

Moderate to severe aortic stenosis: Unraveling risk factors, clinical manifestations, and one-year cardiovascular outcomes

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Abstract

BACKGROUND: Aortic stenosis (AS), a progressively degenerative cardiac condition, poses a substantial burden on morbidity and mortality. This study responds to the scarcity of comprehensive data on moderate to severe AS, focusing on risk factors, clinical manifestations, and one-year outcomes.

METHODS: A retrospective cross-sectional study was conducted at Chamran Hospital (2021–2022) involving 97 patients with moderate-to-severe AS. Exclusion criteria included infiltrative diseases, radiotherapy history, cardiogenic shock, ejection fraction <20%, fever, sepsis, and active infections. Data were collected using a standardized checklist with three sections: baseline demographics and risk factors, echocardiographic parameters, and outcomes (in-hospital events, surgical aortic valve replacement [AVR], and one-year mortality).

RESULTS: Among the patients, 29 (29.9%) were classified as moderate AS and the remainder were severe AS. Severe AS patients exhibited higher systolic pulmonary artery pressure (sPAP) and higher prevalence of moderate to severe diastolic dysfunction and three-vessel disease (3VD). Echocardiographic parameters such as mean pressure gradient (MG), peak velocity (PV), and high sPAP were related to the severity of AS (moderate to severe) by odds ratios of 1.13, 6.09, and 1.15 folds, respectively.

CONCLUSION: AS imposes a significant burden of cardiovascular risk on the population. Patients with severe AS showed higher prevalence of increased filling pressures, moderate to severe diastolic dysfunction, 3VD, and higher sPAP compared with the moderate group, with no difference in clinical presentation and one-year outcome.

Keywords: Aortic Stenosis; Echocardiography; Aortic Valve Replacement; Cardiovascular Disease; Diastolic Dysfunction

Introduction

Aortic stenosis (AS) denotes a persistent degenerative process, narrowing the aortic valve with high pressure load on the left ventricle, characterized by gradual degeneration with increased cardiovascular morbidity and mortality^{1,2}. The occurrence of AS has been estimated to be about 4% within the population of individuals who are at least 70 years old, and it is expected to increase twofold by the year 2040 and triple by the year 2060^{3,4}. A recent investigation revealed an elevated incidence of AS in Iran over the past few decades. In 2017, the prevalence of AS was documented at 215.56 cases per 100,000 individuals^{5,6}.

The pathophysiology of degenerative AS is a tremendously intricate process which comprises inflammation, lipid infiltration, and fibro-calcification^{7,8}. Histological examinations of calcified aortic valve tissues have revealed the presence of inflammatory infiltrates characterized by macrophages and T-cells. Additionally, elevated levels of pro-inflammatory cytokines have been detected in stenotic valves⁹. Clotting also has a role, as clotting factors such as factor VII and factor X have been detected in stenosed aortic valves¹⁰. It is suspected that thrombin and tissue factor contribute to the calcification process in degenerative AS¹¹. Under conditions of inflammation, valvular interstitial cells (VICs) are known to express these factors, potentially initiating the coagulation cascade and resulting in the deposition of fibrin within the valve. In fact, there is a positive correlation between the amount of fibrin present in the aortic valve and the transvalvular pressure gradient¹².

Assessment of AS severity holds great importance in categorizing patient care strategies and determining the opportune moment for surgical intervention. Echocardiography serves as the key approach to assess the extent of AS by measuring transaortic PV, MG, and calculating aortic valve area (AVA)¹³. The severity of stenosis is categorized into three stages-mild, moderate, and severe-based on the specified parameters¹⁴. The extensive documentation of severe,

symptomatic AS has shed light upon its natural history. Nevertheless, the available literature is remarkably heterogeneous and fails to provide a substantial amount of information regarding clinical outcomes in adults with moderate AS^{15,16}. Earlier research conducted on groups of patients identified during cardiac catheterization indicated a rather favorable prognosis among patients with moderate AS^{17,18}. In a study by Horstkotte et al., it was observed that the period between the initial manifestation of moderate AS and the advancement to severe stenosis that necessitates surgical intervention was found to be 13.4 years¹⁸. Contradictory findings characterize the outcomes of existing studies on this matter. Therefore, the present study endeavors to explore the risk factors, clinical manifestations, and one-year outcomes among patients afflicted with moderate to severe AS.

