Calcific Aortic Stenosis: Current Concepts and Management Options

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Citation

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Abstract

Calcific aortic stenosis is the most commonly encountered valvular disease in the western countries that needs surgical attention1. It affects approximately 2-3% of the elderly population above 65 years and it is associated with significant morbidity and mortality1. The most common etiology of acquired aortic stenosis is calcific degeneration. The natural history of aortic stenosis is well known. Patients with mild to moderate AS can be asymptomatic for several years even with the presence of obstruction2. Senile degenerative AS is the most common cause for aortic valvular replacement Aortic stenosis can be diagnosed with good physical examination, Doppler echocardiogram and cardiac catheterization3. Management of symptomatic aortic stenosis is replacement of aortic valve. Recent data suggest that statins may be helpful in slowing the hemodynamic progression of calcific aortic stenosis. This review will focus on etiology, pathophysiology, diagnostic evaluation and therapeutic options of acquired aortic stenosis.

ETIOLOGY AND PATHOPHYSIOLOGY

Calcific aortic stenosis is caused by progressive fibrosis and calfication of valve cusps. The process of calcification appear to be mediated by acute inflammation, lipid deposition and mechanical stress, ultimately vale cusps heavily calcify and cause severe aortic stenosis([4]). This disease process shares similar risk factors as atherosclerosis such as smoking, hypercholesterolemia and hypertension and diabetes mellitus ,Lp(a) raised serum creatinine and raised serum calcium([5]). Thus, modification of these risk factors may slow the progression of aortic valve calcification. Rheumatic valvular disease is common in the developing countries, but it is rarely seen in the developed countries. Gerber et al, reported inflammatory markers like plasma C reactive protein levels are elevated in patients with tricuspid and Bicuspid AS than normal aortic valves. Study by Sanchez et al, reported that there was high rate of progression of AS in patients with CRP levels greater than 0.3mg/dl ([7]). These findings suggest that CRP might help in predicting the hemodynamic progression of AS. Calcific aortic stenosis develops gradually and the cardiac output is maintained initially despite increasing gradient across the aortic valve. As a result, left ventricle becomes hypertrophic, and the patient may develop angina, with out any coronary artery disease ([6]). Eventually left ventricle no longer accommodates the outflow tract obstruction and ultimately starts failing.

Gender and age are important factors; Females tend to develop increased concentric wall thickness and small chamber size compared with men ([9]). Progression of AS with increase in the wall stress and afterload leads to a decrease in the ejection fraction and left ventricular systolic dysfunction. Elderly patients tend to have pronounced diastolic

Figure 1

Table 1

Risk factors for calcification of aortic valve.
Male sex
Age
Hyperlipidemia
Smoking
Diabetes Mellitus
HTN
Renal failure
Hyperparathyroidism.
Raised serum calcium [Hypercalcemia]
Raised serum creatinine

CLINICAL DIAGNOSIS

On physical examination common signs and symptoms are harsh systolic, crescendo-decrescendo murmur, at the left upper sternal border and it is transmitted to the carotids. The ejection systolic murmur is loudest at right second intercoastal space. Loudness of murmur correlates to the severity of stenosis, except in patients in with left ventricular dysfunction. Delayed and diminished carotid artery pulses are better indicator of the severity of the aortic stenosis. Systolic thrill can be palpated at the base of the heart. A palpable S4 is felt in patients with left ventricular hypertrophy due to left atrial contraction in the setting of a hypertrophied ventricle with impaired relaxation. As the AS becomes severe, angina may occur due to increased myocardial oxygen demand. Most likely cause of syncope is multifactorial such as, neurocardiogenic, ventricular arrthymias and inability to augment an appropriate cardiac out put with exercise ([10]). In these patients congestive heart failure can occur with the normal ejection fraction, most likely due to diastolic dysfunction. Presence of angina, heart failure and syncope in AS has to be monitored very closely and it may be an indication for AV replacement. Patients with AS have to be followed periodically in the clinic for the development of the symptoms. Echocardiogram with Doppler is helpful in monitoring progression of AS and has to done periodically to monitor progression of AS. Progression of the AS is related to various factors as mentioned (please refer table No 1).

