Calcific Aortic Valve Disease: Imaging Studies and Therapeutic Interventions

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Echocardiography is the predominant imaging method used for patients with aortic valve disease because of its excellent diagnostic accuracy, high reproducibility and noninvasive nature. Cardiac catheterization is typically reserved for patients in whom the diagnosis remains unclear, those requiring coronary angiography prior to valve replacement, and in the setting of complex valve disease. Cardiac computed tomography (CT) has recently been applied as a research tool to quantify the amount of aortic valve calcium (AVC), which has served as a clinical end point in several medical therapy trials.

Medical therapy for aortic valve disease remains an active area of clinical research. Multiple retrospective studies have shown a benefit for 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) in reducing disease progression. However, two recently completed prospective, randomized trials yielded conflicting results. The data for using angiotensin converting enzyme (ACE) inhibitors are in the preliminary stages. This review will focus on imaging methods that are available for patients with aortic valve disease and summarize the recent trials that have evaluated medical therapy aimed to reduce progression of aortic valve disease.

Key words: aortic valve disease, aortic sclerosis, aortic stenosis, cardiac computed tomography, echocardiography, cardiac catheterization

Accurate imaging in patients with suspected aortic valve disease is essential to establish the diagnosis and determine the severity of disease. Although cardiac catheterization was previously used for these purposes, echocardiography and, more recently, cardiac computed tomography (CT) are now the imaging methods of choice. Treatment trials evaluating new therapies for patients with aortic valve disease have used the aortic jet velocity and aortic valve area as assessed by echocardiography and the amount of aortic valve calcification as assessed by cardiac CT as clinical end points.

Recent retrospective studies using the clinical end points of aortic jet velocity as measured by echocardiography and aortic valve calcification as detected by cardiac CT suggest that lipid lowering with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) reduce disease progression. However, two recently completed prospective trials yielded conflicting results. The data regarding the benefits of angiotensin-converting enzyme (ACE) inhibitors in patients with aortic valve disease are less clear.

This review focuses on (1) imaging methods used for the assessment of aortic valve disease and (2) therapeutic treatment options including medical therapy, aortic balloon valvuloplasty, and percutaneous valve replacement for patients with aortic valve disease.

Imaging Studies

Several imaging methods are used to evaluate patients with aortic valve disease. The purpose of each of these imaging studies is to establish the diagnosis of aortic valve disease (aortic sclerosis and aortic stenosis) and quantify disease severity so that appropriate treatment decisions can be made. Cardiac catheterization was the initial imaging method used, but because
of its invasive nature, with its inherent, albeit small, risks of vascular complications (less than 1%), echocardiography and recently cardiac CT are now more frequently performed.

**Cardiac Catheterization**

The initial imaging method that was used to establish the diagnosis and evaluate the severity of aortic valve disease was cardiac catheterization. This is an invasive procedure that involves placing catheters or tubes within the cardiac chambers, specifically the left ventricle and the ascending aorta. Pressures are measured simultaneously, and the difference between the pressure in the left ventricle and ascending aorta is referred to as the “gradient” across the aortic valve. The maximum difference between these pressures is referred to as the maximum gradient, and the average or mean difference between these pressures is referred to as the mean gradient. The amount of blood flow (cardiac output) across the aortic valve is also measured. Using a formula developed by Gorlin and Gorlin in 1951 (the Gorlin equation), the aortic valve area can then be calculated. The severity of aortic stenosis is then determined using the aortic valve area and the pressure gradients (Table 1). Recent technological advances in echocardiography and the desire to avoid invasive procedures have made cardiac catheterization a less common imaging modality for patients with aortic valve disease. In general, it is now reserved for patients in whom the severity of aortic stenosis remains unclear despite echocardiography, for patients requiring cardiac catheterization for other indications (coronary angiography), and in patients with complex valve disease (aortic stenosis and aortic regurgitation).

**Echocardiography**

Although cardiac catheterization remains the gold standard for diagnosing and confirming the severity of aortic stenosis, echocardiography provides many advantages. These include its noninvasive nature, wide availability, excellent accuracy, and high reproducibility. The echocardiographic assessment of a patient with aortic stenosis involves measuring the velocity of blood flow across the aortic valve (mean and maximum velocities) and measuring the dimensions of the left ventricular outflow tract. In the setting of normal left ventricular function, the velocity of blood flow is related to the pressure difference across the aortic valve according to the simplified Bernoulli equation (pressure difference = 4 × velocity²). From these measurements, the aortic valve area can be calculated using an equation referred to as the continuity equation.

