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C3 – Core Curriculum in Cardiology

Asymptomatic severe aortic stenosis with normal left ventricular function – A review

I. Sathyamurthy [a,*], K. Jayanthi [b]

[a] Apollo Main Hospitals, Chennai, India
[b] SIMS, SRM Institutes for Medical Science, Vadapalani, Chennai, India

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ABSTRACT

Aortic stenosis (AS) is one of the commonest forms of acquired valvular heart disease. Aortic valve replacement (AVR) is the treatment of choice for symptomatic severe AS. Conservative management is usually advocated for asymptomatic severe AS. But there are data on predictors to identify subsets of asymptomatic AS patients at high risk of cardiac events in whom early surgical intervention is warranted. Non-invasive tests like exercise stress test, exercise echocardiography will help us to identify those who are at high risk of developing early symptoms due to LV dysfunction and also those at high risk of sudden death. In this article, an attempt is made to review the literature on this subset of asymptomatic severe AS to help clinicians to decide regarding the need for early aortic valve replacement in them.

1. Introduction

Patients of severe valvular aortic stenosis (AS) with symptoms such as syncope, angina or heart failure carry grave prognosis.[1] Aortic valve replacement (AVR) is known to improve survival and quality of life in them.[2] Patients of asymptomatic AS with normal left ventricular (LV) function are a heterogeneous group with very few of them being at a high risk of sudden death and some of them at risk of developing early symptoms due to progressive myocardial dysfunction. The optimal timing of surgery in this subset of patients is debatable. Asymptomatic subjects need to be examined for denial or downplay of symptoms and also some of them may restrict activities to avoid occurrence of symptoms. The risk vs. benefit of AVR needs to be assessed in asymptomatic individuals keeping in mind the operative risk, morbidity related to valve prosthesis and the risk related to the use of oral anticoagulants.

The risk of AVR in cases of uncomplicated AS is 1–2% at high volume centres[3] and 3–4% at low volume surgical centres.[4] The reported incidence of thromboembolism and bleeding risk related to anticoagulation in the setting of mechanical valve in aortic position is 1.1 and 4.6/100 patient-years respectively.[5] The bleeding risk increases significantly in the elderly (age ≥75 yrs). The incidence of infective endocarditis has been reported to be 0.27% per patient-year in western countries.[6]

The risk of development of complete heart block with need for pacemaker implantation is high in patients who have left bundle branch block (LBBB) and calcification extending into the interventricular septum. Surgical expertise is required to enlarge annular size for those with small aortic annulus which will add to the surgical risk. Another important factor to consider is management of anticoagulation status. Surgical expertise and proper monitoring of anticoagulation status may not be readily available in many rural and semiurban towns in developing countries. These are the issues which raise the question whether we should operate on asymptomatic patients with severe AS as they have less than 1% risk of sudden death.

Early AVR however is expected to result in regression of LV mass. The chances of developing LV dysfunction with AVR are less which may result in improved long-term survival.[7] Certain variables identified as markers of sudden death are LBBB, associated coronary artery disease (CAD), non-sustained ventricular tachycardia by Holter monitoring and densely calcified aortic valve (AV). In severe AS certain factors such as age above 50 years, dense calcification of AV, associated risk factors like hypertension, dyslipidemia and CAD[8] were shown to result in rapid progression of symptoms.

2. Natural history of asymptomatic AS

Natural history of patients with asymptomatic severe AS is shown in Table 1. Various studies differed in their design, inclusion

* Corresponding author at: Apollo Main Hospitals, Chennai, No: 21, Greams Lane, Off Greams Road, Chennai 600006, India.
E-mail address: isathya@hotmail.com (I. Sathyamurthy).

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criteria and duration of follow-up. It has been found that approximately one third of patients become symptomatic within 2 years[9] and two-thirds of them were reported to have had either AVR or sudden cardiac death within 5 years.[8,11,12] Survival in asymptomatic unoperated patients was reported to be 99%, 98% and 93% at the end of 1, 2 and 5 years respectively.[11] It is interesting to note that survival in these patients was noted to be similar to age and sex matched healthy population.[11] Long-term prognosis however worsens with the onset of symptoms.