Strongest predictors of aortic stenosis progression are degree of the stenosis and the degree of aortic valve calcification. Aortic stenosis can be diagnosed with good physical examination and Doppler echocardiogram, cardiac catheterization. Measurement of aortic valve area by echocardiography is the best non invasive imaging modality and the important parameters to measure are mean transvalvular gradient, maximum aortic velocity, valve area. These parameters are important predictors of clinical follow up of the patient. Aortic stenosis can be classified based on aortic velocity mild (2.6 to 3.0m/s), moderate (3 to 4m/s) and severe more than 4m/s of aortic velocity. Among these aortic velocity area is most reproducible and is the strongest predictor of the clinical outcome. Aortic valve area can be calculated using continuity of flow equation ([11]). Aortic valve area (AVA) is calculated based on utilizing the principle that volume flow proximal to the valve equals volume flow through the valve.

Figure 2

Table 2

Measurement of severity of the AS.				
	Normal	Severe	Moderate	Mild
Aortic valve area(cm)²	> 2.0	< 1.0	1.0-1.5	>1.5
Jet velocity (m/s)	1-2	>4	3-4	<3
Mean pressure gradient	gradient 0 mm of Hg	> 40	25-40	<25

Newer imaging modalities useful for assessing AS include MRI (Magnetic Resonance Imaging), EBCT(Electron beam computed tomography). These tools are not currently being used for this indication

Figure 3

Figure1: This is an example of patient with normal aortic valve on TEE (Transesophageal echocardiography)

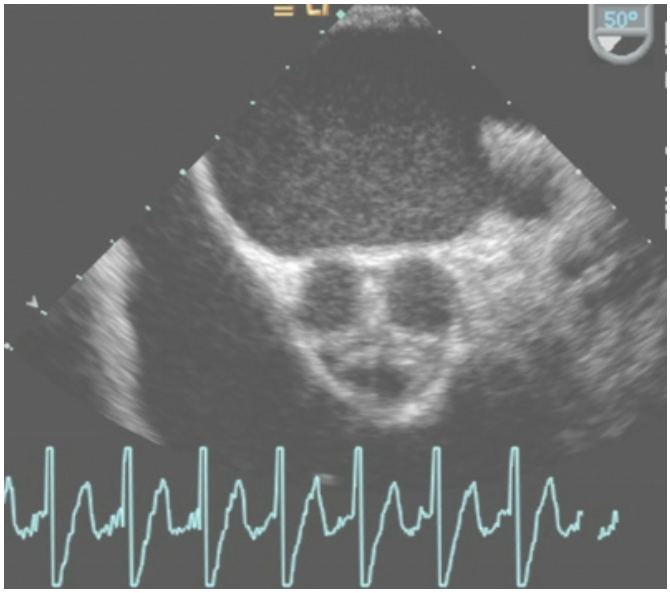
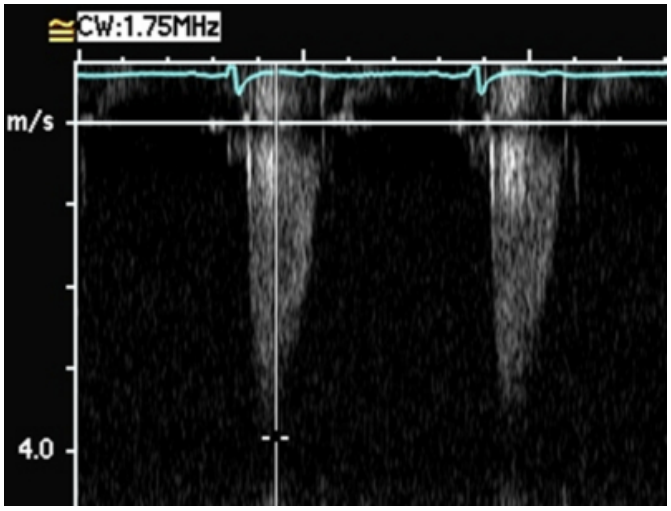


Figure 4

Figure 2: Example of a patient with moderate aortic stenosis with an aortic velocity 3.4 m/s.