Methods

The present project, with code of ethics (IR.MUI.MED.REC.1401.059), was approved by the Research Ethics Committee of Isfahan University of Medical Sciences.

This retrospective cross-sectional study aimed to investigate risk factors, clinical manifestations, and one-year outcomes in patients with moderate to severe AS. The study encompassed all patients who underwent echocardiography at Chamran Hospital between 2021–2022 with a final diagnosis of moderate and severe AS. Exclusions comprised patients with a history of infiltrative diseases, radiotherapy, cardiogenic shock, ejection fraction less than 25%, and current episodes of fever, sepsis, and active infections.

A standardized checklist, comprising three distinct sections, was utilized for the compilation of patient data. The initial segment scrutinized patient baseline attributes, encompassing demographic details and risk factors such as smoking, dyslipidemia, diabetes mellitus, and hypertension (HTN). Additionally, this section encompassed assessments of aortic insufficiency, coronary artery diseases, and heart rhythm at the time of admission. The second

segment comprised diverse echocardiographic parameters including left ventricular ejection fraction (LVEF), mean aortic gradient, peak aortic velocity, aortic valve area assessed by continuity equation, aortic valve area determined by 3D planimetry, and systolic pulmonary arterial pressure (sPAP). The third section evaluated patient outcomes, including early outcome (during hospitalization), the requirement for surgical aortic valve replacement, and mortality rates during one-year follow-up. The mentioned variables were extracted from patients' clinical records.

Severity classification relied on peak aortic velocity (PV), mean gradient (MG), and aortic valve area (AVA), with values of more than 4 cm/s, more than 40 mmHg, and ≤ 1 cm² indicating severe AS, respectively, and measures of AVA at 1–1.5 cm², PV: 3–4 cm/s, and MG: 20–40 mmHg denoting moderate stenosis. All echocardiographic measurements were conducted using a single echocardiography machine (Philips EPIQ 7) and were performed by an expert echocardiologist.

Statistical Analysis

SPSS (version 26) was utilized for statistical analysis. Continuous variables are expressed as mean $\pm$ standard deviation. Mean values were compared using the unpaired Student t-test. Qualitative variables are expressed as frequency (percent). Frequency distribution between two groups was compared using the chi-square test or Fisher exact test. Finally, the univariate logistic regression model was used, and then significant and important variables were entered into the multiple binary logistic regression model. A p-value <0.05 was considered to indicate statistical significance.

Results

Ninety-seven patients with AS were identified, with 29 (29.9%) classified as having moderate AS and the remainder as severe AS. The mean age of patients with severe AS was higher than those with moderate AS (69.47 ± 9.80 vs. 68.86 ± 12.65 years), but this difference was not

statistically significant ($P=0.614$). Of the total, 66 patients (68%) were male, with 20 males (69% of moderate AS patients) in the moderate AS group and 46 males (67.6% of severe AS patients) in the severe AS group ($P=0.999$). The two groups were comparable in terms of underlying comorbidities (BSA, HTN, diabetes, and hyperlipidemia), with no significant differences observed ($P>0.05$). There were also no significant differences in aortic insufficiency or heart rhythm between the groups. However, CAD showed a significant difference: the severe AS group had a higher prevalence of three-vessel disease, while the moderate AS group had more cases of one-vessel disease. Details are summarized in [Table 1](#).