Risk of sudden death in asymptomatic severe AS observed in various prospective and retrospective studies is shown in Table 2. Sudden death rate per year ranged between 0.2% and 3.1%. Pellikka et al.[11] reported sudden death of 1% per year during 5 years follow-up in 622 cases of asymptomatic AS with a peak AV velocity of ≥4 m/s.

Symptoms occur in patients with AS and normal LV systolic function when the stenosis is severe (valve area is <1.0 cm^2, the jet velocity is over 4.0 m/s, and the mean transvalvular gradient ≥40 mmHg). However, some patients may become symptomatic when the stenosis is even moderately severe, particularly if there is coexisting aortic regurgitation. In Rosenhek's study,[18] some patients showed increase in mean gradients as much as 15–19 mmHg per year without progression of symptoms. Similarly, some patients had little or no progression in symptoms though the average rate of decline in valve area observed was 0.1 cm^2/yr.[18]

Taniguchi et al.[19] reported 5-year outcomes of CURRENT AS (Contemporary Outcomes after Surgery and Medical Treatment in Patients with Severe Aortic Stenosis) registry involving 1808 patients of asymptomatic severe AS who were initially treated either conservatively (n = 1517) or with AVR (n = 291). The authors found a higher rate of mortality (26.4% vs. 15.4%; p = 0.009) and hospitalizations for heart failure (19.9% vs. 3.8%; $p < 0.001$) at 5 years of follow-up in patients who were managed conservatively compared to those who underwent AVR. These data seemingly conflict with recommendations of watchful waiting for the development of symptoms.

Table 3
Exercise testing in asymptomatic severe AS.

Positive if patient develops
• Symptoms
• Complex ventricular arrhythmias
• BP failed to rise by 20 mmHg
• Fall in systolic BP
• > 1 mm horizontal/downsloping ST ↓
2 yrs event free survival 19% if test is positive
85% if test is negative
(Amato et al.[13])

3. Role of non-invasive testing

3.1. Electrocardiography (ECG)

In a multivariate analysis, left ventricular hypertrophy (LVH) as per Romhilt and Estes criteria was found to be an independent predictor of early development of symptoms.[20] However, the sensitivity of detecting LVH by ECG was found to be as low as 40%. Recently, by 24 h continuous ECG monitoring, it was shown that Tp-e interval, Tp-e/QT and Tp-e/QTc ratio can be novel indicators for prediction of ventricular arrhythmias and mortality. It was shown that Tp-e/QTc ratio had significant positive correlation with mean aortic gradient.[21]

3.2. Exercise testing

The development of symptoms and abnormal BP response to exercise were associated with poor outcomes. The appearance of symptoms, complex ventricular arrhythmias, fall in systolic BP or failure of BP to rise by 20 mmHg during exercise and ≥1 mm ST depression during exercise were found to have 2 year event free survival of only 19% as reported by Amato et al.[13] (Table 3). The 2-year survival was 85% when the exercise test was negative. Symptoms appearing during stress test predicted development of symptoms in 57% of asymptomatic patients during 1-year follow-up. However, the value of stress ECG was noted to be limited in

Table 1
Natural history of asymptomatic severe AS.

	Symptom definition	Cardiac event (or) end point definition	Symptom-free survival (%)			Event-free survival (%)				
			1 yr	2 yrs	5 yrs	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Pellika et al.[9]	Ang, Dys, syncope	AVR, cardiac death sec to AS	86 ± 3	62 ± 6		93 ± 2				
Otto et al.[10]	Ang, HF, sync, near syn	AVR, cardiac death				93 ± 5		67 ± 10		34 ± 15
Rosenhek et al.[8]	NA	AVR, cardiac death and non-cardiac death				67 ± 5	56 ± 5		33 ± 5	
Pellika et al.[11]	Ang, Dys, syncope	Symptom development, AVR, cardiac death	82	67	33	80	63			25

HF-Heart failure

Table 2
Risk of sudden death in asymptomatic severe AS.