NATRIURETIC PEPTIDES AS MARKERS IN AORTIC VALVE DISEASE.

Numerous studies have reported that natriuretic peptides correlate with the severity of aortic stenosis, expressed either as transvalvular gradient or valve area. ([15], [16], [17]) Correlations are generally closer with BNP and NT-proBNP than with ANP. Gerber et al reported that in aortic stenosis patients with a transvalvular gradient of at least 25 mm Hg, concentrations of natriuretic peptides (BNP, NT-proBNP, and ANP) correlated extensively with measures of the severity of stenosis and measures of LV chamber size, wall thickness and stress, ejection fraction, left atrial size, and right ventricular pressures. Natriuretic peptide concentrations increased steadily with decreasing valve area and increased greatly when ejection fraction fell below 50 %.([18])

Low gradient, Low flow aortic stenosis. Recently lot of attention has been given to low –flow, low-gradient AS. It is defined in the literature as, aortic valve area <1.0 cm² and mean gradient <30 mm of HG and LVEF <40% calculated by both the Gorlin´s and continuity equation. This group comprises 5% of the patients of the patients with significant AS ([31]). Dobutamine stress ECHO helps in grading the aortic stenosis and also tests the left ventricle contractile reserve. Commonly used doses are in the range of 5-20µg/kg/min.Some times there may be a risk of arrhythmia with higher doses and it has to be done in a controlled setting. In severe AS there will relatively large rise in the mean pressure difference and a small rise in the orifice area. ([22]) However moderate stenosis is associated with a small rise in mean pressure difference and larger rise in effective orifice area. In the severe AS patients surgical risk increases significantly if the stroke volume does not increase by more than 20% during the Dobutamine infusion .Presence of the left ventricular contractile reserve determines outcomes after the surgery than the markers of AS . Final decision will depend on the urgent necessity of the surgery and other co morbid conditions.

ROLE OF STATINS

Several studies have shown beneficial effects of statins, stating that they may slow the progression of aortic stenosis Since AS and CAD share similar risk factors, statins may play an important role as pleitropic and anti inflammatory agents. Interestingly this effect is independent of cholesterol lowering effect Results of the retrospective studies showed that statins may slow the progression of the aortic stenosis by their anti-inflammatory and lipid lowering effects. ([23], [24]) Four recently published retrospective studies suggested that statins may decrease the progression of aortic stenosis. But on the contrary in contrary recently published SALTIRE (Scottish aortic stenosis and lipid lowering therapy, impact on regression) Double blind randomized controlled trial did not show any effect on slowing of the progression of disease. There is an argument that SALTIRE trial is not powered to assess the benefits of lipid lowering treatment on cardiovascular end points, such as fatal and non fatal myocardial infarction, but there was a favorable trend in reducing clinical events. Newby et al ([12]) acknowledged that the timing of therapy for aortic valve stenosis may play the key role in the future treatment of this condition disease. The important issue may be treating this disease earlier in its process to slow the progression of bone formation in the aortic valve. Ongoing larger prospective randomized trials like SEAS (Simvastatin and the Ezetimibe in Aortic Stenosis)and ASTRONOMER((Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin) RAAVE ((Rosuvastatin Affecting Aortic Valve Endothelium) STOP-AS(Stop Aortic Stenosis) may give us definitive answer in the near future. ([13])

In the ASTRONOMER (Aortic STenosis pROgressioN:Observation Measuring Effect of Rosuvastatin) study,442 patients with mild to moderate aortic stenosis are being randomly allocated to 40 mg of rosuvastatin daily vs. placebo and followed for a minimum of 3 years. Expected completion is in 2008.

In the SEAS (Simvastatin and Ezetimibe inAortic Stenosis)

study, (Rossebo and Pedersen 2004) is an event driven 4-year study in which treatment with the combination of simvastatin 40 mg plus Ezetimibe 10 mg daily is being compared with placebo in 1870 subjects with moderate, asymptomatic, aortic stenosis. Expected completion is in 2008.

