Lipid Interventions in Aortic Valvular Disease

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Abstract: Aortic valve stenosis is the most common valvular disease in the elderly population. Presently, there is increasing evidence that aortic stenosis (AS) is an active process of lipid deposition, inflammation, fibrosis and calcium deposition. The pathogenesis of AS shares many similarities to that of atherosclerosis; therefore, it was hypothesized that certain lipid interventions could prevent or slow the progression of aortic valve stenosis. Despite the early enthusiasm that statins may slow the progression of AS, recent large clinical trials did not consistently demonstrate a decrease in the progression of AS. However, some researchers believe that statins may have a benefit early on in the disease process, where inflammation (and not calcification) is the predominant process, in contrast to severe or advanced AS, where calcification (and not inflammation) predominates. Positron emission tomography using 18F-fluorodeoxyglucose and 18F-sodium fluoride can demonstrate the relative contributions of valvular calcification and inflammation in AS, and thus this method might potentially be useful in providing the answer as to whether lipid interventions at the earlier stages of AS would be more effective in slowing the progression of the disease. Currently, there is a strong interest in recombinant apolipoprotein A-1 Milano and in the development of new pharmacological agents, targeting reduction of lipoprotein (a) levels and possibly reduction of the expression of lipoprotein-associated phospholipase A2, as potential means to slow the progression of aortic valvular stenosis.

Key Indexing Terms: Aortic stenosis; Inflammation; Calcification; Statins; Apolipoprotein A-1 milano; Lipoprotein (a); Lipoprotein-associated phospholipase A2. **[Am J Med Sci 2015;350(4):313–319.]**

Aortic valve stenosis (AVS) is the most common valvular disease in the elderly population.[1] It is a progressive disease of calcification and degeneration of the valve leaflets. Once thought to be due to a passive process of chronic mechanical stress, currently, there is increasing evidence that aortic stenosis (AS) is an active process of lipid deposition, inflammation, fibrosis and calcium deposition.[2] The pathogenesis of AS shares many similarities to that of atherosclerosis. Additionally, AS has been associated with cardiac risk factors, such as diabetes mellitus, elevated low-density lipoprotein (LDL) cholesterol, hypertension, male gender, age and smoking.[3] In some retrospective studies, statins have significantly decreased the progression of AS. Therefore, it was hypothesized that certain lipid interventions could prevent or slow the progression of AVS.

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RATIONALE

There is increasing evidence that atherosclerotic risk factors and inflammation are involved in the pathogenesis of AS. Several longitudinal studies found cardiac risk factors, mainly hypercholesterolemia, to have an impact on the development of degenerative AVS.[4,5] Researchers described an "early lesion" that shared common features with the early lesion of atherosclerotic plaques histologically, suggesting that calcific AS could be an atherosclerotic disease.[5–7] The accumulation of T lymphocytes in stenotic valves indicates that calcific AS might be based on chronic inflammation.[2,5,8] In addition, genetic polymorphisms may have an impact on the development or degree of calcification of stenotic aortic valves.[5,9–11] Once resident on the valves, leukocytes can induce an "inflammatory tissue milieu," followed by the activation of myofibroblasts and increased cell proliferation, mediated by the release of the pro-inflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α).[5,12,13] There is also activation of matrix metalloproteinases, which promote the profound conversion of the valvular tissue.[5,12–15] TNF-α mediates the formation of an osteoblast-like phenotype of local myofibroblasts in stenotic aortic valves, thus suggesting that the development of calcific AS might be based on an inflammatory mechanism.[5,16]