Study	Design	No. of pts	Mean FU ± SD (months)	Events AVR	Death without preceding symptoms	Sudden death rate per year
Rosenhek et al.[8]	P	128	22 ± 18	59	1	0.43%
Amato et al.[13]	P	66	23.6 ± 12.5	N/A	4	3.1%
Lancellotti et al.[14]	P	69	15 ± 7	12	2	2.3%
Pellikka et al.[11]	R	622	64.8 ± 48	352	11	0.33%
Pai et al.[15]	R	338	42	99	N/A	13.3%
Lancellotti et al.[16]	P	163	20 ± 19	57	3	1.1%
Cioffi et al.[17]	P	209	22 ± 13	72	2	0.52%
Rosenhek et al.[18]	P	116	41 (26–63)	90	1	0.2%

P, prospective; R, retrospective.

Table 4
Exercise testing to predict symptoms within 12 months in patients with asymptomatic AS.[22]

	Sensitivity (%)	Specificity (%)	Positive predictive accuracy (%)	Negative predictive accuracy (%)
Limiting symptoms	72	78	57	87
Age ≤70 yrs in specific activity scale Class I and limiting symptoms	65	93	79	86
Systolic BP decline of <20 mmHg from baseline	39	82	48	78
ST segment depression ≥2 mm	40	79	45	77

those above 70 yrs of age. Table 4 shows value of exercise stress testing in predicting onset of symptoms.[22]

3.3. Echocardiography (echo)

Valve morphology by echo can be a predictor of cardiac events. The degree of AV calcification may actually help to plan optimal timing of surgery. Echo criteria of aortic jet velocity, aortic valve area (AVA) and rate of change of velocity over time have been found to predict clinical outcomes.[10] Rate of progression of jet velocity of 0.3 m/s/yr and decrease in AVA of 0.2 cm^2/yr help us to identify those patients who are likely to develop early symptoms. There was no association found between LV diastolic dysfunction and deterioration of symptoms in asymptomatic AS patients. Left atrial (LA) size and LA area >12.2 cm^2/m^2 have been reported to predict early occurrence of cardiac events.[23,24] Tissue Doppler-derived strain imaging is useful to assess regional and global LA function in normal subjects and in increased afterload states such as hypertension and hypertrophic cardiomyopathy.[25] In the study by Todaro et al.,[26] they found that there was a reduction in LA reservoir function and increased LA stiffness independent of LA size in patients of asymptomatic AS. Though the global longitudinal strain of LV is a strong predictor of prognosis, they suggested that LA functions can be included as part of echocardiographic risk stratification in AS.

The onset of LV systolic dysfunction over a period of time due to inappropriate high LV muscle mass (>110%) can also predict early onset of symptoms. Excessively high LV mass is an independent predictor of adverse prognosis. MicroRNAs (miRs) play crucial role in the regulation of LVH. However, few circulating miRs have been established as predictors of LVH in AS. Circulating levels of miR-1, miR-133 and miR-378 were decreased in AS patients and miR-378 predicts LVH independent of transaortic gradients. Further prospective studies are needed to elucidate whether these circulating miRs affect clinical outcomes.[27] Another important echo variable is impaired longitudinal myocardial strain (15.9%), which has been shown to predict poorer outcomes.[23] Further studies are necessary to assess prognostic value and utility of this variable.

Hachicha et al.[24] introduced a new parameter the "valvulo-arterial impedance" (ZVa) which takes into account the severity of valve stenosis and systemic vascular resistance. A valvulo arterial impedance ≥4.9 mmHg/ml/m^2 was noted to have worst prognosis and is mainly applicable in patients of low flow, low gradient AS with preserved LV function. However, only a minority of this subset of patients are asymptomatic. The role of hypertension in patients with AS is debatable. It is important to consider double LV load in such patients, valvular load imposed by the valve stenosis and an arterial load imposed by coexisting systemic hypertension. In the study by Zito et al.[28] on "Prognostic Significance of Valvuloarterial Impedance and Left Ventricular Longitudinal Function in Asymptomatic Severe Aortic Stenosis Involving Three-Cuspid Valves", they showed that an increased Zva and reduced LV longitudinal strain increased the risk of events. However, the authors cautioned about the results of the study, as the number of patients followed up were small and the fact that presence of CAD was not taken into account while interpreting the data.