RAS INHIBITION AND ROLE OF ACE INHIBITORS.

Conventionally angiotensin-converting enzyme (ACE) inhibitors were considered to be contraindicated in patients with aortic stenosis. These concerns which are primarily regarding safety and tolerability of these agents in patients with aortic stenosis are based on the misclassification of ACE inhibitors as vasodilators rather than being founded on their results of clinical research. ([20]) ACE inhibitors are [I is well] tolerated in symptomatic patients with severe AS. Patients with congestive heart failure with LV dysfunction and low normal blood pressure patients are prone to have hypotension. ACE inhibitors may have an important role in the treatment of AS, because it can decrease the pressure over load of the left ventricle and also stress and strain on the aortic valves ([12]). It is well known that sclerotic aortic valves tissues expresses angiotensin II and ACE which may contribute to the disease progression and inflammation.([14]) Various studies in animal models have shown that long term blockade of the renin-angiotensin system arrested cardiac growth and even resulted in regression of established LVH in aortic stenosis.([21])There are two observational studies which showed mixed results, O Brien et al, reported that in 123 patients who were treated with ACE inhibitors there was 71% decrease in AS calcification. In contrast Rosenhek et al reported that progression of AS was not delayed by the ace ACE inhibitors. Larger clinical trials need to be done to address this issue, till than it can be used cautiously in patients with CAD, HTN, Heart failure and also who can tolerate this medication. However, there is already evidence that ACE inhibitors can be started in patients for hypertension associated with moderate aortic stenosis and these drugs do not need to be stopped in a patient who remains well despite more severe aortic stenosis ([19]).

MEDICAL AND SURGICAL MANAGEMENT OF AORTIC STENOSIS.

Currently, the only definitive therapy for AS is aortic valve replacement (AVR). Management of the asymptomatic patients include good history taking, physical examination and other investigations include such as EKG, Echo with Doppler. Baloon valvuloplasty is done occasionally in severely ill patients with AS if they have any contraindications for aortic valve replacement. Percutaneous replacement of aortic valve is an emerging technique, this may be an option for patients with limited life expectancy. Accurate diagnosis and efficient treatment are increasingly becoming more important as aortic valve replacement is the treatment of choice for severe aortic stenosis ([25]). There is evidence that once AS becomes severe, ischemia and fibrosis occur rapidly, setting up the possibility of heart failure and sudden death even after successful valve replacement ([26]). Therefore aortic valve replacement should be performed before extensive fibrosis occurs ([26]). The favorable long-term outcome following aortic valve replacement and the relatively low operative risk from previous studies emphasize the importance of an accurate and timely diagnosis. ([27,28]). Sharma et al in systematic review reported that in AS patients with LV (left ventricle) dysfunction show a clear functional improvement after AVR. Ventricles regress rapidly and reach their final size within first 6 months of surgery. ([29]) Maillet et al reported in patients with severe AS and reduced LVEF (left ventricular ejection fraction) can undergo valve replacement with low perioperative mortality and moderate postoperative morbidity. ([25]) Chiappinni et al in a retrospective study noted that, the outcome after AVR in octogenarians is excellent, with an acceptable operative risk and the late survival rate is good. They concluded that cardiac surgery can not be withheld on the basis of age alone. ([30]). Please Refer to table no 3 for the indications of aortic valve replacement.

Figure 5

Table 3 ()