Several clinical trials have demonstrated that HMG-CoA reductase inhibitors reduce the mortality in patients with atherosclerotic diseases, primarily by reducing LDL cholesterol serum levels.[5,17–19] HMG-CoA reductase inhibitors also exhibit actions beyond their cholesterol lowering effect, called "pleiotropic effects," and it has been suggested that these primarily anti-inflammatory effects contribute to the positive results of these clinical trials.[5,20] C-reactive protein (CRP), a clinical marker for inflammation, has been suggested to contribute to the development of atherosclerosis.[21] It has also found to be increased in patients with degenerative aortic valvular stenosis.[22] Statin therapy can significantly reduce serum CRP levels in primary and secondary prevention populations in a large LDL independent manner.[23] Most recently, it has been shown that patients with low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the LDL cholesterol level.[24] These studies suggest that statins are effective in decreasing systemic and vascular inflammation, at least in part, independently from their cholesterol-lowering capacity. The statins' "pleiotropic" effects include antioxidation, improvement of endothelial function, antithrombotic actions, plaque stabilization, reduction of the vascular inflammatory process and modulation of the T-cell activation.[25–27] Statins affect both the risk factors and inflammatory pathways through lowering lipid levels and by their anti-inflammatory properties.

The statins' mechanism of action is the inhibition of HMG-CoA reductase, the rate-limiting microsomal enzyme in cholesterol biosynthesis. The inhibition of the conversion of HMG-CoA to mevalonate eventually results in the decline of plasma LDL.[28] However, the lipid-lowering independent "pleiotropic" effects of the statins are believed to be based

primarily on blocking the synthesis of important isoprenoid intermediates of the cholesterol biosynthetic pathway, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These intermediates control the localization and the function of a variety of intracellular signaling molecules, especially the Rho family of small GTP-binding proteins, which play a crucial role in cytoskeletal remodeling, membrane trafficking, transcriptional activation and rate of cell growth.[29–31]

In vitro studies give evidence that supports the anti-inflammatory role of statins. Administration of these agents in cultured cells, assumed to participate in atherosclerosis and valve calcification, diminishes the pro-inflammatory functions implicated in the development of these states.[5] *In vitro* statins have been shown to decrease pro-inflammatory cytokines TNF-α and IL-1β in endothelial cells and TNF-α in macrophages, whereas inhibiting the proliferation of smooth muscle cells (SMCs) through the inhibition of Rho geranylgeranylation.[5,32] Statins have also been shown to decrease the synthesis of monocyte chemotactic protein-1 (MCP-1) and inhibit the secretion of several matrix metalloproteinases[1–3] from both SMCs and macrophages, mediated by the inhibition of prenylation.[33,34] This may be due to the downregulation of activation of nuclear factor NF-K Beta (NF-κB), activator protein 1 and hypoxia-inducible factor 1-alpha in cultured human endothelial and vascular SMCs. NF-κB regulates the expression of genes involved in mediating cell migration, promoting inflammation and controlling the balance between cell proliferation and apoptosis.[5,35–37] Rho-Like GTPases have been implicated in the activation of NF-κB.[31] The effect of statins on activator protein 1 DNA binding may be mediated by the inhibition of prenylation of the small GTP proteins Ras and Rho.[5,38] All these pathways described are mediated by nonsterol mevalonate-derived compounds.[39] In addition, new mechanisms by which statins may modulate immune response have been described recently. Statins can inhibit the interferon-gamma-induced expression of class II major histocompatibility complexes on antigen-presenting cells. Statins are able to selectively block the beta 2 integrin leukocyte function antigen-1, thereby decreasing lymphocyte adhesion and impairing T-cell costimulation.[28] Statins can also decrease T-cell proliferation, probably through direct engagement of the T-cell receptor.[40] Administration of statins may be able to tackle several inflammatory pathways leading to valve calcification. *In vitro* studies have shown that statins can prevent the progression of cardiovascular calcification. Statins inhibited calcification of human vascular SMCs induced by inflammatory mediator.[41] They also inhibited calcification of aortic myofibroblasts by inhibiting the cholesterol synthetic pathway-independent protein prenylation.[42]