Echocardiographic assessment of aortic stenosis has been directly compared with cardiac catheterization, and the results are highly accurate. The noninvasive nature of echocardiography makes it an ideal method to serially follow the progression of aortic valve disease. On average, the maximum aortic jet velocity increases by 0.2 to 0.4 m/s per year and the aortic valve area decreases by 0 to 0.3 cm² per year. However, for an individual patient, there can be tremendous variability.

The maximum aortic jet velocity also predicts clinical outcome. In a study of 123 initially asymptomatic patients with aortic stenosis, those with a maximum aortic jet velocity of > 4.0 m/s (severe aortic stenosis) at study entry reached the clinical end point of alive without aortic valve replacement at 2 years of 21% compared with 84% for those with a jet velocity of < 3.0 m/s.

**Cardiac CT**

Cardiac CT is increasingly being used to evaluate patients with coronary artery disease. During cardiac CT scanning, the aortic valve is also imaged, usually within three to four slices. The aortic valve lies within the contiguous plane that travels between the left ventricle and the ascending aorta. If calcium is present within the aortic valve leaflets (aortic valve calcium [AVC]), it can be easily identified (Figure 1). AVC can also be quantified using either the Agatston or volumetric scoring methods in a manner similar to that used for coronary artery calcium scoring.

In general, the amount of AVC appears to be related to the severity of aortic valve disease, with higher AVC scores associated with more severe aortic stenosis. However, it remains difficult to define specific levels of AVC that correlate with echocardiographic and invasive (cardiac catheterization) measures of aortic stenosis severity. One recent study found that in asymptomatic patients with aortic stenosis, higher levels of AVC were associated with worse clinical outcome.

### Table 1: Severity of Aortic Stenosis Determined Based on the Pressure Gradient across the Aortic Valve and the Aortic Valve Area

| Aortic Stenosis Severity | Aortic Valve Area (cm²) | Mean Gradient (mm Hg) | Maximum Gradient (mm Hg) |
|--------------------------|-------------------------|----------------------|-------------------------|
| Mild                     | 1.5–2.0                 | < 20                 |                         |
| Moderate                 | 1.0–1.5                 | 20–40                |                         |
| Severe                   | < 1.0                   | > 40                 | > 60                    |
| Critical                 | < 0.5                   | > 60                 | > 80                    |
Given that cardiac CT imaging of the aortic valve is rapid, noninvasive, and accurate, it is also an ideal imaging method for the serial assessment of patients with aortic valve disease. As discussed below, several studies that have used cardiac CT assessed AVC as a clinical end point for therapeutic treatment trials.

**Therapeutic Interventions**

Surgical replacement of the aortic valve remains the only currently accepted treatment option for patients with severe, symptomatic aortic stenosis. However, the majority of patients with aortic valve disease are often asymptomatic with only mild to moderate aortic stenosis when initially diagnosed and therefore do not require surgical intervention. Because of this, there has been tremendous interest in developing therapies to reduce disease progression. In addition, because of the inherent risks associated with aortic valve replacement, there has also been interest in developing alternatives to traditional surgery.

**Basis for Drug Therapy**

The basis for considering that drug therapy may be beneficial in patients with aortic stenosis relies on (1) studies that have characterized the histologic appearance of early aortic stenosis lesion, (2) epidemiologic studies that have clarified the clinical risk factors associated with aortic stenosis, and (3) recent observations using a newly established animal model of aortic stenosis.

Histologic studies have shown that the early lesions of aortic stenosis are characterized by (1) chronic inflammatory cells including macrophages and T lymphocytes,11 (2) lipid accumulation including atherogenic lipoproteins,12 (3) α-actin-expressing cells, (4) active regulation of calcification via proteins such as osteopontin,13 and (5) components of the renin-angiotensin-aldosterone system, such as ACE, angiotensin II, and angiotensin receptors.14 These histologic findings are markedly similar to atherosclerosis and suggest that aortic stenosis occurs because of an active, highly regulated disease process within the valve leaflets. The previously held belief that aortic stenosis was a consequence of the normal aging process and the result of a wear-and-tear phenomenon on the valve leaflets no longer appears to be valid.

