Degenerative aortic stenosis is the valve lesion in which our understanding of pathophysiology is most advanced. Degenerative changes in the aortic valve increase with age but do not inexorably lead to stenosis (1). Degenerative aortic stenosis has many similarities to atherosclerotic plaque histologically, and has many similar predisposing risk factors (2,3). Genetic factors also play a role, and specific isoforms of both apolipoproteins and vitamin D receptors increase the likelihood of disease (4,5). In experimental animal models, very-high-cholesterol diets produce degenerative changes in the aortic valve similar to those seen in humans.

In these models, oxidized low-density lipoprotein (LDL) cholesterol induces the production of calcium-binding proteins and the transformation of valve cells into chondroblasts and osteoblasts that may lead to cartilage and bone formation, findings recorded in human aortic valves in late-stage untreated stenosis (6–8). Valve tissue is normally relatively avascular. However, with inflammation angiogenesis occurs, especially at the site of tissue damage. It has been reported recently that a protein chondromodulin-1 is an antiangiogenesis factor in normal valves and is present in significant amounts at the site of tissue damage, especially in aortic valves (9). Clearly, therefore, the aortic valve is a complex structure with many separate processes that may modulate disease.

Statin therapy has been proposed as a way to slow the rate of progression of aortic stenosis given the similarity with atherosclerosis. Retrospective studies have indicated a benefit of statins in reducing the rate of progression of aortic stenosis (10–14). In all of these studies, patients received statins based on their physician’s preference, and those receiving statins had greater concentrations of standard risk factors for atheroma and aortic valve degeneration such as hyperlipidemia, coronary artery disease, and diabetes. Statin therapy slowed the rate of progression as compared with the rate in those patients not receiving statins. Most of the patients in these studies had mild or moderate aortic stenosis, but in one study a beneficial effect of statin therapy was seen even in those with severely narrowed valves (14). In each of these studies, the effect of statin therapy in reducing the progression of aortic stenosis bore little relationship to the quantitative reduction in LDL cholesterol.

There are now 2 prospective studies of statin treatment reported, one of which is published in this issue of the Journal (15,16). Prospective studies in this area are difficult because many of the subjects with degenerative aortic stenosis have comorbid conditions that mandate statin therapy. These include coronary artery disease, diabetes, and severe hyperlipidemia. Both prospective studies have managed this problem differently. Not surprisingly, therefore, their findings and conclusions are also different. In the SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) study performed in Scotland, 155 patients, 70% of whom were men and whose mean age was 68 years, were prospectively randomized to atorvastatin 80 mg or placebo and were followed up for 2 years with echocardiograms performed at yearly intervals (15). Only those patients in whom statins were not indicated for other reasons were included in the study. Thus, the patients included in the study had an LDL cholesterol average of 134 mg/dl and there were relatively few patients with diabetes, although a significant minority had coronary or other vascular disease. The average valve area at inception in the study was 1 cm², and the calcification of the valves as assessed by computed tomographic (CT) scanning was extensive. Statin therapy had no effect on the rate of progression of aortic stenosis over the 2 years of follow-up as assessed by Doppler echocardiography or by change in CT calcium score of the valve, despite reducing the LDL cholesterol by more than 50%. The average reduction in aortic valve area in the treatment and control arm was 0.08 cm² per year, which is similar to that recorded in natural history studies of aortic stenosis, in which an average rate of progression of 0.1 cm² per year has been reported. In prespecified analyses, the effect of treatment was evaluated in subgroups of severity of aortic stenosis based on a peak aortic jet velocity at baseline of 4 m/s and also based on length of follow-up. Although those with more severe stenosis progressed significantly more rapidly than those with less severe stenosis, statins did not affect progression rate in either group. Similarly statin therapy was ineffective in slowing progression regardless of duration of follow-up. Secondary end points such as death, need for aortic valve replacement, or hospitalization were somewhat higher in the control group but were not statistically different.
In the second prospective study of statins in degenerative aortic stenosis, by Moura et al. (16), those patients with degenerative aortic stenosis for whom statin therapy is indicated because of hyperlipidemia are used as the active treatment arm, although any patient with known coronary disease was excluded from the study. These patients were given rosuvastatin 20 mg. The control arm of the study consisted of patients with degenerative aortic stenosis in whom statin therapy was not mandated by treatment guidelines. Thus, although prospective, this current study was not randomized. The average age of the 121 patients was 74 years, and 47% were men. Only those with an aortic valve area of >1 cm² were included, and the average valve area in both the control and the treatment arms was 1.2 cm². However, the statin group had by design LDL levels of >130 mg/dl (on average 160 mg/dl), whereas those receiving no statin treatment had an LDL <130 mg/dl (average level 118 mg/dl). There were other significant differences between the treatment groups. Only 34% of those given statins were men, as compared with 60% in the nontreatment arm, and those receiving statins were more likely to be hypertensive and diabetic and had higher triglyceride levels than those in the untreated group. The annualized reduction of the valve area in those receiving statins was 0.05 cm² per year, versus 0.1 cm² in those not receiving statins. The LDL cholesterol level did not change significantly over the 18 months of follow-up in the nontreatment arm, whereas it decreased more than 40% in the statin arm. The rate of progression of stenosis was modestly inversely correlated with the change in LDL level over the duration of follow-up.

So how do we resolve the differences in the findings of the two prospective trials of statin therapy in degenerative aortic stenosis and integrate them with the extensive experimental and retrospective studies that suggest that statin therapy may slow the rate of progression of degenerative aortic stenosis? From a clinical viewpoint, those patients with comorbid conditions such as coronary artery disease or diabetes or who are significantly hyperlipidemic will be treated with statins anyway. The wealth of evidence, including the present study, suggests that such patients will also enjoy a beneficial effect in terms of slowing the progression of aortic stenosis in addition to reduction in other cardiovascular end points. The target LDL in this group of patients needed to maximize the effects on aortic valve progression is unknown. Given the modest correlation between beneficial valve effect and LDL reduction, the target LDL required for treatment of the primary disease for which statins are being prescribed will likely be adequate, at least until more evidence is available. Similarly, there is no evidence yet of a unique advantage in terms of beneficial effects on the aortic valve of any specific statin.

What of those patients with degenerative aortic stenosis in which current lipid treatment guidelines do not mandate statin therapy? Will these patients benefit from statin therapy? Unfortunately, the study by Moura et al. (16) does not help us that much in this regard, because many of the patients in the active treatment arm would likely meet guidelines for statin therapy anyway based on their risk factors. In the SALTIRE study, such patients did not seem to benefit from statin therapy, at least over 2 years of follow-up. However, the SALTIRE study is a relatively small one and the patients had relatively advanced aortic stenosis not just in terms of valve area, but also in terms of the calcification of the valve at the onset of the trial, and may therefore have been less amenable to a treatment effect of statins. It is also possible that in patients without severe hyperlipidemia, progression of aortic valve disease is modulated by factors other than lipid metabolism. Until further data are available, there does not seem to be an indication for statin therapy just on the basis of aortic stenosis alone if conventional guidelines for statin therapy are not met. Fortunately, other trials are currently in process that may help address not just whether statins affect progression of aortic valve disease but also whether they affect more significant end points such as mortality or the need for aortic valve surgery. The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial in process is randomizing 1,800 patients with asymptomatic aortic stenosis to simvastatin 40 mg and ezetimibe 10 mg daily or placebo to determine the effect of active treatment on such end points. Given that even those patients with aortic sclerosis have a significantly higher risk for cardiovascular events, the results should be interesting indeed (17).

References