RETROSPECTIVE HUMAN STUDIES

In a retrospective analysis, a stage-related effect of statin treatment on the progression of aortic valve sclerosis/stenosis was demonstrated.[43] One thousand forty-six patients were taken from a database between the years of 1998 and 2007, and of these, 309 patients were treated with statins. Patients with moderate to severe aortic regurgitation, bicuspid aortic valve, rheumatic heart disease and left ventricular ejection fraction lower than 40% were excluded. During a median follow-up of 5.6 years, the progression of AS, as measured by peak aortic jet velocity on transthoracic echocardiography, was slower in those statin-treated patients with aortic sclerosis and mild AS when compared with placebo (aortic sclerosis: $0.04 \pm 0.09\ m \cdot s^{-1} \cdot yr^{-1}$ versus $0.07 \pm 0.10\ m \cdot s^{-1} \cdot yr^{-1}$; mild AS: $0.09 \pm 0.15\ m \cdot s^{-1} \cdot yr^{-1}$ versus $0.15 \pm 0.15\ m \cdot s^{-1} \cdot yr^{-1}$). In contrast, in moderate AS, the progression of AS was not slowed when compared with placebo ($0.21 \pm 0.18\ m \cdot s^{-1} \cdot yr^{-1}$ versus $0.22 \pm 0.15\ m \cdot s^{-1} \cdot yr^{-1}$). The results suggest that statin therapy may be more effective in the early stages of the disease, but once the aortic valve becomes heavily calcified, it is unlikely that LDL reduction with statins will be of benefit.

In another retrospective study, researchers showed a significant correlation between serum LDL levels and the progression of aortic valve calcification and coronary calcification.[44] A total of 104 patients were divided by LDL cholesterol level, either greater than or lower than 3.36 mmol/L (130 mg/dL). Using electron beam tomography to quantify the degree of calcification, the results showed that the degree of aortic valve calcification was significantly lower in patients with LDL level less than 3.36 mmol/L, as compared with those with LDL levels greater than 3.36 mmol/L (mean annual progression of calcification of 9.1 ± 22% versus 43.3 ± 44%, respectively). The strong association demonstrated between LDL cholesterol level and the progression of aortic valve calcification in this study may suggest that lipid-lowering therapy may decrease the progression of aortic valve calcification and aortic sclerosis. Furthermore, it was shown that the degree of progression of coronary calcification also increased with increased LDL cholesterol levels and that, independent of risk factors, the progression of aortic valve calcification was more rapid in patients with a rapid progression of coronary artery calcification.[44] However, this study only assessed aortic valve calcification and no measurements concerning the functional status of aortic valve (peak aortic jet velocity, mean gradient and aortic valve area) were performed.

In another retrospective study, researchers studied the role of positron emission tomography in patients with AS.[45] To demonstrate the relative contributions of valvular calcification and inflammation in AS, they used 2 radioactive tracers, 18F-fluorodeoxyglucose (18F-FDG) and 18F-sodium fluoride (18F-NaF), which exhibit selective uptake in areas of inflammation and calcification. 18F-FDG, which is a glucose analog, is taken up into cells of glucose transport proteins and enters the glycolytic metabolic pathway. After the initial hexokinase step, 18F-FDG-6-phosphate cannot be metabolized further and is trapped within cells that have high metabolic requirements, such as macrophages.[45–47] The plaque macrophage burden correlates to inflammation.[45,47] The other radioactive tracer, 18F-NaF, is selectively taken up into exposed bone crystals (hydroxyapatite) through an exchange mechanism with hydroxyl groups.[45,48,49] It is thought that it can detect areas of novel calcification within atherosclerotic plaques, and thus it was used in this study with AS.[45,46] The study demonstrated that 18F-NaF and 18F-FDG activities were increased in patients with aortic sclerosis and stenosis with a progressive rise in uptake with increasing disease severity.[45] Of importance, calcification rather than inflammation seems to be the predominant process affecting the valve, particularly in the more advanced stages of the disease, in which a more marked progression in 18F-NaF activity was observed that was disproportionate to the 18F-FDG activity. In the early stages of AS, endothelial damage secondary to mechanical stress and lipid deposition triggers an inflammatory response within the valve. There is an increase in macrophages and T cells within the valve leaflets and an increase in the expression of pro-inflammatory cytokines, including growth factor B1, TNF-α and IL-1β. This then triggers the fibrotic and calcific processes that subsequently drive orifice narrowing.[45] This method of identification of the extent of inflammation and calcification in the aortic valve may be actually used in the future to test the hypothesis that lipid interventions may be