Calcific Aortic Stenosis — Time to Look More Closely at the Valve

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Calcific aortic stenosis is a progressive disease that results in stiff valve leaflets with eventual obstruction to left ventricular outflow. Once symptoms occur, valve replacement is the only effective treatment, and there are no known therapies to prevent disease progression. However, several lines of evidence suggest that calcific valve disease is not simply due to age-related degeneration but, rather, is an active disease process with identifiable initiating factors, clinical and genetic risk factors, and cellular and molecular pathways that mediate disease progression.

The key initiating factor in the development of calcific aortic stenosis appears to be mechanical stress. Specifically, a congenitally bicuspid valve, which is present in about 0.5 to 0.8% of the population, is the underlying anatomy in the majority of valve replacements for aortic stenosis. Blood-flow dynamics may also play a role, since early lesions are located on the aortic side of the valve in regions with low shear stress.

Clinical factors that are associated with the presence of calcific valve disease include older age, male sex, elevated serum levels of low-density lipoprotein and lipoprotein(a), smoking, hypertension, diabetes, and the metabolic syndrome. The presence of mild valve changes, even in the absence of obstruction to blood flow, is associated with an increase of 50% in the risk of myocardial infarction and death from cardiovascular causes during the next 5 years. Genetic factors are difficult to study in a disease that often is not evident until the sixth or seventh decade of life. However, in a subgroup of families, a bicuspid valve appears to be inherited in an autosomal dominant pattern. In one study in France, familial clustering of calcific disease in trileaflet valves also was shown. Mutations in the signaling and transcriptional regulator NOTCH1 gene have been identified in families with bicuspid aortic valves and leaflet calcification. Case-control studies have suggested an association between calcific aortic stenosis and genetic polymorphisms in the vitamin D receptor, estrogen receptor, apolipoprotein E4, and interleukin-10 alleles.

Our understanding of disease progression at the tissue level is based on human valve studies of either early lesions or end-stage disease, with the assumption that these processes represent the ends of a disease spectrum (Fig. 1). Experimental models support this assumption, with the demonstration that valve lesions occur in the
Figure 1. Disease Progression in Calcific Aortic Stenosis, Showing Changes in Aortic-Valve Histologic Features, Leaflet Opening in Systole, and Doppler Velocities.

In Panel A, the histology of the early lesion is characterized by a subendothelial accumulation of oxidized low-density lipoprotein (LDL), production of angiotensin (Ang) II, and inflammation with T lymphocytes and macrophages. Disease progression occurs by several mechanisms, including local production of proteins, such as osteopontin, osteocalcin, and bone morphogenic protein 2 (BMP-2), which mediate tissue calcification; activation of inflammatory signaling pathways, including tumor necrosis factor α (TNF-α), tumor growth factor β (TGF-β), the complement system, C-reactive protein, and interleukin-1β; and changes in tissue matrix, including the accumulation of tenascin C, and up-regulation of matrix metalloproteinase 2 and alkaline phosphatase activity. In addition, leaflet fibroblasts undergo phenotypic transformation into osteoblasts, regulated by the Wnt3–Lrp5–β catenin signaling pathway. Microscopic accumulations of extracellular calcification (Ca^{2+}) are present early in the disease process, with progressive calcification as the disease progresses and areas of frank bone formation in end-stage disease. The corresponding changes in aortic-valve anatomy are viewed from the aortic side with the valve open in systole (Panel B) and in Doppler aortic-jet velocity (Panel C).
presence of hypercholesterolemia, resulting in leaflet calcification and valve obstruction.\cite{6} Taken together, the association of calcific aortic stenosis with elevated serum lipid levels, the presence of lipid accumulation in the leaflets, and the increased risk of atherosclerotic clinical end points all lead to the hypothesis that lipid-lowering therapy might slow or prevent disease progression. This hypothesis was supported by several retrospective clinical studies indicating slower hemodynamic progression or leaflet calcification in patients who were receiving lipid-lowering medications than in control subjects and by experimental models showing that lipid-lowering therapy blocks the development of valve lesions.\cite{7}

Thus, the results of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study (ClinicalTrials.gov number, NCT00092677) that are reported in this issue of the *Journal* are disappointing. In this large, randomized, prospective clinical trial, Rossebø et al. convincingly show that aggressive lipid lowering does not affect either hemodynamic progression or the time to valve replacement in adults with aortic stenosis.\cite{8} Although it is possible that treatment even earlier in the disease process might have some benefit, the study patients had only mild-to-moderate disease. Other than those with a bicuspid valve or specific genetic markers, earlier identification of patients at risk would be problematic. The reduction in atherosclerotic clinical end points in this study is encouraging. However, the clinical effect was small, given that benefit was primarily due to a reduced rate of coronary bypass grafting at the time of valve replacement.

