Aortic valve stenosis (AS) is the end stage of an active fibrocalkic process with local inflammation, lipid deposition, fibrosis, and calcification as its key features. Adverse remodeling of a stenotic valve includes collagen deposition and elastin degradation, resulting from myofibroblast proliferation and activation, recruitment of inflammatory cells, and expression of proinflammatory cytokines. Activation of local calcific mediators results in massive calcification and even bone formation in the affected leaflets. In addition, oxidative stress is increased and neovascularization occurs in the normally avascular valve tissue. Lipid accumulation and oxidation may further contribute to a proinflammatory impetus toward calcification and ossification. Moreover, valvular myofibroblasts undergo phenotypic transdifferentiation into osteoblastic cells, which spontaneously form calcific nodules, a process accelerated by inflammatory cytokines and oxidized cholesterol. Furthermore, in experimental animal models, hypercholesterolemia increases aortic valve cholesterol content and results in osteoblastic differentiation and bone formation; these adverse changes can be prevented by atorvastatin. Indeed, several experimental and retrospective clinical studies have suggested that statins may retard AS development.

Inspired by these observations and epidemiological studies revealing an association between AS and hypercholesterolemia, several prospective trials of statins in patients with AS have been conducted. The prospective but not randomized Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) trial (n = 121) showed a smaller decline in valve area in AS patients receiving rosuvastatin. However, only patients with elevated serum low-density lipoprotein received the investigational drug. In contrast, 2 prospective randomized lipid-lowering trials both failed to show a decrease in hemodynamic progression of AS or a delay in aortic valve replacements: the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) compared atorvastatin to placebo in 155 patients, and the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial compared simvastatin-ezetimibe therapy to placebo in 1873 patients with mild-to-moderate asymptomatic AS.

Although results from the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial involving 272 AS patients are still awaited, given these rather discouraging negative studies it is reasonable to question the rationale for continuing to investigate lipid-lowering treatments in AS. Particularly given the power and sample size of the randomized SEAS trial, it seems more logical to explore alternative pharmacological approaches. At the same time, we need to consider whether some important information perhaps will remain unnoticed if lipid-lowering trials are abandoned altogether for this disease.

In this issue of Circulation, Miller and colleagues describe a hypercholesterolemic Reversa mouse, which developed aortic valvular changes characteristic for early lesions of human AS during 6 months of hyperlipidemia. These adverse histopathological alterations, including myofibroblast activation, attenuated superoxide levels, deposition of lipids and calcium, and expression of pro-osteogenic proteins, were further accentuated during an additional hypercholesterolemic period of 6 months, along with narrowing of the aortic valve orifice. Importantly, normalization of blood cholesterol levels by a “genetic switch” at 6 months of age reversed adverse valvular changes including lipid deposition and calcification and prevented the reduction of cusp mobility, which would otherwise have led to impairment of valve function. According to these observations, normalization of plasma lipid levels at early stages of aortic valve disease could reverse the disease-initiating cascade of molecular events, possibly halting the progression of AS.

These findings raise an important question. If lipid-lowering therapy has the potential to prevent AS progression, why have results of prospective randomized trials been negative? One possibility is that statin treatment was initiated far too late in the disease course, even though patients with mild and moderate AS were included. In the work by Miller et al., the genetic switch for lipid-lowering was initiated early in the disease process before any hemodynamic changes were present. Thus, their results suggest that lowering of blood lipids should be achieved at a very early stage of the disease, probably at the onset of aortic sclerosis without any transvalvular gradient. Consequently, comparing mice at different stages of valvular changes to determine the “point of no return” of the adverse changes in the valves potentially is of great value. The hypothesis of early lipid-lowering treatment is supported by a recent retrospective echocardiographic database analysis of 1046 patients with aortic sclerosis and mild-to-moderate AS, in which statin treatment was associated with a slower progression of aortic valve disease in
patients with aortic sclerosis and mild AS, but no longer in moderate AS.9

Another possible explanation for negative clinical trials is that only certain periods of disease development are susceptible to modulation by a specific targeted drug intervention. During different phases of AS development, the prevailing cell populations and their state of activation (eg, transdifferentiation of myofibroblasts and activation of pro-osteogenic effectors) in valves may differ temporally as well as locally. Consequently, targeted pharmacological therapy initiated at the stage in which transformation of myofibroblast into bone-forming osteoblastic cells has already occurred and calcification of the valves is in progress may no longer be able to interfere with the pathogenesis of the disease. Indeed, certain histopathological features of AS, such as neovascularization, are more prominent in valves with low or intermediate grades of calcification but are attenuated in the severely calcified end-stage valves.3 Taken together, it is conceivable that despite the decades-long slow progression of AS, a relatively narrow time window exists during which lipid-lowering pharmacotherapy must be initiated to be effective in delaying, or even halting, the progression of valve pathology.

