

**GIAN M. NOVARO, MD***Department of Cardiovascular Medicine,
The Cleveland Clinic, Weston, Florida**BRIAN P. GRIFFIN, MD†**Department of Cardiovascular Medicine,
The Cleveland Clinic

Calcific aortic stenosis: Another face of atherosclerosis?

ABSTRACT

Calcific aortic stenosis is not the result of decades of wear and tear alone. Rather, it is being increasingly recognized as an inflammatory, atheromatous, and potentially modifiable disease. Exciting new research suggests that medical therapies may soon be available to retard its progression and reduce the need for surgery.

KEY POINTS

The lesion of calcific aortic stenosis shares histologic similarities with atheromatous coronary artery disease, and its development and progression are linked to various traditional risk factors for atherosclerosis.

For unclear reasons, only about 40% of patients with calcific aortic stenosis also have coronary artery disease, and most people with coronary artery disease do not have calcific aortic stenosis.

Hypertension, smoking, and diabetes mellitus have consistently been linked to the development of aortic stenosis. Endothelial injury or other processes that contribute to coronary disease may play a similar role in calcific aortic stenosis.

In observational studies, aortic stenosis progressed at a slower rate in patients who received statin drugs than in those who did not.

CALCIFIC AORTIC STENOSIS has a lot in common with atherosclerotic coronary artery disease. So can lipid-lowering statin drugs stop it?

Historically, calcific aortic stenosis was thought to result from aging and “wear and tear” of the aortic valve.^{1,2} Hence it was designated “degenerative” or “senile-type.”

This perception is changing. Over the last decade, a growing understanding of the risk factors for calcific aortic stenosis and of its histologic characteristics have led to new insights into how it develops. Investigators have found histologic similarities between the lesion of aortic stenosis and atheromatous coronary artery disease^{3,4} and have established an association between traditional atherosclerotic risk factors and the development of calcific aortic valve disease.^{5–14}

This condition is the most common reason for valve replacement in the United States,¹⁵ and when it is severe it accounts for considerable disease and death, especially in older patients.

Up to now, the only established treatment for symptomatic aortic valve stenosis has been to replace the valve. Newer therapies that may modify or reduce the likelihood of developing aortic valve disease are highly desirable and are currently under investigation.

In this article we summarize what is known about the possible role of lipids, infection, and other risk factors in nonrheumatic calcific aortic sclerosis and stenosis and potential treatments. We use valve “sclerosis” to mean a thickening of the aortic valve leaflets, often with superimposed calcification, whereas valve “stenosis” implies a more advanced situation in which the leaflets stick and do not open normally.

*The author has indicated that he has received grant or research support from Pfizer Inc.

†The author has indicated that he is on the speakers' bureau of the Merck corporation and has received grant or research support from Pfizer Inc.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

■ AGING NOT THE ONLY CAUSE

The debate over the pathogenesis of non-rheumatic calcific aortic stenosis (ie, stenosis of a trileaflet aortic valve) dates back to 1904, when Mönckeberg first described dystrophic calcification of the aortic valve.¹⁶ The conventionally accepted hypothesis has been that with age, repeated mechanical stimuli and hemodynamic forces lead to leaflet injury and dystrophic calcification.^{1,2,17}

Although age-related changes in the valve do occur,³ aging should not be considered synonymous with aortic valve disease, because many elderly people do not develop aortic stenosis.¹¹

Moreover, over the last decade, studies have linked the development and progression of calcific aortic valve disease to various traditional risk factors for atherosclerosis. Further support for the hypothesis that the condition is not just age-related comes from the work of Otto et al³ and O'Brien et al,⁴ who found that the “early lesion” of aortic stenosis is microscopically similar to atheroma in several ways.

Nevertheless, key questions remain:

- Nearly 40% of patients with aortic valve stenosis also have significant coronary artery disease, defined as a narrowing of the luminal diameter of an epicardial coronary artery of 70% or more.¹⁸ Why does the disease involve only the aortic valve and spare the coronary arteries in the other 60% of cases?
- Conversely, why do most people with coronary artery disease not have aortic valve stenosis, despite similar risk profiles?
- Aortic sclerosis is found in approximately 25% of elderly people in the United States, whereas aortic stenosis develops in only 2% to 3% of people older than 75 years.^{11,19} Why is it that most patients with aortic sclerosis do not develop progressive, obstructive aortic valve disease?