Epidemiologic studies have identified that the risk factors for developing aortic stenosis are also similar to those for atherosclerosis and include advanced age, male gender, smoking, diabetes mellitus, and hyperlipidemia.15

More recently, an animal model of aortic stenosis was developed by Rajamannan and colleagues using rabbits given a high-cholesterol diet.16 In this model, experimental hyperlipidemia resulted in aortic valve lesions that appeared similar to those in human aortic valve lesions. In addition, the aortic valve lesions contained cells that expressed genes similar to those found in skeletal bone formation.

Based on these observations, a number of studies have evaluated two classes of medications in patients with aortic valve disease: HMG-CoA reductase inhibitors and ACE inhibitors.

**HMG-CoA Reductase Inhibitors**

To date, seven retrospective studies have evaluated whether HMG-CoA reductase inhibitors result in less progression of aortic valve disease (Table 2). Each of these studies used either echocardiography or cardiac CT as the end point to evaluate for disease progression. In general, all of these studies, except for that by Antonini-Canterin and colleagues,17 showed that statin therapy was associated with less rapid disease progression. Looking more closely at the study by Antonini-Canterin and colleagues, of the 1,136 patients included, 52 had aortic sclerosis and 1,084 had aortic stenosis.17 Of those with aortic sclerosis, statin therapy was beneficial and significantly reduced the rate of change in aortic jet velocity over time. Although those with aortic sclerosis represented a small subgroup of the overall study population, this observation suggests that statin therapy may be more beneficial earlier in the

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**Figure 1** Aortic valve calcium (AVC) as imaged with cardiac computed tomography. A, B, and C show a low-power magnification view and D, E, and F show a high-power magnification view at the area of the aortic valve. A and D show no AVC (arrow), B and E show mild AVC (arrow), and C and F show severe AVC (arrow).
disease course, that is, prior to the onset of severe valve calcification and severe leaflet restriction.

Currently, there are two completed prospective studies of statin therapy for aortic valve disease (Table 3). In the Scottish Aortic Stenosis and Lipid Lowering Impact on Regression Trial (SALTIRE), 156 patients with an aortic jet velocity of $>2.5$ m/s were randomized to either 80 mg/d of atorvastatin or placebo. The end point of the study was the change in aortic jet velocity as measured by echocardiography and the change in AVC as assessed by cardiac CT. Whereas low-density lipoprotein (LDL) cholesterol was reduced to 63 mg/dL in those receiving atorvastatin, there was no difference in the aortic jet velocity or AVC score between those receiving atorvastatin and placebo. In the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) trial, 121 patients with moderate to severe aortic stenosis were prospectively treated with rosuvastatin based on their LDL cholesterol at study entry. If the LDL cholesterol was greater than 130 mg/dL, they received rosuvastatin 20 mg per day, and if the LDL cholesterol was $\leq 130$ mg/dL, they received placebo. The study end point was the change in the aortic valve area and aortic jet velocity as measured by echocardiography. Those treated with rosuvastatin had a smaller decrease in aortic valve area and a smaller increase in aortic jet velocity compared with the placebo group, indicating that rosuvastatin decreased disease progression.

Although these disparate results are disappointing, there were significant differences between the SALTIRE and the RAAVE trial. Despite similar aortic jet velocities at study entry, patients enrolled in the SALTIRE were required to have AVC present, suggesting that they had more severe aortic stenosis compared with the RAAVE cohort. The randomization to statin therapy was also different; in the SALTIRE, patients were randomized regardless of LDL level, whereas in the RAAVE trial, only those with an LDL greater than 130 mg/dL received statin therapy. In addition, a different statin agent was used in each of the trials and a different level of LDL was achieved in the statin arms.

Several large-scale, ongoing trials (Simvastatin and Ezetimide in Aortic Stenosis [SEAS] and Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin [ASTRONOMER]) using the hard clinical end points of aortic valve replacement and death are attempting to clarify the issue of whether statins are beneficial in patients with aortic valve disease. Until the results of these trials are available, it remains speculative whether patients with aortic valve disease derive benefit from statin therapy.

### ACE Inhibitors

The interest in using ACE inhibitors in patients with aortic valve disease is based on (1) the finding of ACE protein and other components of the renin-

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**Table 2**  Retrospective Studies of HMG-CoA Reductase Inhibitors in Patients with Aortic Valve Disease

| Study (Year)     | n  | Statin vs No Statin | Benefit of Statin |
|------------------|----|---------------------|-------------------|
| Shavell et al (2002) | 65 | ΔAVC: 9% vs 43%*   | Yes               |
| Antonini-Canterin et al (2005) | 1,136 | ΔAS jet: 0.13 vs 0.14* | No                |
| Aronow et al (2001) | 180 |                     | Yes               |
| Pohle et al (2001) | 104 | ΔAVC: 25% vs 48%*** | Yes               |
| Novaro et al (2001) | 174 | ΔAVA: −0.06 vs −0.11* | Yes               |
| Bellamy et al (2002) | 156 | ΔAVA: −0.04 vs −0.09* | Yes               |
| Rosenhek et al (2004) | 211 | ΔAS jet: 0.10 vs 0.39** | Yes               |

AS jet = aortic jet velocity; AVA = aortic valve area; AVC = aortic valve calcium; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

1. *p = not significant; *p < .05; **p < .01; ***p < .001.