3.4. Exercise echocardiography

An increase in mean aortic gradient of >18 mmHg and decrease in aortic valve area of <0.75 cm^2 at peak exercise were shown to predict occurrence of early cardiac events as reported by Lancellotti et al.[14] Fig. 1 (flow chart) shows non-invasive stress testing in patients of asymptomatic AS.[29]

3.5. Electronic beam computed tomography

In patients of asymptomatic AS calcium score of ≥1100 Agatston units has 82% specificity and 93% sensitivity as an independent predictor for survival,[30] death, need for AVR and early onset of symptoms during next 2 years.

3.6. Cardiac magnetic resonance imaging (CMR)

Determination of myocardial perfusion reserve by CMR was assessed in a prospective study[31] of 46 patients with severe AS. Though CMR can identify and quantify distribution of myocardial fibrosis with gadolinium enhancement sequences, there were no studies reported in asymptomatic AS patients using this technique to guide clinical decision making. Further studies are needed to use CMR for assessment of risk stratification in routine clinical practice.

3.7. Brain natriuretic peptide (BNP)

Elevated BNP levels were found to have significant prognostic value in patients with asymptomatic severe AS. The study by Monin et al.[32] attempted to develop a risk score based on female gender, annual rate of progression of aortic jet velocity by echo and BNP levels. Asymptomatic severe AS patients had 9 months symptom-free survival of 90% with BNP or NT Pro BNP levels <130 pg/ml and <80 pmol/l respectively as reported by Bergler-Klein et al.[33] Serial measurements of BNP might add additional information to identify optimal timing of AVR.[34]

3.8. Exercise BNP

Capoulade et al.[35] concluded from their study that peak exercise BNP levels provide significant incremental prognostic value beyond what was observed by demographic, echocardiographic and resting BNP levels.

What do the guidelines recommend (Table 5)

According to 2014 ACC/AHA valve guidelines,[36] asymptomatic severe AS patients fall into Stage C aortic stenosis. This is further subdivided into C1 – patients with normal LV function and C2 – patients with reduced LV function.

1) AVR is recommended for asymptomatic severe AS and LVEF <50% (Stage C2 disease category) – Class I – Level B indication.