■ LIPIDS, LIPOPROTEINS, AND AORTIC VALVE DISEASE

From small case series to large population-based studies, aortic sclerosis and stenosis have both been repeatedly found to be associated with dyslipidemia, specifically:

- Elevated total cholesterol^{5,6,8,12,20–23}

- Elevated low-density lipoprotein (LDL) cholesterol^{11,14}
- Elevated triglycerides^{7,14}
- Low high-density lipoprotein (HDL) cholesterol. This has not been well studied. One case report²⁴ described the premature development of aortic stenosis in a young man with Tangier disease, a hereditary condition with markedly low HDL levels; the only other report was a cross-sectional analysis that correlated low HDL levels with aortic sclerosis in an elderly cohort.⁶
- Elevated lipoprotein(a): Two population-based studies showed that serum lipoprotein(a) levels closely correlate with the presence of aortic sclerosis, independent of LDL levels.^{10,11}

We investigated the concept of an “atheromatous valvulopathy” by examining the lipid profiles of 2,356 patients who underwent aortic valve replacement with or without concomitant coronary bypass grafting.¹⁴ Patients who underwent isolated valve replacement for aortic valve stenosis had significantly higher total cholesterol and LDL cholesterol levels than patients who had valve surgery for aortic regurgitation. These levels were even higher for those who also underwent bypass grafting.

■ HISTOLOGIC FEATURES

In the 1970s and 1980s, Pomerance¹ and Roberts²⁵ described calcification of the aortic cusps that was “preceded by lipid deposition” and shared “the same etiology as the coronary atherosclerotic plaques.”²⁵

Similarities with coronary disease

Otto et al³ and others^{4,26–28} elegantly characterized the histologic features of calcific aortic valve disease.

On gross inspection, diseased aortic valves have areas of irregular thickening and calcification on the aortic side (FIGURE 1). Microscopically, all diseased aortic leaflets reveal disruption of the endothelium on the aortic side.

This process, similar to what occurs in coronary artery disease,²⁹ constitutes the initial injury to the leaflet, whereby inflammatory cells and cholesterol can enter. Once the endothelium is disrupted, possibly by mechan-

