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EDITORIAL COMMENT

Lipoprotein-Associated Phospholipase A_2 and Aortic Stenosis

Biomarker or New Target for an Old Foe?*

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These are certain signs to know
Faithful friend from flattering foe…
—William Shakespeare, Sonnets to Sundry Notes of Music. VI (1)

There has been great progress in treatment of aortic stenosis, with development of prosthetic, bioprosthetic, and percutaneous prosthetic valves. A medical treatment for aortic stenosis, however, remains elusive.

In these comments, we consider 2 questions. In addition to being a biomarker, is lipoprotein-associated phospholipase A2 ($LpPLA_2$) a promising target to slow progression of aortic stenosis? In light of evidence that inhibitors of $LpPLA_2$ are ineffective in acute coronary syndrome or stable ischemic heart disease, what makes aortic stenosis a more promising target?

Analysis of a subgroup of the prospective, randomized PROGRESSA (Metabolic Determinants Of The Progression Of Aortic Stenosis) study (2) suggests that, in patients with mild (but not moderate/severe) aortic stenosis, plasma $LpPLA_2$ activity is predictive of rate of progression of aortic stenosis. One implication of the finding is that $LpPLA_2$ may be useful as a predictor of patients that may be at greatest risk of developing severe aortic stenosis, and therefore may be appropriate for an experimental treatment. Another implication, which is not as well founded, is that $LpPLA_2$ may be a therapeutic target in patients with mild aortic stenosis. This latter possibility can be viewed as high risk/high gain.

An appropriate question relates to biologic plausibility: is $LpPLA_2$ involved in development and progression of aortic stenosis? If so, it is an attractive target for treatment. If not, its potential role is limited to a biomarker.

LpPLA$_2$ AS A BIOMARKER

The West of Scotland Coronary Prevention Study Group suggested that $LpPLA_2$ is associated with atherosclerotic vascular disease (3). $LpPLA_2$ is an enzyme expressed by inflammatory cells in atherosclerotic plaques, and is found in the circulation bound to low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol, and lipoprotein(a) (4).

The possibility that $LpPLA_2$ might be causally related to atherosclerosis, and perhaps unstable plaques, was supported by treatment with an $LpPLA_2$ in a porcine experimental model (5). Because lysophospholipids are chemoattractants, an inhibitor of $LpPLA_2$ might be protective. On the other hand, because $LpPLA_2$ may be protective, by converting a toxic phospholipid to a lysophospholipid, an inhibitor of $LpPLA_2$ may be harmful. Several trials indicate that $LpPLA_2$ is a disappointing target for treatment of acute coronary syndrome and stable ischemic heart disease (6–8).

In the STABILITY trial, darapladib (an inhibitor of Lp-PLA2) failed to reduce the risk of death, myocardial infarction, or stroke in patients with stable coronary artery disease (6). Similarly, in the SOLID-TIMI 52 trial, darapladib failed to reduce the risk of major coronary events in patients with recent acute coronary syndrome (7). In the VISTA-16 trial, varespladib, an inhibitor of secretory Lp-PLA2, increased the risk of myocardial infarction in patients with recent acute coronary syndrome, leading to early termination of the trial (8). The failure of these inhibitors to improve cardiovascular outcomes reflects gaps in our knowledge of the pathobiology of Lp-PLA2.

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LpPLA$_2$ IN AORTIC STENOSIS

In this issue of *iJACC*, Capoulade et al. (2) report that higher plasma Lp-PLA$_2$ activity is associated with more rapid progression of aortic stenosis, as measured by Doppler echocardiography (**Figure 1**). This effect was noted only in the subset of patients with mild stenosis (defined as peak aortic jet velocity <3.0 m/s) at baseline. Thus, Lp-PLA$_2$ was a marker of progression of aortic stenosis, and the authors suggested that it should be considered as a target for clinical trials in patients with mild aortic stenosis.

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In light of failure of several trials in relation to coronary heart disease, why is there reason to suggest that aortic stenosis may be more amenable to reduction of LpPLA$_2$? There are several differences between blood vessels and the aortic valve (2,9), which may predict a different role for LpPLA$_2$. The differences between blood vessels and the aortic valve reduce the predictive value of trials in vascular disease.

The authors focus on calcification of the aortic valve as the predominant mechanism for stenosis. This assumption is far from conclusive. In patients, calcification may not be associated with severity of aortic stenosis (10). We have suggested that the term "fibrocalcific aortic valve stenosis" may be more accurate than calcific aortic stenosis (11), because it is not clear whether fibrosis and/or calcification are predominant mechanisms of stenosis.

MEDICAL TREATMENT OF AORTIC STENOSIS

An important question is that, because no medical treatment has been effective in slowing progression of aortic stenosis, is treatment possible? It is of interest, and not surprising, that levels of LpPLA$_2$ are associated with slower progression only in mild, but not moderate/severe, aortic stenosis. Capoulade et al. (2) speculate that early aortic stenosis is lipid-mediated, and therefore associated with LpPLA$_2$, and more advanced aortic stenosis is associated with calcification, and therefore is not associated with LpPLA$_2$.