This study evaluated echocardiographic characteristics of patients with moderate and severe AS, and the results revealed statistically significant differences in MG, PV, AVA by CE, AVA by planimetry, sPAP, and diastolic dysfunction ($P<0.001$). As expected, the MG was significantly higher in the severe AS group (47.97 ± 17.05 vs. 28.14 ± 9.14). Peak velocity was higher in the severe AS group (4.32 ± 0.88 vs. 3.05 ± 0.61). AVA (CE) was higher in the moderate AS group (1.25 ± 0.12 vs. 0.72 ± 0.15). AVA (planimetry) was also higher in the moderate AS group (1.25 ± 0.15 vs. 0.73 ± 0.70). Systolic PAP was more elevated in the severe AS group compared with the moderate AS group (43.90 ± 14.12 mmHg vs. 30.8 ± 5.96 mmHg). Mild diastolic dysfunction was more prevalent in the moderate group (58.6%), while moderate-to-severe diastolic dysfunction was more common in the severe AS group (52.9%) ([Table 2](#)).

Clinical manifestations of the next hospital admission were also examined, revealing higher rates of cardiac symptoms in patients with severe AS. However, statistical analysis indicated no significant difference between the two groups in terms of clinical manifestations. One-year consequences were assessed, including variables such as sudden cardiac death and surgical aortic valve replacement. While the rate of death was higher in the severe AS group, statistical significance was not reached. Sixty-

Table 1. Risk factor characteristics of patients with Moderate to Severe AS

Variable		All patients (n=97)	AS		P-value
			Moderate (n= 29)	Severe (n= 68)	
Age		69.29±10.67	68.86±12.65	69.47±9.80	0.614
Sex	Male	66(68%)	20(69%)	46(67.6%)	0.999
	Female	31(32%)	9(31%)	22(32.4%)	
BSA		1.80±0.17	1.78±0.15	1.83±0.19	0.284
Smoking		48(49.5%)	12(41.4%)	36(52.9%)	0.297
Dyslipidemia		55(56.7%)	18(62.1%)	37(54.4%)	0.460
Diabetes Mellitus		54(55.7%)	19(65.5%)	35(51.5%)	0.202
HTN		65(67%)	21(72.4%)	44(64.7%)	0.460
Aortic Insufficiency	mild	27(27.8%)	11(37.9%)	16(23.5%)	0.198
	moderate	60(61.9%)	14(48.3%)	46(67.6%)	
	severe	10(10.3%)	4(13.8%)	6(8.8%)	
	1vd	25(25.8%)	13(44.8%)	12(17.6%)	
CAD	2vd	21(21.6%)	5(17.2%)	16(16.5%)	0.005*
	3vd	26(21.6%)	2(6.9%)	24(35.3%)	
	no	25(25.8%)	9(31%)	16(23.5%)	
	AF	16(16.5%)	4(13.8%)	12(17.6%)	
Heart Rhythm	CHB	5(5.2%)	1(3.4%)	4(5.9%)	0.504
	PAC	1(1.0%)	1(3.4%)	0(0%)	
	PVC	7(7.2%)	3(10.3%)	4(5.9%)	
	sinus	68(70.1%)	20(69.0%)	48(70.6%)	

BSA: Body Surface Index, HTN: hypertension; CAD: Coronary Artery Disease, 1 VD: 1 vessel disease, 2 VD: 2 vessel disease, 3VD: 3 vessel disease, AF: Atrial Fibrillation, CHB: Complete Heart Block, PAC: Premature Atrial Complex, PVC: Premature Ventricular Complex, *: p value is significant.