High
cholesterol
plays a role in
aortic stenosis

■ Aortic valve stenosis: Similar to coronary artery disease

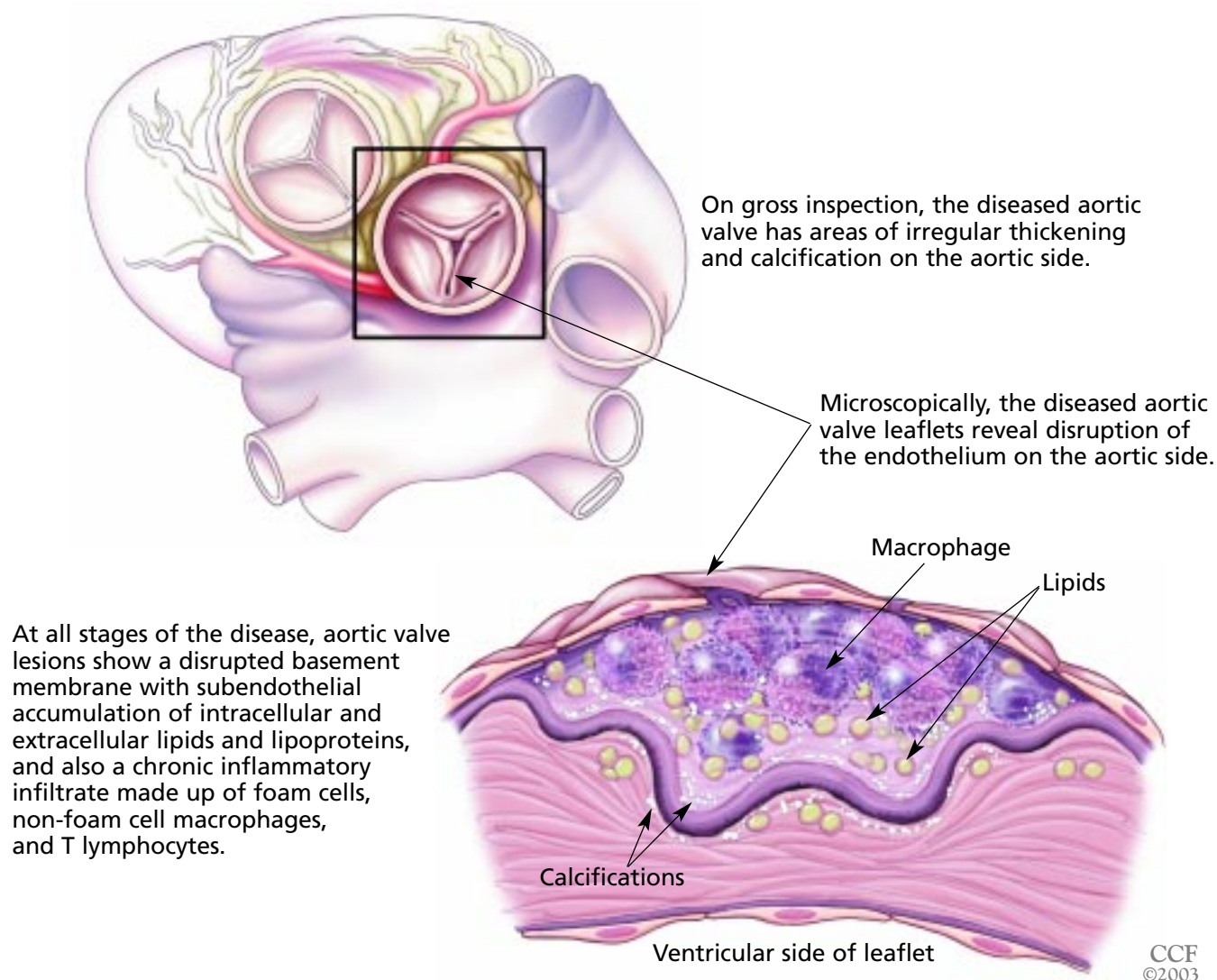


FIGURE 1. Disruption of the endothelium, which also occurs in coronary artery disease, constitutes the initial injury to the leaflet, whereby inflammatory cells and cholesterol can enter. Once the endothelium is disrupted by mechanical stress or other factors, the disease progresses through its various stages of sclerosis and stenosis.

ical stress or other factors, the disease progresses through its various stages of sclerosis and stenosis. But regardless of stage, aortic valve lesions demonstrate an overlying disrupted basement membrane with subendothelial accumulation of intracellular and extracellular lipids and lipoproteins.^{3,4}

A chronic inflammatory infiltrate is also present, made up of foam cells, non-foam cell

macrophages, and T lymphocytes (FIGURE 1).³

Additional evidence comes from patients with familial hypercholesterolemia. People who are homozygous for this trait often have premature coronary disease, but aortic valve disease is another common but under-appreciated feature. In these people, lipids infiltrate the aortic cusps and consequently cause them to thicken and stick together, restricting their

mobility and rendering the valve stenotic.^{20,21,30,31} Aortic valve cusps from homozygotic patients who undergo aortic valve replacement show significant thickening with foam cell deposition surrounded by dystrophic calcification.³¹ These findings occur in trileaflet, congenitally normal aortic valves and as early as in the second decade of life.

The regions containing lipoproteins occur at the same location as areas of calcification.⁴ From the subendothelium, the lesions extend to the leaflet's central portion, called the fibrosa, and most often involve the base of the leaflet. These findings appear more advanced as the clinical grade of aortic stenosis progresses.

Dissimilarities with coronary disease

Although aortic stenosis and coronary artery lesions share many atheromatous features, there are notable dissimilarities. For example, in aortic valve disease there are fewer smooth muscle cells, and there is more dystrophic calcification. This greater degree of calcification has generated considerable interest in possible specific cellular and, more recently, genetic mechanisms of aortic stenosis.