In light of efficacy of "statins" in treatment of atherosclerotic coronary disease, why are statins ineffective in slowing progression of aortic stenosis (11)? One possibility is that trials of statins in aortic stenosis have targeted patients with moderate/severe stenosis, and not mild stenosis. Another explanation may involve consequences of reduction of LDL in unstable plaques in blood vessels, versus effects on the aortic valve. In unstable plaques, reduction of LDL with statins results in reduction of lipids and inflammatory cells, with replacement by fibrous tissue (and perhaps calcium). These changes in composition of the vessel reduce the risk of plaque rupture. Similar structural changes may occur in the aortic valve: reduction of LDL may reduce lipids and inflammatory cells, with replacement by fibrous tissue.

A key point is that functional consequences of these tissue changes may differ profoundly: fibrosis probably is protective in the unstable plaque, but harmful in the aortic valve. We do not know whether these observations and speculation are pertinent

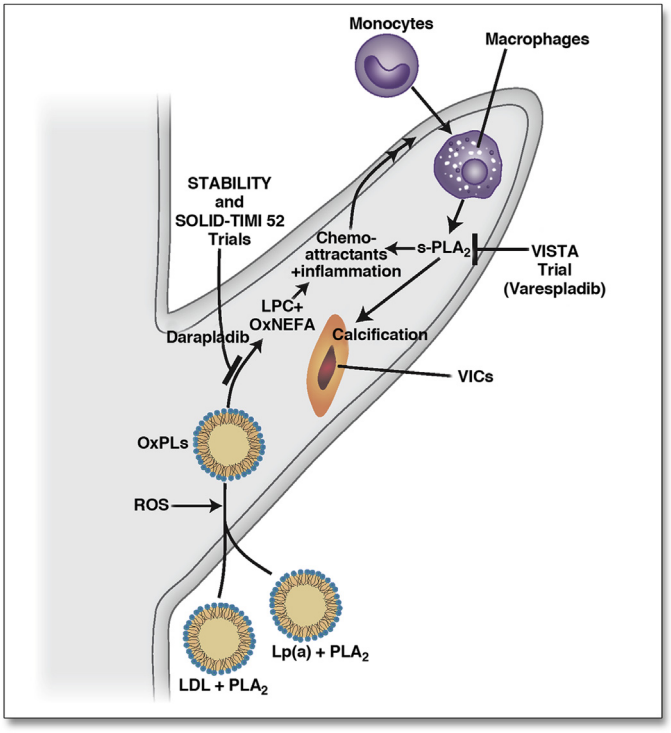

FIGURE 1 Schematic of a Leaflet of the Aortic Valve

Lipoprotein-associated phospholipase A2 (Lp-PLA$_2$) is an enzyme that is expressed by inflammatory cells. LpPLA$_2$ is carried in the circulation predominately bound to low-density lipoprotein (LDL)+PLA$_2$ and to Lp(a)[Lp(a)+PLA$_2$]. LDL and Lp(a) undergo oxidation by reactive oxygen species (ROS) in the aortic valve. These oxidized phospholipids (OxPLs) are subsequently converted to lysophosphatidylcholine (LPC) and oxidized nonesterified fatty acids (OxNEFA), both of which are chemoattractants that recruit monocytes to the valve. Activated monocytes/macrophages release secretory phospholipase A2 (s-PLA$_2$), which promotes further breakdown of OxPLs to chemoattractants. LPC is also a stimulus for calcification of valve interstitial cells (VICS). The figure shows targets of darapladib, an Lp-PLA$_2$ inhibitor used in the SOLID-TIMI 52 and STABILITY trials, and varespladib (s-PLA$_2$ inhibitor), used in the VISTA-16 trial. Lp(a) = lipoprotein(a); SOLID-TIMI 52 = The Stabilization Of plaques using Darapladib-Thrombolysis In Myocardial Infarction 52; STABILITY = Stabilization of Atherosclerotic plaque by initiation of darapladib therapy; VISTA-16 = Vascular Inflammation Suppression to Treat Acute coronary syndrome-16.

to the association of $LpPLA_2$ with progression of aortic stenosis. It is challenging to identify a specific mechanism that may explain failure of treatment with $LpPLA_2$ in acute coronary syndrome and stable ischemic heart disease versus prediction of efficacy of treatment in aortic stenosis.

CONCLUSIONS

It seems premature to consign Lp-PLA_2 as a target for fibrocalcific aortic valve stenosis, especially keeping in mind the results of the VISTA-16 trial, which showed an increased incidence of myocardial infarction. One would be reluctant to treat patients with a secretory phospholipase A_2 inhibitor (varespladib), with the goal of slowing progression of aortic stenosis but with the possibility of increasing the risk of myocardial infarction (7). A trial with darapladib to slow progression of aortic stenosis may have fewer safety concerns. Further work is needed to elucidate the role of Lp-PLA_2 in the pathophysiology of aortic stenosis—to establish its role as a biomarker (i.e., a friend with a warning), or a foe with potential as a therapeutic target.

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