Table 2. Echocardiographic features of the patients with Moderate to Severe AS

Variable		All patients (n=97)	AS		P-value
			Moderate (n= 29)	Severe (n= 68)	
EF		0.38±0.11	0.39±0.13	0.38±0.1	0.795
Mean gradient		42.04±17.62	28.14±9.14	47.97±17.05	<0.001*
Peak Velocity		3.94±0.99	3.05±0.61	4.32±0.88	<0.001*
AVA(CE)		0.88±0.28	1.25±0.12	0.72±0.15	<0.001*
AVA (planimetry)		0.92±0.30	1.25±0.15	0.73±0.17	<0.001*
sPAP		39.99±13.63	30.83±5.96	43.90±14.12	<0.001*
RWMA		36(37.1%)	10(34.5%)	26(38.2%)	.0726
PFO		4(4.1%)	0	4(5.9%)	0.314
LVH		29(29.9%)	5(17.2%)	24(35.3%)	0.075
Bicuspid Aortic valve		9(9.3%)	4(13.8%)	5(7.4%)	0.317
Diastolic Dysfunction	Mild	33(34%)	17(58.6%)	16(23.5%)	0.001*
	Moderate	48(49.5%)	12(41.4%)	36(52.9%)	
	Severe	16(16.5%)	0	16(23.5%)	

EF: Ejection Fraction; AVA: Aortic Valve Area; CE: Continuity Equation; PAP: Pulmonary Artery Pressure; RWMA: Regional Wall Motion Abnormality; PFO: Patent Foramen Ovale; LVH: Left Ventricular Hypertrophy; *: p value is significant

six patients out of 97 underwent AVR, with a significantly higher rate of AVR in the severe group (62 patients in the severe group compared with 4) ($p<0.001$). Details are available in [Table 3](#).

In this study, a univariate logistic regression model was initially performed, and the results revealed that the associations of CAD, MG, PV, AVA (CE), sPAP, diastolic dysfunction, and AVR surgery were statistically significant with the severity of AS. Specifically, CAD showed a

protective effect in patients with severe AS: 1VD (OR 1vd: 0.148, 95% CI: 0.028–0.78) and 2VD (OR 2vd: 0.077, 95% CI: 0.15–0.39). As expected, MG had a direct positive association with severe AS (OR: 1.13, 95% CI: 1.07–1.20). PV was directly associated with severe AS (OR: 6.09, 95% CI: 2.90–12.69). sPAP showed a direct increasing effect (OR: 1.15, 95% CI: 1.06–1.25). Mild diastolic dysfunction (compared to moderate-to-severe dysfunction) was associated with a higher

Table 3. Outcomes of patients with moderate to severe AS during 1 year follow-up

Variable		All patients (n=97)	AS		P-value
			Moderate (n= 29)	Severe (n= 68)	
Symptoms	Chest pain	28(28.9%)	9(31.0%)	19(27.9%)	0.319
During	Dyspnea	42(43.3%)	12(41.4%)	30(44.1%)	
Hospitalization	Syncopal	20(20.6%)	4(13.8%)	16(23.5%)	
	Other	7(7.2%)	4(13.8%)	3(4.4%)	
Death		6(6.2%)	1(3.4%)	5(7.4%)	0.665
AVR Surgery		66(68%)	4(13.8%)	62(91.2%)	<0.001

Table 4. Result of univariate binary logistic regression for patients with moderate to severe AS

