Secretory Phospholipase A2 and Lipoprotein-Associated Phospholipase A2 as Biomarkers of Cardiovascular Disease and Therapeutic Targets

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Atherosclerosis is not only a lipid-driven disease but it is an intricate process that also involves the simultaneous and combined effect of inflammatory and immunological factors. A substantial body of peer-reviewed studies has validated the cardiovascular risk predictive value of a variety of inflammatory markers including two members of the phospholipase A2 (PLA2) superfamily, the type IIA secretory PLA2 (sPLA2) and the lipoprotein-associated phospholipase A2 (Lp-PLA2). In animal, pathological and epidemiological studies, the increased levels of these two PLA2 have been related to an increase in complex coronary artery lesions and an increase in major cardiovascular clinical events. Therefore, inhibition of these enzymes has become the focus of research in the last decennium. Novel pharmacological inhibitors of those enzymes emerge as promising therapeutical options for treating patients with coronary artery disease (CAD).

The type IIA secretory PLA2 (sPLA2) is a Ca²⁺-dependent enzyme expressed in hepatocytes, macrophages, platelets, and vascular smooth muscle cells. The catalytic function of this enzyme is related to the hydrolysis of the sn-2 acyl group of glycerophospholipids with further liberation of fatty acids and lysophospholipids, all playing an important role in the biosynthesis of lipid mediators such as platelet activating factor (PAF), leukotrienes, prostaglandins, and eicosanoids. Possible atherogenic mechanisms of sPLA2 include its effects on lipoproteins, which results in the release of various lipid mediators at the site of lipoprotein retention in the arterial wall that in turn may trigger local inflammatory cellular responses. Furthermore, in arterial tissue, sPLA2 may also directly modify LDL particles to become more atherogenic and may increase the affinity of apolipoprotein B-100 on LDL to glycosaminoglycans and proteoglycans. sPLA2 is also implicated in the production of isoprostanes which exhibit strong mitogenic activity and induce platelet aggregation and vasoconstriction. High sPLA2 concentrations may predict CAD events in patients with stable coronary artery disease and unstable angina, and all-cause mortality in patients with acute myocardial infarction. Raised sPLA2 concentration and activity is also associated with increased risk of incident CAD events in apparently healthy men and women. Recently it was also shown that sPLA2 mass and activity, may be predictive of secondary cardiovascular events in patients with CAD.

It is well established that substituted indoles, 6,7-benzoindoles and indolizines are potent inhibitors of sPLA2. Among them varespladib methyl (1-H-indole-3-glyoxamide; A-002; Anthera Pharmaceuticals, San Mateo, CA) is an oral selective sPLA2 inhibitor. The effect of this inhibitor on enzyme concentration and on plasma...
lipoproteins in patients with stable CAD was evaluated in the PLASMA IV (Phospholipase Levels and Serological Markers of Atherosclerosis) study, a Phase II, randomized, double-blind, placebo controlled parallel arm dose-response study. A total of 393 patients were randomly assigned to receive either placebo (n=79) or one of four doses of A-002; 50 mg [n=79], 100 mg [n=80], 250 mg [n=78], or 500 mg [n=77] twice daily, for 8 weeks. The primary endpoint was the change in sPLA2 concentration or activity from baseline to week 8. Mean sPLA2 concentration fell by 86.7% in the overall active treatment group and by 48% in the placebo group (p <0.0001). The reductions in sPLA2 concentration in the A-002 groups were greater compared with placebo (P <0.001 at week 12). In the IBIS-2 (Integrated Biomarkers and Imaging Study-2) trial, a multicenter, randomized, double-blind, placebo-controlled study in 330 patients with angiographically confirmed CAD, darapladib halted the increase in the necrotic core volume compared with placebo without affecting total atheroma volume. Lp-PLA2 inhibition may represent a new approach for the treatment of atherosclerosis, however, the benefit of this intervention need to be established by on-going event-driven outcomes trials such as the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial.

**SUGGESTED BIBLIOGRAPHY**


15. STABILITY trial: [http://www.vigour.ualberta.ca/nav02.cfm?nav02=85287&nav01=58271](http://www.vigour.ualberta.ca/nav02.cfm?nav02=85287&nav01=58271)