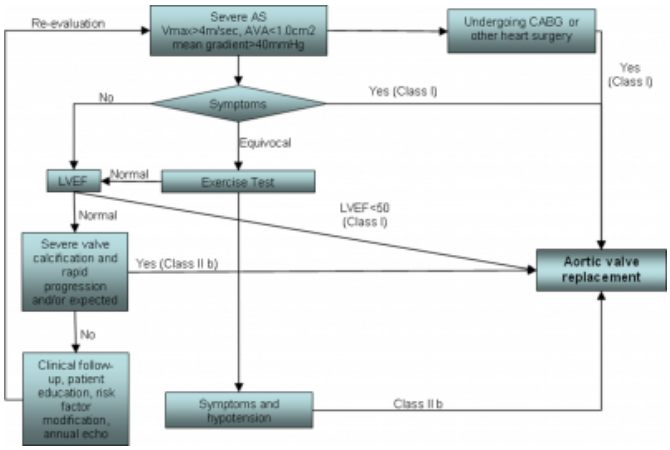
Indications for Aortic Valve Replacement	
Class I	
1. AVR is indicated for symptomatic patients with severe AS.* *(Level of Evidence: B)*	
2. AVR is indicated for patients with severe AS* undergoing coronary artery bypass graft surgery (CABG). *(Level of Evidence: C)*	
3. AVR is indicated for patients with severe AS* undergoing surgery on the aorta or other heart valves. *(Level of Evidence: C)*	
4.AVR is recommended for patients with severe AS* and LV systolic dysfunction (ejection fraction less than 0.50). *(Level of Evidence: C)*	
Class IIa	
AVR is reasonable for patients with moderate AS* undergoing CABG or surgery on the aorta or other heart valves (see Section 3.7 of the original guideline document on combined multiple valve disease and Section 10.4 of the original guideline document on AVR in patients undergoing CABG). *(Level of Evidence: B)*	
Class IIb	
1. AVR may be considered for asymptomatic patients with severe AS* and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension). *(Level of Evidence: C)*	
2. AVR may be considered for adults with severe asymptomatic AS* if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset. *(Level of Evidence: C)*	
3. AVR may be considered in patients undergoing CABG who have mild AS* when there is evidence, such as moderate to severe valve calcification, that progression may be rapid. *(Level of Evidence: C)*	
4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area less than 0.6 cm^2, mean gradient greater than 60 mm Hg, and jet velocity greater than 5.0 m per second) when the patient's expected operative mortality is 1.0% or less. *(Level of Evidence: C)*	
Class III	
AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class IIa/IIb recommendations. *(Level of Evidence: B)*	

Figure 6

Indications for Aortic Balloon Valvotomy
Class IIb
1.Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with AS who are at high risk for AVR. *(Level of Evidence: C)*
2.Aortic balloon valvotomy might be reasonable for palliation in adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions. *(Level of Evidence: C)*
Class III
Aortic balloon valvotomy is not recommended as an alternative to AVR in adult patients with AS; certain younger adults without valve calcification may be an exception (see Section 6.1.3 of the original guideline document). *(Level of Evidence: B)*

Figure 7

Figure 3 ():Severe Aortic Stenosis Management Strategy.



References

1. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol. 1993 Apr; 21(5):1220-5.
2. Rajamannan NM, Gersh B, Bonow RO. Calcific aortic stenosis: from bench to the bedside emerging clinical and cellular concepts. Heart. 2003 Jul; 89(7):801-5.
3. Botkin NF, Aurigemma GP. Aortic valve disease: a practical clinical approach. Minerva Cardioangiol. 2004 Aug; 52(4):263-72.
4. Freeman RV, Crittenden G, Otto C. Acquired aortic stenosis. Expert Rev Cardiovasc Ther. 2004 Jan; 2(1):107-16.
5. Baumgartner H. Aortic stenosis: medical and surgical management. Heart. 2005 Nov; 91(11):1483-8.
6. Boon NA, Bloomfield P.The medical management of valvular heart disease. Heart. 2002 Apr; 87(4):395-400.
7. Rossebo AB, Pedersen TR. Hyperlipidaemia and aortic valve disease. Curr Opin Lipidol. 2004 Aug; 15(4).
8. Douglas PS, Otto CM, Mickel MC, Labovitz A, Reid CL, Davis KB. Gender differences in left ventricle geometry and function in patients undergoing balloon dilatation of the aortic valve for isolated aortic stenosis. NHLBI Balloon Valvuloplasty Registry. Br Heart J. 1995 Jun; 73(6):548-54.
9. Aurigemma GP, Silver KH, McLaughlin M, Mauser J, Gaasch WH. Impact of chamber geometry and gender on left ventricular systolic function in patients > 60 years of age with aortic stenosis. Am J Cardiol. 1994 Oct 15; 74(8):794-8.
10. Richards AM, Nicholls MG, Ikram H, Hamilton EJ, Richards RD. Syncope in aortic valvular stenosis. Lancet. 1984 Nov 17; 2(8412):1113-6
11. Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. J Am Coll Cardiol. 2006 Jun 6; 47(11):2141-51.
12. Newby DE, Cowell SJ, Boon NA. Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both? Heart. 2006 Jun; 92(6):729-34.
13. Rajamannan NM. Calcific aortic stenosis: a disease ready for prime time. Circulation. 2006 Nov 7; 114(19):2007-9.
14. Helske S, Lindstedt KA, Laine M, Mayranpaa M, Werkkala K, Lommi J, Turto H, Kupari M, Kovanen PT.