	B	SE	OR	95% C.I for OR	P value
Risk factors					
Age	0.005	0.021	1.005	(0.96-1.05)	0.796
Sex (male)	-0.061	0.478	0.941	(0.37-2.40)	0.899
BSA	1.97	1.79	7.16	(0.212-241.7)	0.273
Smoking	0.47	0.45	1.59	(0.66-3.84)	0.299
Dyslipidemia	-0.316	0.454	0.729	(0.30-1.77)	0.487
Diabetes Mellitus	-0.58	0.460	0.558	(0.227-1.37)	0.205
HTN	-0.359	0.487	0.698	(0.27-1.81)	0.461
Aortic Insufficiency					
Mild	-0.031	0.755	0.970	(0.22-4.26)	0.967
moderate	0.784	0.714	2.19	(0.54-8.88)	0.272
Severe			Ref	Ref	-
CAD					
No			Ref	Ref	-
1vd	-1.90	0.846	0.148	(0.028-0.78)	0.024*
2vd	-2.56	0.838	0.077	(0.015-0.39)	0.002*
3vd	-1.32	0.897	0.267	(0.046-1.55)	0.140
Heart Rhythm					
AF	0.629	0.87	1.875	(0.382-9.20)	0.438
sinus	0.405	0.625	1.50	(0.44-5.15)	0.519
Other			Ref	Ref	-
Echocardiography					
EF	-1.17	2.05	1.31	(0.006-17.37)	0.568
MG	0.125	0.028	1.13	(1.07-1.20)	<0.001*
PV	1.81	0.37	6.09	(2.92-12.69)	<0.001*
sPAP	0.142	0.039	1.15	(1.06-1.25)	<0.001*
RWMA	0.162	0.464	1.18	(0.48-2.92)	0.726
LVH	0.962	0.553	2.62	(0.88-7.74)	0.082
Bicuspid Aortic valve	-0.701	0.711	0.496	(0.123-2.0)	0.324
Diastolic Dysfunction					
Moderate to severe			Ref.	Ref.	-
Mild	1.53	0.473	4.60	(1.82-11.64)	0.001*
Outcomes					
Symptoms During Hospitalization (base: other)					
Other symptoms			Ref	Ref	-
Chest pain	1.035	0.86	2.815	(0.517-15.32)	0.231
Dyspnea	1.20	0.837	3.33	(0.647-17.18)	0.150
Syncopal	1.67	0.946	5.33	(0.84-34.09)	0.077
Death	0.799	1.11	2.22	(0.248-19.91)	0.475
AVR Surgery	4.168	0.688	64.58	(16.78-248.54)	<0.001

EF: Ejection Fraction, AVA: Aortic Valve Area, CE: continuity equation, BSA: Body Surface Index, HTN: hypertension; CAD: Coronary Artery Disease, 1VD: 1 vessel disease, 2VD: 2 vessel disease, 3VD: 3 vessel disease, AF: Atrial Fibrillation, sPAP: systolic Pulmonary Artery pressure, RWMA: Regional Wall Motion Abnormality, LVH: Left Ventricular Hypertrophy, AVR: aortic valve replacement, *: p value is significant

risk (OR: 4.60, 95% CI: 1.82–11.62). AVR surgery also demonstrated a significant direct effect (OR: 64.58, 95% CI: 16.78–248.54) (Table 4).

The results of multiple logistic regression model for patients with moderate to severe AS are presented in Table 5. The only parameter

Table 5. Result of multiple logistic regression for significant variables in univariate logistic regression

Variables	B	S.E	OR	95% C.I for OR	P
CAD					0.333
Non			Ref.	Ref.	-
1vd	-1.190	1.192	0.304	(0.029-3.148)	0.318
2vd	-2.397	1.307	0.091	(0.007-1.179)	0.067
3vd	-1.518	1.254	0.219	(0.019-2.556)	0.226
MG	0.078	0.063	1.082	(0.956-1.224)	0.215
PV	1.555	0.909	4.737	(0.798-28.120)	0.087
sPAP	0.159	0.058	1.173	(1.047-1.313)	0.006*
Diastolic Dysfunction					
Moderate to severe			Ref.	Ref.	-
Mild	0.548	0.875	1.730	(0.311-9.611)	0.531
AVR Surgery	6.836	2.631	930.35	(5.36-161368.10)	0.09

CAD: Coronary Artery Disease, 1 VD: 1 vessel disease, 2 VD: 2 vessel disease, 3VD: 3 vessel disease, MG: mean gradient, PV: peak velocity; sPAP: systolic Pulmonary Artery pressure, AVR: aortic valve replacement *: p value is significant

that has association with severe AS was high SPAP (OR=1.17, 95%CI (1.05-1.31)).

Discussion

In the current retrospective study, we compared one-year outcomes and echocardiographic features of patients with severe and moderate AS. The findings revealed significantly worse echocardiographic features, including more severe diastolic dysfunction and higher sPAP in severe AS patients.