2. Pohle et al evaluated patients based on low-density lipoprotein cholesterol at study entry and not the use of statin therapy.

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**Table 3**  Prospective Studies of HMG-CoA Reductase Inhibitors in Patients with Aortic Valve Disease

| Study (Year)     | n  | Statin Agent Dose | Imaging Method Used as End Point | Findings            |
|------------------|----|-------------------|---------------------------------|---------------------|
| Cowell et al (2005) | 155 | Atorvastatin 80 mg/d | Cardiac CT and echocardiography | No benefit of statin therapy |
| Moura et al (2007) | 121 | Rosuvastatin 20 mg/d | Echocardiography                | Less progressive with statin therapy |

CT = computed tomography; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.
angiotensin-aldosterone system within aortic valve lesions and (2) the clear benefits that have been demonstrated with ACE inhibitors in patients with atherosclerosis. However, a significant concern to administer ACE inhibitors to patients with aortic stenosis remains. This is based on the belief that in the setting of a fixed and narrowed aortic valve, the reduction in afterload caused by an ACE inhibitor may result in systemic hypotension secondary to a reduction in cardiac output. Although this remains a theoretical concern, there is little evidence in the medical literature to support this. Furthermore, there are now four published studies indicating that using ACE inhibitors in patients with aortic stenosis is, in general, safe and well tolerated.

To date, there have been only two published retrospective studies evaluating whether ACE inhibitors reduce disease progression in patients with aortic valve disease. O’Brien and colleagues evaluated 123 patients with AVC by cardiac CT and found that those receiving ACE inhibitors had less disease progression over a mean follow-up of 2.7 years. In contrast, Rosenhek and colleagues did not find a benefit for the use of ACE inhibitors in a study of 211 patients using aortic jet velocity as the end point. With only these two studies available, conclusions regarding the benefits of ACE inhibitors in patients with aortic valve disease remain speculative.

Balloon Aortic Valvuloplasty

In the early 1980s, there was tremendous enthusiasm for the use of balloon valvuloplasty in treating symptomatic patients with severe aortic stenosis. This procedure involves placing a large balloon within the aortic valve leaflets and inflating the balloon to effectively “tear” the leaflets apart (Figure 2). Although the early hemodynamic results following balloon valvuloplasty showed promise (ie, there was an increase in the aortic valve area and a decrease in the pressure gradient), within 6 months, the majority of patients had recurrent severe aortic stenosis related to restenosis within the valve leaflets. As such, the natural history of the disease process remains unaffected by the valvuloplasty procedure.

Currently, balloon valvuloplasty is used only in patients considered to be at high risk for surgical valve replacement (elderly age, comorbid conditions), in those who are critically ill and need stabilization prior to definitive surgical intervention, for palliation in patients with a limited life expectancy, and in selected patients with severe aortic stenosis in need of emergent, noncardiac surgery.

Percutaneous Aortic Valve Replacement

Given that the benefits of balloon valvuloplasty are limited by restenosis, it would seem logical that placement of a percutaneous valve may be beneficial. In 2002, Cribier and colleagues placed the first percutaneous aortic valve in a critically ill patient with severe aortic stenosis. Although the aortic valve area increased from 0.6 to 1.9 cm² and the mean gradient decreased to 6 mm Hg following placement of the valve, the patient died 17 weeks following the procedure from a multitude of complications. Ongoing studies are evaluating whether percutaneous valve replacement will have a role in the treatment of patients with aortic valve disease.

Summary

Currently, invasive cardiac catheterization is reserved for specific patients with aortic valve disease and echocardiography has evolved into the imaging method of choice. Cardiac CT is increasingly being used to quantify the amount of AVC and in clinical trials to evaluate the effects of medical therapy on disease progression. Whereas retrospective studies of HMG-Co A reductase inhibitors suggested a benefit in patients with aortic valve disease, recently completed
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