Osteopontin and other bone proteins have been found in calcified aortic valves.^{26,32} Mohler et al²⁸ recently reported on the common finding of heterotopic ossification and active bone remodeling in diseased aortic and mitral valves. Lamellar bone was found in 13% of valves with dystrophic calcification.

Recently, Ortlepp et al³³ identified a potential genetic marker for the development of calcific aortic stenosis. In a case-control study, subjects with aortic stenosis had a higher prevalence of the B allele of the gene encoding the vitamin D receptor than of the b allele. This polymorphism has been previously associated with greater bone loss³⁴ and lower bone density,³⁵ and these observations led the authors to suggest that the B allele may render a patient more susceptible to dystrophic valvular calcification.

This study may provide a clue to the suggested association between osteoporosis and calcification of the mitral and aortic valves.^{9,11} The exact interaction between this polymorphism, lipids, and inflammation and its role in the development and progression of aortic valve disease remain unclear.

■ NONLIPID RISK FACTORS FOR CALCIFIC AORTIC STENOSIS

Hypertension,^{6,9,11,22} smoking,^{7,11} and diabetes mellitus^{5,6,14} have consistently been linked to the development of aortic stenosis, although their exact disease-promoting actions are unclear. Endothelial injury or other processes at work in coronary disease may play a similar role in calcific aortic stenosis.

Other factors that may be associated with aortic valve disease include:

- Age^{8-11,22}
- Male sex^{7,11}
- Obesity⁸
- Uremia³⁶
- Elevated calcium³⁷
- Elevated parathyroid hormone^{9,38}
- Osteoporosis^{9,11}
- Paget disease³⁹
- Significant renal failure.^{36,40}
- The high cardiac-output state, which can coexist with Paget disease and renal failure, may also promote the valvular disease process.

Novel risk factors

Not all patients with risk factors for calcific aortic stenosis develop the condition. Conversely, some patients develop the condition despite having only a few risk factors, so yet-unidentified disease-promoting factors may play a role.

Infectious agents, mainly *Chlamydia pneumoniae*, stirred interest as possible causes of coronary disease and have also been considered as possible causes or promoters of calcific aortic valve disease. Although the data conflict, most studies found *C pneumoniae* to be more prevalent in diseased aortic valves than in normal aortic valves.^{41,42}

What role this or any other infectious agent plays needs to be better defined. Moreover, whether antibiotic therapy has any effect on slowing the progression of valvular disease is not known.

Elevated homocysteine. Calcific aortic valve disease begins with some form of endothelial injury, and homocysteine can damage the endothelium. Is there a connection?

We recently assessed the association between plasma homocysteine and various

Hypertension, smoking, and diabetes mellitus are linked to aortic stenosis

**TABLE 1****Do statins slow the progression of aortic stenosis?
Observational data**

MEASURE	CHANGE OVER 21 MONTHS		P VALUE
	STATIN (N = 117)	NO STATIN (N = 57)	
Peak transvalvular gradient (mm Hg)	5.3	9.5	.03
Mean transvalvular gradient (mm Hg)	4.2	5.8	.19
Aortic valve area (cm ²)	− 0.12	− 0.19	.03

DATA FROM NOVARO GM, TIONG IY, PEARCE GL, LAUER MS, SPRECHER DS, GRIFFIN BP. EFFECT OF HMG-COA REDUCTASE INHIBITORS ON THE PROGRESSION OF CALCIFIC AORTIC STENOSIS. CIRCULATION 2001; 104:2205–2209.

degrees of aortic valve disease in 76 surgical patients.⁴³ The mean homocysteine level was 10.9 $\mu\text{mol/L}$ in patients with normal aortic valves, 11.4 in those with aortic sclerosis, and 15.4 in those with aortic stenosis, but the association was not statistically significant in a multivariate regression model. However, as we anticipated, plasma homocysteine levels were closely associated with increasing age and serum creatinine levels; thus, it is conceivable that the elevated homocysteine levels seen in patients with renal impairment or older age could contribute to the more rapid progression of aortic stenosis observed in these patient populations.