There was no significant difference in LVEF in severe AS patients compared with moderate ones. However, the LVEF values in the current study (38±11%) were lower than the values reported in prior studies. An observational study by Martins et al. in 2023 in Portugal estimated the EF of moderate AS at 62±8.6%¹⁹. However, other studies reported higher values for severe AS. This difference could be explained by various factors, such as differences in patient selection and ischemic heart disease prevalence, as well as the duration of AS²⁰.

The mean AVA value for the severe AS group was calculated as 0.72, consistent with previous studies. Mean gradient was also calculated for

both groups, with a higher value for severe AS. Other echocardiographic parameters, such as sPAP and diastolic dysfunction, reported values consistent with previous studies^{21,22}. Systolic PAP is considered to have prognostic value for one-year cardiovascular outcomes, and patients with higher PAP showed worse long-term clinical outcomes, especially mortality²³. Diastolic dysfunction is reported to be present in 50% of patients with severe AS with normal LV function, and in all patients with depressed LV function. We detected a higher prevalence of more advanced diastolic dysfunction in the severe group, which is due to the progressive nature of AS and myocardial impairment²⁴. It is estimated that higher sPAP and severity of diastolic dysfunction are indicators of high-pressure overload on the left ventricle for a long time, detected as left ventricular hypertrophy in echocardiogram and electrocardiogram, which leads to ventricular fibrosis and stiffness—more prominent in cases with severe AS compared with moderate ones²².

Regarding risk factors associated with AS progression, no significant differences were found between groups. However, the prevalence

of these risk factors was non-significantly higher in the severe AS group. This contradicts some previous studies, while others reported no association between risk factors such as diabetes or previous coronary artery disease in patients. This discrepancy could be explained by differences in patient populations, such as cases of congenital bicuspid AV without traditional risk factors for CAD²⁵.

The onset of symptoms is considered to be a critical determinant of outcome, although symptoms at advanced age may be related to comorbidities, and there is overlap in the etiology of symptoms. At the time of symptom onset in aortic stenosis, life expectancy without treatment is estimated to be between 2–5 years, with worse prognoses for syncope, followed by dyspnea²⁶. The prevalence of different clinical manifestations was also examined in our study, showing the highest prevalence for dyspnea in both groups, consistent with previous literature²⁷.

In a recent large-scale study, four-year all-cause mortality associated with AS diagnosis of none, mild, mild-to-moderate, moderate, moderate-to-severe, or severe was 13.5%, 25.0%, 29.7%, 33.5%, 45.7%, and 44.9%, respectively, in 595,120 patients with available AS severity assessment in the United States²⁸. In terms of one-year clinical consequences, patients in the severe AS group reported a higher prevalence of sudden cardiac death. A recent meta-analysis examining the impact of AS severity on clinical outcomes showed that moderate AS exhibits a mortality risk intermediate between no or mild AS and severe AS, with variations in specific population subsets. The heightened risk in moderate AS suggests consideration for early intervention, particularly in patients displaying high-risk features²⁹. We detected a lower prevalence of patients with moderate AS who underwent AVR compared with previous studies; most of them were cases that became candidates for coronary artery bypass graft or surgery on other cardiac valves²².

Considering the aging of the population and, as a result, the growing prevalence of

AS, the information from our study about echocardiographic parameters and outcomes of moderate to severe AS provides further insights for future research. However, these findings should be validated with a larger number of patients.

Limitations

The present study has limitations, including its retrospective nature, which could increase the risk of inaccurate data. Additionally, a proportion of included patients died during the study, increasing the chance of bias. Furthermore, the lack of a system for reporting the causes of death in patients may lower the accuracy of reported consequences.

Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: AS

Data Acquisition: AS, NK

Data Analysis or Interpretation: AS, NK, MJ

Manuscript Drafting: AS, NK, MJ, ZS

Critical Manuscript Revision: AS, MJ, ZS

All authors have approved the final manuscript and are responsible for all aspects of the work.

