Aortic stenosis: An update

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Abstract
Aortic stenosis (AS) is the most common valvular heart disease in the world. It is a disease of the elderly and as our population is getting older in both the developed and the developing world, there has been an increase in the prevalence of AS. It is impacting the mortality and morbidity of our elderly population. It is also causing a huge burden on the healthcare system. There has been tremendous progress in our understanding of AS in recent years. Lately, studies have shown that AS is not just a disease of the aortic valve but it affects the entire systemic vasculature. There are studies looking at more sophisticated measures of disease severity that might better predict the optimal timing of valve replacement. The improvement in our understanding in etiology and pathophysiology of the disease process has led to a number of trials with possible treatment options for AS. In this review, we talk about our understanding of the disease and latest developments in disease assessment and management. We look forward to a time when there will be medical treatment for AS.

Key words: Aortic stenosis; Valvular heart disease; Diagnosis of aortic stenosis; Medical management of aortic stenosis

INTRODUCTION
Aortic stenosis (AS) is the most common valvular heart disease and the third most common cardiovascular disease after hypertension and coronary artery disease in the western world[1]. The prevalence of AS increases from 2% in adults over 65 years to 4% in adults over 85 years of age[2]. AS is a progressive condition and after the onset of heart failure, survival is < 2 years without valve replacement[3]. 50% of patients with AS presenting with angina, syncope or heart failure survive for 5, 3 or 2 years respectively without aortic valve replacement (AVR). As life spans increase, the burden of senile AS on the healthcare system is expected to increase. Close monitoring and use of AVR when the disease becomes significant remains the standard of care[4]. AS is the most common reason for AVR in the developed world. Though the disease has been known for decades, little has been known about the pathophysiology, and a lot of work is going into the understanding of possible etio-pathogenesis. New innovative techniques and management have been studied to stop or reduce the progression of AS. To date though, no medical therapy has been proven to alter the natural history of patients with AS. In this review, we talk about our understanding of the disease and latest developments in its management.
ETIOLOGY OF CALCIFIC AS

AS was always thought to be due to a passive, degenerative process leading to accumulation of calcium and causing narrowing of the valve. The pathogenesis of AS, however, is still not well understood. The risk factors for calcific aortic valve disease are similar to the risk factors for atherosclerosis, which includes male sex, hypertension, elevated levels of low density lipoprotein (LDL) cholesterol, and smoking[1,2,6-8]. The incidence of AS is higher in patients with chronic kidney disease and patients who have had radiotherapy in the past. It has been shown from the valve specimens taken during surgery for AS that there are increased levels of inflammation, which might lead to calcification[9,15,16]. There are also increased levels of LDL, which might lead to inflammation and calcification[16,17].

Recent studies have shown specific bone-cell phenotypes are present in calcifying human valves[18,20]. Specific markers of bone formation have been identified in calcified aortic valves; it includes the bone matrix proteins osteopontin, osteocalcin and bone sialoprotein[19,21-23], and the osteoblast transcription factor Runx2[20,21,22,24]. Genetic studies are also evolving, which point towards genetic factors that predispose individuals to developing calcific AS.

DIAGNOSIS

Patients may present with symptoms of exertional chest pain, breathlessness or syncope but the majority of patients are asymptomatic. AS is suspected when an ejection systolic murmur (ESM) is heard in the precordium in symptomatic or asymptomatic patients. Diagnosis of AS is by detailed history and physical examination, echocardiography and confirmation with cardiac catheterization.

Clinical evaluation

History and physical examination is very important in patients with AS. It helps not only for the diagnosis but also to assess severity. Patients with AS usually have ESM in the precordium. Patients with exertional symptoms have hemodynamically significant valvular stenosis and hence need treatment. The severity of AS in asymptomatic patients can be assessed by other clinical findings - poorly palpable pulse, late peaking of ESM and reversal of S2 split.

Echocardiography

Echocardiography is the most commonly used noninvasive test of choice for patients with suspected AS. The severity of AS is determined by echocardiography by the mean and peak aortic valve gradients (AVG), aortic valve area (AVA) and aortic valve velocity. Echocardiography does not measure the pressures directly and the AVA is also a derived value[25]. The AVG is also dependent on left ventricular systolic function, severe AS is defined as a peak AS velocity > 4 m/s, a mean transaortic pressure gradient > 40 mmHg, or an AVA < 1 cm2. A valve area index < 0.6 cm2/m2 is also indicative of severe AS[26-28]. The management of severe AS has historically been surgery, but other treatment options have been looked at.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors

Lipids are known to be the key in the development of fibrosis and then calcification of aortic valves leading to stenosis. Hence lipid lowering agents, hydroxymethylglutaryl-coenzyme A reductase inhibitors, or statins, may be a potential agent for halting the progression of AS. Studies have shown variable results.
The Rosuvastatin Affecting Aortic Valve Endothelium study was a prospective study looking at 121 patients with asymptomatic moderate to severe AS with AVA of 1.0 to 1.5 cm² and followed them by echocardiogram. Patients with a LDL cholesterol > 3.4 mmol/L were treated with rosvuastatin while those with an LDL < 3.4 mmol/L received no lipid lowering therapy. Over a mean follow-up of 73 wk there was reduced progression of AS in the rosvuastatin group compared to the control group (increase in AS velocity of 0.04 m/s per year in the rosvuastatin group vs 0.24 m/s per year in the control group, \( P = 0.007 \); decrease in AVA of 0.05 cm² per year in the rosvuastatin group vs 0.10 cm² per year in the control group, \( P = 0.041 \)). This study showed promise for statins in reducing progression of AS\(^{28}\).

The Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression study was a randomized trial on 155 patients who received either atorvastatin 80 mg daily or placebo. Patients with increased peak AS velocity and aortic valve calcification on echocardiography were enrolled. The average peak AS velocity was 3.43 m/s, the average AVA was 1.03 cm², and aortic valve calcium score was 5920 log arbitrary units. Thirty-six patients had severe AS based on a peak AS velocity. Patients were followed for a median of 25 mo. Despite a significant change in the mean LDL cholesterol between the two groups following treatment (\( P < 0.001 \)), there was no difference in measures of AS progression between the two groups (increase in peak aortic jet velocity of 0.20 m/s in both groups, \( P = 0.95 \); increase in valvular calcification 22.3% per year in the atorvastatin group vs 21.7% per year in the placebo group, \( P = 0.93 \)).

Simvastatin and Ezetimibe in Aortic Stenosis was a randomized, double-blind trial involving 1873 patients with mild-to-moderate asymptomatic AS. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, AVR, nonfatal myocardial infarction, and hospitalization for unstable angina pectoris, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. During a median follow-up of 52.2 mo, the primary outcome occurred in 333 patients (35.3%) in the simvastatin-ezetimibe group and in 355 patients (38.2%) in the placebo group [hazard ratio in the simvastatin-ezetimibe group, 0.96; 95% confidence interval (CI): 0.83-1.12, \( P = 0.59 \)]. AVR was performed in 267 patients (28.3%) in the simvastatin-ezetimibe group and in 278 patients (29.9%) in the placebo group [hazard ratio, 1.00; 95% CI: 0.84-1.18, \( P = 0.97 \)]. This study showed that cholesterol lowering medications, simvastatin and ezetimibe did not reduce the composite outcome of combined aortic valve events. This therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic valve stenosis.

The Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin trial is a randomized, double-blind, placebo-controlled trial in asymptomatic patients with mild to moderate AS and no clinical indications for cholesterol lowering. The patients were randomized to receive either placebo or rosvuastatin. A total of 269 patients were randomized: 134 patients to rosvuastatin 40 mg daily and 135 patients to placebo. The median follow-up was 3.5 years. The annualized increase in the peak AS gradient was 6.3 mmHg in the rosvuastatin group and 6.1 mmHg in the placebo group (\( P = 0.83 \)). Hence this was again a negative study for use of statins in AS.

The effect of statins on the progression of AS is still not clear. The latest trials do not show any benefit in established AS. We may have to look at high risk patients like possible gene linkage or patients with end-stage renal disease and trying to prevent AS. We might also have to look at patients with mild disease and see if it reduces the disease progression. Further studies are required to answer our questions.

**Angiotensin-converting enzyme inhibitors**

Angiotensin-converting enzyme (ACE) and angiotensin II receptors have been found in stenotic aortic valves. This leads to the hypothesis that the renin-angiotensin system may play a role in disease progression. This led to trials with ACE inhibitors (ACEi) looking for their effect in AS. Two hundred and eleven patients with asymptomatic AS and a peak AS velocity of ≥ 2.5 m/s (average peak AS velocity 3.96 m/s; mean AVA 0.84 cm²) were retrospectively identified and the rates of hemodynamic progression of AS were compared between patients who were taking an ACEi vs those who were not\(^{31}\). No difference was found (increase in peak AS velocity of 0.29 m/s per year vs 0.35 m/s per year, respectively, \( P = 0.29 \)). To date, there is no randomized trial looking at the effect of ACEi in AS.