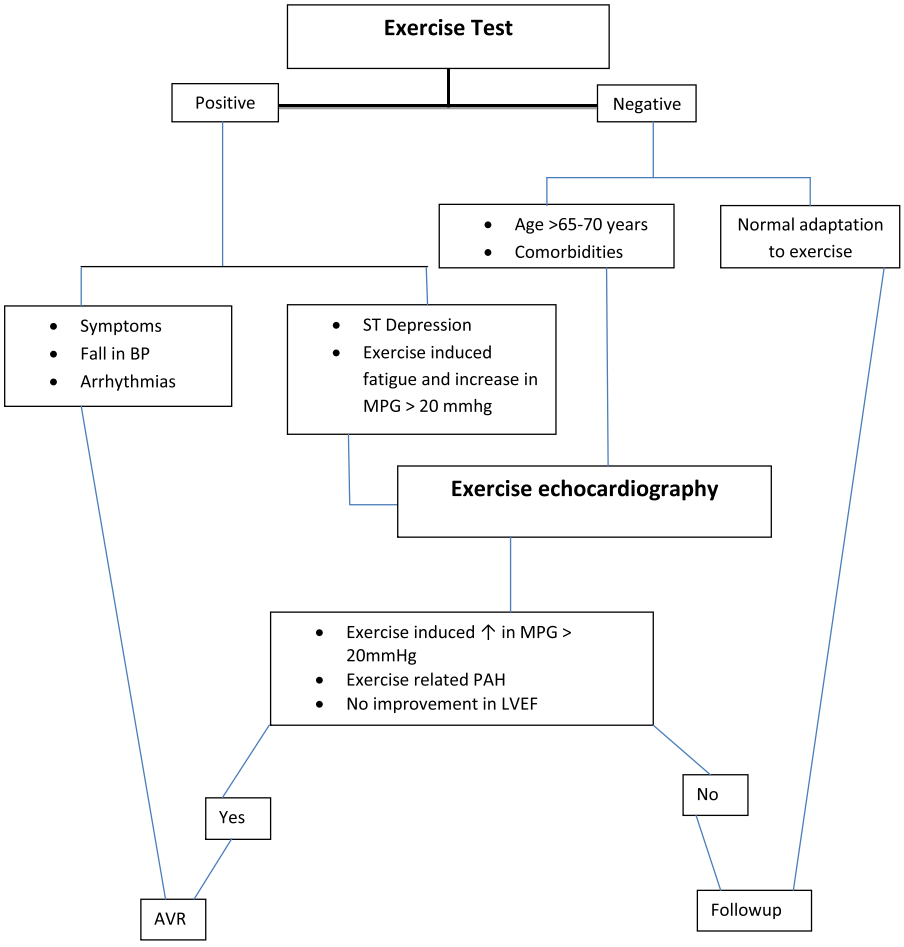

Fig. 1. Flow chart shows non-invasive stress testing in asymptomatic severe AS with preserved LV function.[29]

Table 5
Asymptomatic severe AS patients at high risk.[36]

Risk factor	High risk value	Guideline recommendation for AVR
Valve assessment		
Peak jet velocity	>5 m/s	AHA IIb
AV area	<0.6 cm^2	AHA IIb
Rate of progression of jet velocity	>0.3 m/s/year	ESC IIa (moderate–severe AS)
Degree of valve calcification	Dense – all cusps	
Valvulo arterial impedance	>4.5–4.9 mmHg/mm/m^2	
LV assessment		
LV systolic dysfunction	EF < 50%	ESC I and AHA I
LVH	>15 mm without high BP	ESC IIb
LV mass	>110% expected for body size and gender	
Strain	Global longitudinal strain <15.9%	
Indexed LA area	>12.2 cm^2/m^2	
Stress test		
TMT	Symptoms	ESC I and AHA IIb
	Fall in BP	ESC IIa and AHA IIb
	Complex arrhythmias	ESC IIb
Exercise echo	Mean pressure increase by 18–20 mmHg	

2) AVR is indicated for patients with severe AS (Stage C1 and C2 disease category) when undergoing other cardiac surgery – Class I – Level B indication.
3) AVR is reasonable in asymptomatic patients with severe AS (Stage C1 disease category) in the following subset of patients: (Class IIa – Level B indication)
   a) Aortic velocity ≥5 m/s and low surgical risk
   b) Patient with reduced effort tolerance and a fall in BP on exercise
   c) In patients with rapid disease progression

Patients with normal LV systolic function without symptoms need transthoracic echocardiography at intervals of 6 months to 1 year.

4. Conclusions

Should patients of asymptomatic severe AS with normal LVEF be subjected to AVR is debatable. Certain prognostic markers have been identified with newer non-invasive modalities which will help us to identify patients at high risk of sudden death and those who are likely to develop early symptoms due to worsening of LV function. Data is lacking in identifying one or two variables as risk factors for sudden death or to identify those at high risk of developing early symptoms warranting early AVR.[37] Further studies are needed to identify adverse outcomes in asymptomatic cases of AS with normal LVEF who are subjected to early AVR.

Asymptomatic patients require frequent monitoring and close watch for progression of disease. "Wait and watch policy" is best in these cases.

Conflicts of interest

The authors have none to declare.