■ PREDICTING STENOSIS PROGRESSION

Aortic stenosis tends to progress: the valve area decreases by an average of 0.1 cm² per year in this condition, and the transvalvular pressure gradient increases by 6 to 8 mm Hg per year.^{44–47}

However, these rates are averages, with wide individual variation. Moreover, it is not currently possible to forecast the progression of aortic sclerosis or stenosis in an individual patient.

Factors associated with progression of stenosis include:

- Increasing age^{45,48,49}
- Male sex⁵⁰
- Dyslipidemia^{7,50–52}
- Tobacco use^{7,50–53}
- Hypertension⁵⁰
- Diabetes mellitus⁵⁰
- Obesity⁵³

- Elevated serum calcium⁵¹
- Elevated serum creatinine⁵¹
- Aortic valve calcification.^{46,54}

These associations are not definitive, as the studies referred to were all either retrospective or relatively small. Further investigation is warranted to pinpoint specific predictors of rapid disease progression.

■ EFFECT OF LIPID-LOWERING AGENTS

No medical therapy has yet been proven to alter the natural history of aortic stenosis. Such a therapy would be of considerable importance, as it might delay or even obviate the need for valve replacement in some patients.

What about HMG-coenzyme A reductase inhibitors (statins)? They have been shown to slow the progression of coronary artery disease. Given the similarities of this condition to calcific aortic stenosis, statins might, in theory, reduce the progression of aortic stenosis.

In an observational study, we compared the rate of progression of aortic stenosis in patients who received a statin with those who did not.⁴⁹ In 174 patients with mild to moderate calcific aortic stenosis, statin use was a significant independent predictor of a lesser increase in peak gradient and of a smaller decrease in valve area (**TABLE 1**). The aortic valve area decreased by 0.11 ± 0.18 cm² per year in those not taking a statin vs 0.06 ± 0.16 cm² in those taking a statin ($P = .01$ by multivariate analysis).

The association between statin use and slower progression of stenosis has been repro-

No drug has been shown to alter the natural history of aortic stenosis

duced in one additional retrospective study in similar patients.⁵⁰

These studies seem to justify a prospective trial to substantiate whether drug therapy with statins slows the progression of aortic stenosis. This is currently in progress.

FUTURE DIRECTIONS

New genetic markers, such as the B allele of the vitamin D receptor, may help us to assess an indi-

vidual's risk of developing aortic valve disease.

The role of novel cellular components of diseased valves, such as matrix proteins and mast cells, is an area of increasing interest and research.

Potential markers of disease progression, such as C-reactive protein,⁵⁵ may be useful tools in deciding the optimal time for valve surgery in patients with mild aortic disease undergoing open-heart surgery for another condition.