**Bisphosphonates**

Rajamanickam et al\(^{33,34}\) showed that the mechanism for aortic valve calcification is similar to that for skeletal bone formation and that this process is mediated by an osteoblast-like phenotype. Innasmithu et al\(^{33,34}\) did a retrospective study on patients > 70 years, who had transthoracic echocardiograms (TTE) > 1 year apart and an initial AVA of 0.6-2.0 cm². Patients were excluded if they had an ejection fraction < 40%, other significant valvular or congenital heart disease, end-stage renal disease or heart transplant. The cohort was divided depending on the use of bisphosphonates. AVA, peak and mean aortic valve gradient, and the change between the studies were calculated. Seventy six patients fit study criteria with 8 in the bisphosphonate group and 68 in the non-bisphosphonate group. The period between the TTEs was 23 ± 5 mo in both the groups. AVA in the non-bisphosphonate group worsened by 0.2 cm² and in the bisphosphonate group it improved by 0.1 cm² (\( P = 0.001 \)).

Skolnick et al\(^{35}\) did an observational study of patients with AS from the echocardiographic database comparing...
18 patients on treatment for osteoporosis (bisphosphonates, calcitonin, or estrogen receptor modulators) with 37 patients not on the treatment. AVA was calculated using the continuity equation. Mean baseline AVA was 1.33 cm² and not significantly different between groups. After a mean of 2.4 years, mean annual changes in AVA were reduction by 0.22 cm² in those not on treatment for osteoporosis and 0.10 cm² in patients receiving osteoporosis treatment (P = 0.025). In a multivariable analysis including age, gender, and statin use, only the treatment group was associated with a change in AVA\[37\]. There has recently been increased interest in bisphosphonates as a medication in reducing the disease progression. These two studies are retrospective and used observational data and hence randomized trials are required to assess its effect on AS.

**Transcatheter aortic valve implantation**

In 2002, the first patient underwent transcatheter aortic valve implantation (AVI) for the treatment of severe asymptomatic AS. There have been studies looking at the feasibility of percutaneous transvenous, transarterial, and transapical placement of the aortic valve. There were several single-center trials, which demonstrated that this new approach was a reasonable treatment option for patients who were inoperable or at a very high risk for surgery. The results of recent multicenter trials have shown that the procedure is safe and effective. These were associated with success rates of > 90% and 30-d procedural mortality rates of < 10% even though the trials involved very high-risk patients\[36,37\]. The prospective randomized PARTNER study, whose results will be available towards the end of 2010, will make a significant contribution to clearly establishing the safety and efficacy of percutaneous placement of the aortic valve in patients who are inoperable or at a high surgical risk.

**Surgery**

AVR is the definitive therapy for severe AS. Over time, the operative risk has dramatically decreased; currently operative mortality of isolated AVR is 2%-5% in patients over 70 years and 5%-15% in older adults. After valve replacement, symptoms diminish, quality of life improves, and long-term survival is similar to that expected for an age-matched population\[38\]. Patient-prosthesis mismatch could result in significant mortality and morbidity in patients after AVR. Hence careful selection of prostheses is important for the longevity of the replaced valve\[39,40\].

**CONCLUSION**

AS is a very common valvular heart disease and it can lead to significant mortality and morbidity in the elderly population. Severity of the disease is estimated by symptoms, clinical evaluation, echocardiography and cardiac catheterization. We need more studies looking at new techniques to assess the severity of AS more accurately and to predict the optimal timing of surgery. The only known effective treatment with documented benefits is AVR. There are a number of studies looking at the possible benefit of medications in reducing the progression of AS and transcatheter AVI in inoperable patients. We need more randomized controlled trials looking at the effective use of medications and minimally invasive procedures.

**REFERENCES**

1. Rajamannan NM, Bonow RO, Rahimtoola SH. Calcific aortic stenosis: an update. *Nat Clin Pract Cardiovasc Med* 2007; 4: 254-262
2. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997; 29: 630-634
3. 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
4. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Llytle BW, Nishimura RA, O’Gara PT, O’Rourke RA, Otto CM, Shah PM, Shanevise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Llytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006; 48: e1-e142
5. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Llytle BW, Nishimura RA, O’Gara PT, O’Rourke RA, Otto CM, Shah PM, Shanevise JS. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; 52: e1-e142
6. 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 in elderly patients. *Am J Med* 1987; 59: 998-999
7. 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. *Cin Cardiol* 1991; 14: 995-999
8. Pohle K, Maffert R, Ropers D, Maffert W, Stilianakis N, Daniel WG, Achenbach S. Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. *Circulation* 2001; 104: 1927-1932
9. Galante A, Pietrauski A, Vellini M, Piccolo P, Possati G, De Bonis M, Grilli RL, Fontana C, Favalli C. C-reactive protein is increased in patients with degenerative aortic valvular stenosis. *J Am Coll Cardiol* 2001; 38: 1078-1082
10. Soini Y, Sato T, Satta J. Angiogenesis is involved in the pathogenesis of nonrheumatic aortic valve stenosis. *Hum Cardiovasc Anesthesiology*.
Nathaniel S et al. Aortic stenosis