If intensive lipid-lowering therapy is not the answer to the prevention of aortic stenosis progression, where do we go from here? Many adults with calcific valve disease meet current indications for lipid-lowering therapy, and the SEAS study certainly supports the evaluation and reduction of risk factors in patients with aortic stenosis, as recommended for all adults by established guidelines. However, we can no longer reassure ourselves that either the lipid-lowering or pleiotropic effects of potent agents such as statins and ezetimibe might change the disease process in the valve leaflets. We need to explore other potential therapeutic targets, especially the pathways that lead to tissue calcification. Calcific aortic stenosis is not atherosclerosis. Although there is overlap in clinical risk factors, in tissue characteristics, and in the association between the presence of calcific valve disease and atherosclerotic clinical events, there also are major differences. In aortic valve stenosis, tissue calcification is more severe; the mechanism of clinical events is increased leaflet stiffness, not plaque rupture; and the severity of coronary and valve disease in an individual patient often is discordant.

Demonstrating clinical benefit of potential therapies for calcific aortic stenosis will be challenging. The evaluation of clinical end points requires a large study group, and enrollment in prospective, randomized trials is slow, given the relatively low prevalence of valve disease. Calcific valve disease progresses slowly over decades, whereas clinical trials usually follow patients for only a few years. Clinical end points often are difficult to assess because indications for valve replacement remain somewhat subjective and because therapy may affect other cardiovascular end points, which limits our understanding of the mechanism of benefit. Doppler echocardiography allows assessment of the effect of therapy on the degree of stenosis, but it is not perfect, because hemodynamic obstruction occurs only with a substantial amount of leaflet thickening. The ideal end point for measuring the effect of therapy would be direct evaluation of tissue changes in the valve leaflets. Such analysis is possible in experimental models but in humans is limited to the examination of leaflets removed at the time of valve surgery.\cite{9} Computed tomographic imaging allows measurement of leaflet calcification but not of other tissue components. In the future, molecular imaging approaches may provide sensitive measures of tissue changes sequentially over time, allowing detection of significant differences between small study groups.\cite{10}

It is time to integrate and expand our understanding of the interactions between initiating factors, genetic and clinical cofactors, and the mechanisms of progression from an early inflammatory lesion to phenotypic transformation of valve myofibroblasts and then to the end stage of severe valve calcification. Discovery of an effective medical therapy for calcific aortic stenosis will require innovative approaches to disease prevention and ingenuity in proving the mechanism of benefit.

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Ezetimibe and Cancer — An Uncertain Association

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The randomized clinical trial is considered to be the most reliable tool to assess the efficacy and safety of new drugs. At times, however, randomized trials detect adverse events that are unanticipated and not easily explained on the basis of current knowledge. An unexpected finding of this kind may ultimately prove to be due to chance, but follow-up studies sometimes confirm the adverse drug effect. Particularly when an unexpected finding raises a safety concern with regard to a drug, physicians face uncertainty about how to act on the information.

In this issue of the Journal, we publish the results of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (ClinicalTrials.gov number, NCT00092677), a clinical trial of lipid-lowering therapy that, even before its publication, has generated considerable public attention. In the trial, a combination of simvastatin and ezetimibe was compared with placebo with respect to the incidence of cardiovascular events in older people with aortic-valve stenosis. The treatment had no impact on the progression of aortic stenosis or on cardiovascular clinical events in general, with the exception of coronary-artery bypass surgery, which was performed (usually at the time of aortic-valve replacement) less frequently in the active-treatment group than in the placebo group. There was little uncertainty, however, that the primary end point was null, since the hazard ratio for treatment relative to placebo was 0.96, with a 95% confidence interval (CI) of 0.83 to 1.12.

There was, however, an unexpected finding in the trial. An excess of incident cancers was observed in the simvastatin–ezetimibe group, with 105 in that group as compared with 70 in the placebo group (P=0.01). There was an increase in the incidence of a variety of cancers, including prostate, gastrointestinal, and skin cancers. Also, deaths from cancer were more frequent in the active-treatment group (39 deaths, vs. 23 in the placebo group), although the difference achieved only borderline statistical significance (P=0.05).

The SEAS investigators suggested that the difference in incident cancers could have occurred by chance but acknowledged that the unanticipated findings should be pursued through additional studies. Using existing data, the Clinical Trial Service Unit and Epidemiological Studies Unit at Oxford University were able to undertake such a study. The researchers had access to interim cancer data in two large ongoing clinical trials, the Study of Heart and Renal Protection (SHARP) (NCT00125593) and the Improved Reduction of