The nonpharmacological lipid-lowering approach in the current study cannot be directly extrapolated to humans and any confounding pleiotropic effects of statins are not addressed by this study. It is still ambiguous what exact molecular effects of statin therapy would be efficient enough to cause clinically relevant tissue changes; histopathological data from the valves of AS patients involved in the large prospective trials to date will be of interest, if available, to determine whether any tissue changes in response to statin therapy can be observed. Accordingly, besides statins, other pharmaceutical tools to alter blood lipid profiles may have a role in the treatment of AS. In a recent hypercholesterolemic rabbit model, infusion of apolipoprotein A-I mimetic peptides resulted in regression of experimental AS including attenuation of valvular calcification.10 These data suggest high-density lipoprotein–based therapies as a potent candidate for AS treatment. It is noteworthy that in the investigations by Miller et al,5 even though aortic valve superoxide levels, myofibroblast activation, valvular calcium burden, and pro-osteogenic signaling were reduced after normalization of blood cholesterol levels, no regression of valvular fibrosis occurred. Because AS involves upregulation of both valvular collagen content and profibrotic mediators,2 failure to interfere with valvular fibrosis offers yet another explanation for the negative results seen in clinical prospective trials of statin therapy. Finally, by reducing the expression of regulators of G protein–mediated signaling proteins, statins augment the activation of extracellular-regulated kinases11 and may thus unfavorably stimulate myofibroblast proliferation in the valves leading to accentuated fibrosis and thickening of the leaflets.

The pathobiology of AS involves a complex interplay between various molecular effectors; the assumption that lipid accumulation is the only focal point of disease pathogenesis is no longer tenable. For example, inhibition of the renin-angiotensin system is a potential target for therapy. Importantly, angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and the profibrotic angiotensin type 1 receptors are present locally in stenotic aortic valves,12 and the expression and enzymatic activity of ACE are augmented in the diseased valves.13 Furthermore, the overall Ang II–forming potential is accentuated in stenotic valves, given that besides ACE, 2 alternative Ang II–forming enzymes, chymase and cathepsin G, are upregulated in the affected valves.2,13 The elevated amounts of Ang II may exert various profibrotic and proinflammatory actions in the valves and also enhance lipid accumulation in the lesions,1,12 whereas the increased activity of ACE and neutral endopeptidase in stenotic valves leads to augmented degradation of the antifibrotic bradykinin, thus shifting the local balance of the fibrotic and antifibrotic systems in the fibrosis-promoting direction. Clinical studies of ACE inhibitors in AS have been discordant. In one retrospective trial, ACE inhibitors were associated with a slower progression of aortic valve calcification,14 whereas another retrospective study failed to show a change in the hemodynamic progression of AS in patients using ACE inhibitor therapy.15 Considering the upregulation of 3 Ang II–forming enzymes in stenotic valves, AT-1R antagonists, which inhibit the effects of Ang II independent of the enzyme responsible for its generation, could be more efficient local effectors in this disease. Interestingly, olmesartan has been shown to reduce aortic valvular atherosclerotic changes and inhibit transdifferentiation of myofibroblasts into osteoblastic cells in hypercholesterolemic rabbits,5 but clinical data on angiotensin type 1 receptor antagonists or neutral endopeptidase inhibitors in AS are unfortunately lacking. Besides offering local valvular protection, pharmacological inhibition of renin-angiotensin system components and reinforcement of the antifibrotic systems may prevent left ventricular hypertrophy and myocardial fibrosis associated with the chronic pressure overload in AS and thus provide myocardial protection for these patients.

Additional potential targets of medical therapy in AS include the pathways of valvular calcification, extracellular matrix remodeling, fibrosis, accumulation and activation of inflammation cells, and neovascularization. Although direct inhibitors for these adverse processes are not currently available, future pharmacological tools may provide targeted approaches to inhibit adverse remodeling and calcification locally in the valve tissue. As distinct from coronary atherosclerosis, calcification accounts for the major clinical manifestations of AS, and massive calcification of aortic valves is related to rapid disease progression and poor patient prognosis.1 Consequently, targeted inhibitors of calcification and ossification that exert their effects only on the aortic valve, not the skeleton, would be a possible favorable future remedy for AS.

Because current evidence suggests that blood lipid-lowering or any pharmacological treatment, if effective overall, should be initiated at early stages of AS, we require more sensitive diagnostic tools that could find AS patients at earlier stages of the disease. Molecular imaging approaches that could sensitively measure local valvular remodeling and tissue changes over time would open novel possibilities for the management of the growing group of patients with valvular diseases. Specifically, direct visualization of the aortic valve and its contents of lipids, calcium, inflammatory...
cells, and collagen in vivo could become a tool for identifying patients with aortic valve disease in its earlier stages and could potentially also separate patients at risk of rapid disease progression, even before any irreversible changes have occurred. Implementation of prospective trials with AS patients has been challenging because AS progresses slowly over decades whereas the duration of clinical trials is generally only a few years. Thus, early identification of patients with quickly progressing disease and high-risk valves would justify a prospective trial of lipid-lowering or other targeted therapy. Furthermore, the importance of early diagnosis is supported by the epidemiological observation that even patients with aortic sclerosis, without valve obstruction, have an increased risk of morbidity and mortality from cardiovascular causes, although the exact etiology of this phenomena remains obscure. Because the rate of AS progression varies greatly between individuals, identification of specific pathobiological markers characteristic for rapid disease progression is a challenge for future research. Identification of these markers, as well as molecular pathways of the disease amenable to pharmacological prevention, requires intense investigations using both experimental models and histopathological specimens obtained from surgically removed aortic valves. Therefore, additional basic research into the pathogenesis of AS is mandatory in order to further define the cellular and molecular pathways that mediate the disease process and to create a ground for future clinical trials exploring either lipid-lowering or other pharmaceutical tools in this disease.

Disclosures

None.

References


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