Pathol 2003; 34: 756-763

11 Rajamannan NM, Nealis TB, Subramaniam M, Pandya S, Stock SR, Ignatiev CI, Sebo TJ, Rosengart TK, Edwards WD, McCarthy PM, Bonow RO, Spelsberg TC. Calcified rheumatic valve neoangiogenesis is associated with vascular endothelial growth factor expression and osteoblast-like bone formation. Circulation 2005; 111: 3296-3301

12 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

13 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

14 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

15 Rajamannan NM, Subramaniam M, Richard D, Stock SR, Donovan J, Springett M, Orszulak T, Fullerton DA, Tajik AJ, Bonow RO, Spelsberg T. Human aortic valve calcification is associated with an osteoblast phenotype. Circulation 2003; 107: 2181-2184

16 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

17 O’Brien KD, Kuusisto J, Reichenbach DD, Ferguson M, Giachelli C, Alpers CE, Otto CM. Osteopontin is expressed in human aortic valvular lesions. Circulation 1995; 92: 2163-2168

18 Caira FC, Stock SR, Gleason TG, McGee EC, Huang J, Bonow RO, Spelsberg TC, McCarthy PM, Rahimtoola SH, Rajamannan NM. Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation. J Am Coll Cardiol 2006; 47: 1707-1712

19 Kaden JJ, Bickelhaupt S, Grobholz R, Vahl CF, Hagl S, Brueckmann M, Haase KK, Dempfle CE, Borrgere M. Expression of bone sialoprotein and bone morphogenetic protein-2 in calcific aortic stenosis. J Heart Valve Dis 2004; 13: 560-566

20 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

21 Mathieu P, Voisine P, Pepe A, Shetty R, Savard N, Alpers CE, Otto CM. Risk stratification of patients with aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010; 121: 306-314

22 O’Brien KD, Shavellle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM, Probstfield JL. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. Circulation 2002; 106: 2224-2230

23 Chan KL, Teo K, Dumesnil JG, Spi, Tam J. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010; 121: 306-314

24 Rossebro AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerds T, Gohlk-Bärwolf C, Holme I, Kesäniemi YA, Malbeq W, Nienaber CA, Ray S, Skaerpe T, Wachtell K, Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008; 359: 1343-1356

25 Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010; 121: 306-314

26 Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. J Am Coll Cardiol 2006; 47: 2141-2151

27 Pouleur AC, le Polain de Waroux JB, Pasquet A, Vanoverschelde JL, Gerber BL. Aortic valve area assessment: multitarget CT compared with cine MR imaging and trans thorasic and transesophageal echocardiography. Radiology 2007; 244: 745-754

28 Moura LM, Ramos SF, Zamorano JL, Barros IM, Azevedo LF, Rocha-Gonçalves F, Rajamannan NM. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. J Am Coll Cardiol 2007; 49: 554-561

29 Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005; 352: 2389-2397

30 Rossebro AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerds T, Gohlk-Bärwolf C, Holme I, Kesäniemi YA, Malbeq W, Nienaber CA, Ray S, Skaerpe T, Wachtell K, Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008; 359: 1343-1356

31 Innasimuthu AL, Katz WE. Effect of bisphosphonates on progression of aortic stenosis [Abstract]. J Am Coll Cardiol 2009; 53: A413

32 Innasimuthu AL, Katz WE. Effect of bisphosphonates on progression of degenerative aortic stenosis. Echoardiography 2010; In press

33 Skolnick AH, Ozsanek M, Formica P, Kronzon I. Osteoporosis treatment and progression of aortic stenosis. Ann J Cardiol 2009; 104: 122-124

34 Doguet F, Godin M, Lebreton G, Eltchaninoff H, Cribier A, Bessou JP, Litzler PY. Aortic valve replacement after percutaneous valvuloplasty - an approach in otherwise inoperable patients. Eur J Cardiothoracic Surg 2010; Epub ahead of print

35 Webb JG, Altwegg L, Boone RH, Cheung A, Ye J, Lichtenstein S, Lee M, Masson JB, Thompson C, Moss R, Carere R, Munt B, Nietlispach F, Humphries K. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation 2009; 119: 3009-3016

36 Kvidal P, Bergström R, Hörte LG, Stählé E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol 2000; 35: 747-756

37 Vahanian A, Otto CM. Risk stratification of patients with aortic stenosis. Eur Heart J 2010; 31: 416-423

38 Rao V, Jamieson WR, Ivanov J, Armstrong S, David TE. Prosthesis-patient mismatch affects survival after aortic valve replacement. Circulation 2000; 102: II5-II19

39 Flameng W, Herregods MC, Vercalsteren M, Herrigers P, Bogaerts K, Meurs B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. Circulation 2010; 121: 2123-2129

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