REFERENCES

- Pomerance A. Ageing changes in human heart valves. *Br Heart J* 1967; 29:222-231.
- Pomerance A. Pathogenesis of aortic stenosis and its relation to age. *Br Heart J* 1972; 34:569-574.
- Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of "degenerative" valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994; 90:844-853.
- O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of "degenerative" valvular aortic stenosis. *Arterioscler Thromb Vasc Biol* 1996; 16:523-532.
- Deutscher S, Rockette HE, Krishnaswami V. Diabetes and hypercholesterolemia among patients with calcific aortic stenosis. *J Chronic Dis* 1984; 37:407-415.
- Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. *Am J Cardiol* 1987; 59:998-999.
- Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors—a causal relationship? A clinical morphologic study. *Clin Cardiol* 1991; 14:995-999.
- Mautner GC, Mautner SL, Cannon RO 3rd, Hunsberger SA, Roberts WC. Clinical factors useful in predicting aortic valve structure in patients over 40 years of age with isolated valvular aortic stenosis. *Am J Cardiol* 1993; 72:194-198.
- Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J* 1994; 15:865-870.
- Gotoh T, Kuroda T, Yamasawa M, et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). *Am J Cardiol* 1995; 76:928-932.
- Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997; 29:630-634.
- Wilmschurst PT, Stevenson RN, Griffiths H, Lord JR. A case-control investigation of the relation between hyperlipidaemia and calcific aortic valve stenosis. *Heart* 1997; 78:475-479.
- Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999; 341:142-147.
- Novaro GM, Pearce GL, Sprecher DL, Griffin BP. Comparison of cardiovascular risk and lipid profiles in patients undergoing aortic valve surgery versus those undergoing coronary artery bypass grafting. *J Heart Valve Dis* 2001; 10:19-24.
- Carabello BA, Crawford FA Jr. Valvular heart disease. *N Engl J Med* 1997; 337:32-41.
- Mönckeberg JG. Der normale histologische Bau und die Sklerose der Aortenklappen. *Virchows Arch Pathol Anat Physiol* 1904; 176:472-514.
- Thubrikar MJ, Aouad J, Nolan SP. Patterns of calcific deposits in operatively excised stenotic or purely regurgitant aortic valves and their relation to mechanical stress. *Am J Cardiol* 1986; 58:304-308.
- Rapp AH, Hillis LD, Lange RA, Cigarroa JE. Prevalence of coronary artery disease in patients with aortic stenosis with and without angina pectoris. *Am J Cardiol* 2001; 87:1216-1217.
- Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993; 21:1220-1225.
- Sprecher DL, Schaefer EJ, Kent KM, et al. Cardiovascular features of homozygous familial hypercholesterolemia: analysis of 16 patients. *Am J Cardiol* 1984; 54:20-30.
- Rallidis L, Naoumova RP, Thompson GR, Nihoyannopoulos P. Extent and severity of atherosclerotic involvement of the aortic valve and root in familial hypercholesterolemia. *Heart* 1998; 80:583-590.
- Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. *Heart* 1997; 78:472-474.
- Chui MCK, Newby DE, Panarelli M, Bloomfield P, Boon NA. Association between calcific aortic stenosis and hypercholesterolemia: is there a need for a randomized controlled trial of cholesterol-lowering therapy? *Clin Cardiol* 2001; 24:52-55.
- Burnett JR, Law AJ, Yeong ML, Crooke MJ, Sharma AK. Severe aortic stenosis and atherosclerosis in a young man with Tangier disease. *Am J Cardiol* 1994; 73:923-925.
- Roberts WC. The senile cardiac calcification syndrome. *Am J Cardiol* 1986; 58:572-574.
- Mohler ER 3rd, Adam LP, McClelland P, Graham L, Hathaway DR. Detection of osteopontin in calcified human aortic valves. *Arterioscler Thromb Vasc Biol* 1997; 17:547-552.
- Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arterioscler Thromb Vasc Biol* 1999; 19:1218-1222.
- Mohler ER 3rd, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. *Circulation* 2001; 103:1522-1528.
- Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999; 340:115-126.
- Roberts WC, Ferrans VJ, Levy RI, Fredrickson DS. Cardiovascular pathology in hyperlipoproteinemia. Anatomic observations in 42 necropsy patients with normal or abnormal serum lipoprotein patterns. *Am J Cardiol* 1973; 31:557-570.
- Kawaguchi A, Miyatake K, Yutani C, et al. Characteristic cardiovascular manifestation in homozygous and heterozygous familial hypercholesterolemia. *Am Heart J* 1999; 137:410-418.
- O'Brien KD, Kuusisto J, Reichenbach DD, et al. Osteopontin is expressed in human aortic valvular lesions. *Circulation* 1995; 92:2163-2168.
- Ortlepp JR, Hoffmann R, Ohme F, Lauscher J, Bleckmann F, Hanrath P. The vitamin D receptor genotype predisposes to the development of calcific aortic valve stenosis. *Heart* 2001; 85:635-638.
- Ferrari S, Rizzoli R, Chevalley T, Slosman D, Eisman JA, Bonjour JP. Vitamin-D-receptor-gene polymorphisms and change in lumbar-spine bone mineral density. *Lancet* 1995; 345:423-424.
- Morrison NA, Qi JC, Tokita A, et al. Prediction of bone density from vitamin D receptor alleles. *Nature* 1994; 367:284-287.

