts as an Lp-PLA<sub>2</sub> inhibitor and reduces lysophosphatidylcholine content in the atherosclerotic plaque in animal models [32]. In humans, administration of Darapladib decreases Lp-PLA<sub>2</sub> activity and markers of inflammation [33] and it has been shown to prevent the expansion of the necrotic core in coronary lesions [34]. However, in the STABILITY Trial (Stabilization of Atherosclerotic plaque By Initiation of Darapladib Therapy) Darapladib administration, when added to standard of care, did not significantly reduce the risk of the primary composite end point of cardiovascular death, myocardial infarction, or stroke in 7,924 patients with stable coronary heart

disease [35]. Furthermore, the recently announced results of the SOLID - TIMI 52 Trial (Stabilization Of plaques using Darapladib - Thrombolysis in Myocardial Infarction 52) [36] were negative in reducing the time to the first occurrence of major coronary events with administration of Darapladib in the setting of an acute coronary event.

In conclusion, the need for better cardiovascular risk prediction and the possibility of pharmaceutical intervention in the field of phospholipases, in order to offer a more focused therapy, has not shown promising results yet. Research in this field is, however, ongoing and novel biomarkers and treatment medications may emerge, allowing us to optimally manage CVD patients in the future.

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