References

1. Ross J, Braunwald E. Aortic stenosis. *Circulation.* 1968;36:381–386.
2. Schwartz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. *Circulation.* 1982;66:1105–1110.
3. Bonow RO, Carabello BA, Chatterjee K, et al. 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 patient with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2006;48:e1–e148.
4. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.* 2003;24:1231–1243.
5. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation.* 1994;89:635–641.
6. Piper C, Korfer R, Horstkotte D. Prosthetic valve endocarditis. *Heart.* 2001;85:590–593.
7. Kang DH, Park SJ, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation.* 2010;121:1502–1509.
8. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe asymptomatic aortic stenosis. *N Engl J Med.* 2000;343:611–617.
9. Pellika PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol.* 1990;15:1012–1017.
10. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic and exercise predictors of outcome. *Circulation.* 1997;95:2262–2270.
11. Pellikka PA, Sarono ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged followup. *Circulation.* 2005;111:3290–3295.
12. Casaclang-Verzosa G, Malouf JF, Scott CG, et al. Does left atrial size predict mortality in asymptomatic patients with severe aortic stenosis? *Echocardiography.* 2010;27:105–109.
13. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart.* 2001;86:381–386.
14. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation.* 2005;112:1377–1382.
15. Pai R, Kapoor N, bansal RC, et al. Natural malignant history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *Ann Thorac Surg.* 2006;82:2116–2122.
16. Lancellotti P, Donal E, Magne J, et al. Risk stratification in asymptomatic moderate to severe AS: the importance of the valvular, arterial and ventricular interplay. *Heart.* 2010;96:1364–1371.
17. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart.* 2011;97:301.
18. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation.* 2010;121:151–156.
19. Taniguchi T, Morimoto T, Shiomi H, et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol.* 2015;66:2827–2838.
20. Romhilt AW, Estes Jr EH. A point of score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J.* 1968;75:752–758.
21. Yayla C, Biglgin M, Akboqa MK, et al. Evaluation of Tp-E interval and Tp-E/QT ratio in patients with aortic stenosis. *Ann Noninvasive Electrocardiol.* 2015. http://dx.doi.org/10.1111/anec.12298. [Abstract].
22. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J.* 2005;26:1309–1313.
23. Conolly HM, Oh JK, Orszulak TA, et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. *Circulation.* 1997;95:2395–2400.
24. Hachicha Z, Dumesnil JG, Pibarot P, et al. Usefulness of the valvulo-arterial impedence to predict adverse outcome in asymptomatic aortic stenosis. *J Am Coll Cardiol.* 2009;54:1003–1011.
25. Galli E, Fournet M, Chabanne C, et al. Prognostic value of left atrial reservoir function in patients with severe aortic stenosis: a 2D speckle tracking echocardiographic study. *Eur Heart J Cardiovasc Imaging.* 2016;17:533–541.
26. Todaro MC, Carerj S, Khandheria B, et al. Usefulness of atrial function for risk stratification in asymptomatic severe aortic stenosis. *J Cardiol.* 2016;67(1):71–79.
27. Chen Z, Li C, Xu Y, Li Y, Yang H, Rao L. Circulating levels of miR-378 predict left ventricular hypertrophy in patients with aortic stenosis. *PLOS ONE.* 2014;(8). http://dx.doi.org/10.1371/journal.pone.0105702.
28. Zito C, Salvia J, Cusmà-Piccione M, et al. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. *Am J Cardiol.* 2011;108(10):1463–1469.
29. Magne J, Lancellotti P, Pierard LA. Exercise testing in asymptomatic severe aortic stenosis. *JACC Cardiovasc Imaging.* 2014;7:188–199.
30. Messika-Zeitonn D, Anbry MC, Detaint D, et al. Evaluation and clinical implications of aortic valve calcification measured by electron beam computed tomography. *Circulation.* 2004;110:356–362.
31. Steadman CD, Jerosch-Herold M, Grundy B, et al. Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis. *JACC Cardiovasc Imaging.* 2012;5:182–189.
32. Monin J, Lancellotti P, Monchi M, et al. Risk score for predicting outcome in patients with asymptomatic severe aortic stenosis. *Circulation.* 2009;120:69–75.
33. Bergler-Klein J, Klaarr U, Hegar M, et al. Natriuretic peptides predict symptom free survival and post-operative outcome in severe aortic stenosis. *Circulation.* 2004;109:2302–2308.
34. Baumgarttner H. Aortic stenosis medical and surgical management. *Heart.* 2005;91:1483–1488.
35. Capoulade R, Magne J, Dulgheru R, et al. Prognostic value of plasma B-type natriuretic peptide levels after exercise in patients with severe asymptomatic aortic stenosis. *Heart.* 2014;100:1606–1612.
36. Nishimura RA, Otto CM, Bonow RO, et al. 2014 ACC/AHA Guideline for the Management of Patients with valvular heart disease. A report of the ACC/AHA Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(22):e57–e185.
37. Brown ML, Pellikka PA, Schaff HV. The benefit of early valve replacement in asymptomatic patients with severe aortic stenosis. *J Thorac Cardiovasc Surg.* 2008;135:308–315.