Induction of local angiotensin II-producing systems in stenotic aortic valves.J Am Coll Cardiol. 2004 Nov 2; 44(9):1859-66.
15. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose Dobutamine echocardiography.
J Am Coll Cardiol. 2001 Jun 15; 37(8):2101-7.
16. Weber M, Arnold R, Rau M, et al. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. Am J Cardiol 2004; 94:740-5?
17. Qi W, Mathisen P, Kjekhus J, et al. Natriuretic peptides in patients with aortic stenosis. Am Heart J 2001; 142:725-32.
18. Talwar S, Downie PF, Squire IB, et al. Plasma N-terminal pro BNP and cardiotropin-1 are elevated in aortic stenosis. Eur J Heart Fail 2001; 3:15-9.
19. Gerber IL, Stewart RAH, Legget ME, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation 2003; 107:1884-90.
20. Chambers J.The left ventricle in aortic stenosis: evidence for the use of ACE inhibitors. Heart. 2006 Mar; 92(3):420-3.
21. Routledge HC, Townend JN.ACE inhibition in aortic stenosis: dangerous medicine golden opportunity? J Hum Hypertension. 2001 Oct; 15(10):659-67.
22. Bruckschlegel G et al. Blockade of the renin-angiotensin system in cardiac pressure-overload hypertrophy in rats. Hypertension 1995; 25: 250-259.
23. Chambers J. Low "gradient", low flow aortic stenosis. Heart. 2006 Apr; 92(4):554-8.
24. Rosenhek R, Rader F, Loho N, Gabriel H, Heger M, Klaar U, Schemper M, Binder T, Maurer G, Baumgartner H. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. Circulation. 2004 Sep 7; 110(10):1291-5.
25. Novaro GM, Tiong IY, Pearce GL, Lauer MS, Sprecher DL, Griffin BP.Effect of hydroxymethylglutaryl coenzyme a reductase inhibitors on the progression of calcific aortic stenosis . Circulation. 2001 Oct 30; 104(18):2205-9.
26. Maillet JM, Le Besnerais P, Benvenuti C, Noblesse E, Ruffenach A, Nataf P, Brodaty D. Outcome after valve replacement for severe aortic stenosis associated with reduced left ventricular ejection fraction's Heart Valve Dis. 2005 Nov; 14(6): 760.
27. Cheitlin MD. Asymptomatic adult patients with aortic stenosis: should they ever have aortic valve replacement? Am Heart Hosp J. 2005 Fall; 3(4): 243.
28. Pereira JJ, Lauer MS, Bashir M, Afridi I, Blackstone EH, Stewart WJ, McCarthy PM, Thomas JD, Asher CR.Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. Am Coll Cardiol. 2002 Apr 17; 39(8): 1356-63. 10.
29. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. Circulation. 2000 Apr 25; 101(16): 1940-6.
30. Sharma UC, Barenbrug P, Pokharel S, Dassen WR, Pinto YM, Maessen JG Systematic review of the outcome of aortic valve replacement in patients with aortic stenosis. Ann Thorac Surg. 2004 Jul; 78(1): 90-5.
31. Chiappini B, Camurri N, Loforte A, Di Marco L, Di Bartolomeo R, Marinelli G.Outcome after aortic valve replacement in octogenarians.Ann Thorac Surg. 2004 Jul;78(1):85-9.
32. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle 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.

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