References

1. Eugène M, Duchnowski P, Prendergast B, Wendler O, Laroche C, Monin JL, et al. Contemporary Management of Severe Symptomatic Aortic Stenosis. *J Am Coll Cardiol*. 2021 Nov 30;78(22):2131-43. <https://doi.org/10.1016/j.jacc.2021.09.864>
2. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. *N Engl J Med*. 2014 Aug 21;371(8):744-56. <https://doi.org/10.1056/nejmra1313875>
3. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: the AGES-Reykjavík study. *Int J Cardiol*. 2014 Oct 20;176(3):916-22. <https://doi.org/10.1016/j.ijcard.2014.08.053>

4. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. *Circulation*. 2015 Mar 17;131(11):988-94. <https://doi.org/10.1161/circulationaha.114.012906>
5. Arabloo J, Omid N, Rezapour A, Sarabi Asiabar A, Mojtaba Ghorashi S, Azari S. The burden of nonrheumatic valvular heart diseases in Iran between 1990 and 2017: Results from the global burden of disease study 2017. *Int J Cardiol Heart Vasc*. 2022 Jan 17;39:100956. <https://doi.org/10.1016/j.ijcha.2022.100956>
6. Chen JH, Simmons CA. Cell-matrix interactions in the pathobiology of calcific aortic valve disease: critical roles for matricellular, matricrine, and matrix mechanics cues. *Circ Res*. 2011 Jun 10;108(12):1510-24. <https://doi.org/10.1161/circresaha.110.234237>
7. Myasoedova VA, Ravani AL, Frigerio B, Valerio V, Moschetta D, Songia P, et al. Novel pharmacological targets for calcific aortic valve disease: Prevention and treatments. *Pharmacol Res*. 2018 Oct;136:74-82. <https://doi.org/10.1016/j.phrs.2018.08.020>
8. Demir B, Caglar IM, Ugurlucan M, Ozde C, Tureli HO, Cifci S, et al. The relationship between severity of calcific aortic stenosis and serum uric acid levels. *Angiology*. 2012 Nov;63(8):603-8. <https://doi.org/10.1177/0003319711433198>
9. Lindman BR, Clavel MA, Mathieu P, Iung B, Lancellotti P, Otto CM, et al. Calcific aortic stenosis. *Nat Rev Dis Primers*. 2016 Mar 3;2:16006. <https://doi.org/10.1038/nrdp.2016.6>
10. Wypasek E, Natarska J, Mazur P, Kopytek M, Gawęda B, Kapusta P, et al. Effects of rivaroxaban and dabigatran on local expression of coagulation and inflammatory factors within human aortic stenotic valves. *Vascul Pharmacol*. 2020 Jul;130:106679. <https://doi.org/10.1016/j.vph.2020.106679>
11. Breyne J, Juthier F, Corseaux D, Marechaux S, Zawadzki C, Jeanpierre E, et al. Atherosclerotic-like process in aortic stenosis: activation of the tissue factor-thrombin pathway and potential role through osteopontin alteration. *Atherosclerosis*. 2010 Dec;213(2):369-76. <https://doi.org/10.1016/j.atherosclerosis.2010.07.047>
12. Natarska J, Marek G, Hlawaty M, Sadowski J, Tracz W, Undas A. Fibrin presence within aortic valves in patients with aortic stenosis: association with in vivo thrombin generation and fibrin clot properties. *Thromb Haemost*. 2011 Feb;105(2):254-60. <https://doi.org/10.1160/th10-09-0612>
13. Ahn Y, Choi SJ, Lim S, Kim JB, Song J-M, Kang D-H, et al. Classification of severe aortic stenosis and outcomes after aortic valve replacement. *Sci Rep*. 2022 May 7;12(1):7506. <https://doi.org/10.1038/s41598-022-11491-3>
14. Rana M. Aortic Valve Stenosis: Diagnostic Approaches and Recommendations of the 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease -A Review of the Literature. *Cardiol Cardiovasc Med*. 2022 Jun;6(3):315-324. <https://doi.org/10.26502/fccm.92920267>
15. Frank S, Johnson A, Ross J Jr. Natural history of valvular aortic stenosis. *Br Heart J*. 1973 Jan;35(1):41-6. <https://doi.org/10.1136/hrt.35.1.41>
16. Chizner MA, Pearle DL, deLeon AC Jr. The natural history of aortic stenosis in adults. *Am Heart J*. 1980 Apr;99(4):419-24. [https://doi.org/10.1016/0002-8703\(80\)90375-0](https://doi.org/10.1016/0002-8703(80)90375-0)
17. Turina J, Hess O, Sepulcri F, Kräyenbühl HP. Spontaneous course of aortic valve disease. *Eur Heart J*. 1987 May;8(5):471-83. <https://doi.org/10.1093/oxfordjournals.eurheartj.a062307>
18. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J*. 1988 Apr;9 Suppl E:57-64. https://doi.org/10.1093/eurheartj/9.suppl_e.57
19. Martins A, Alves Da Silva P, Brito J, Valente-Silva B, Oliveira C, Garcia B, et al. Moderate aortic stenosis: not as benign as it seems. *Eur Heart J Cardiovasc Imaging*. 2023;24(Suppl 1):jead119.413. <https://doi.org/10.1093/ehjci/jead119.413>
20. Hita A, Baratta S, Vaccarino G, Navia J, Olano D, Telayna JM, et al. Severe aortic stenosis with preserved ejection fraction and evidence of impairment in structure, myocardial strain and ventricular function: A new contribution to clinical decision making. *Cardiol J*. 2015;22(6):613-21. <https://doi.org/10.5603/cj.a2015.0034>
21. Schwartzberg S, Vatury M, Wiessman M, Shechter A, Morelli O, Ofek H, et al. Severe aortic stenosis echocardiographic thresholds revisited. *Echocardiography*. 2021 Dec;38(12):2016-24. <https://doi.org/10.1111/echo.15241>
22. Badiani S, Bhattacharyya S, Azimnia N, Treibel TA, Lloyd G. Moderate Aortic Stenosis: What is it and When Should We Intervene? *Interv Cardiol*. 2021 May 27;16:e09. <https://doi.org/10.15420/icr.2021.04>
23. Luçon A, Oger E, Bedossa M, Boulmier D, Verhoye JP, Eltchaninoff H, et al. Prognostic implications of pulmonary hypertension in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation: study from the FRANCE 2 Registry. *Circ Cardiovasc Interv*. 2014 Apr;7(2):240-7. <https://doi.org/10.1161/circinterventions.113.000482>
24. Hess OM, Villari B, Kräyenbühl HP. Diastolic dysfunction in aortic stenosis. *Circulation*. 1993

- May;87(5 Suppl):IV73-6.
25. Amanullah MR, Pio SM, Sin KY, Marsan NA, Ding ZP, Stassen J, et al. Factors Affecting Rate of Progression of Aortic Stenosis and Its Impact on Outcomes. *Am J Cardiol.* 2022 Dec 15;185:53-62. <https://doi.org/10.1016/j.amjcard.2022.09.016>
26. Carabello BA. Introduction to aortic stenosis. *Circ Res.* 2013 Jul 5;113(2):179-85. <https://doi.org/10.1161/circresaha.113.300156>
27. Nishizaki Y, Daimon M, Miyazaki S, Suzuki H, Kawata T, Miyauchi K, et al. Clinical factors associated with classical symptoms of aortic valve stenosis. *J Heart Valve Dis.* 2013 May;22(3):287-94.
28. Généreux P, Sharma RP, Cubeddu RJ, Aaron L, Abdelfattah OM, Koulogiannis KP, et al. The Mortality Burden of Untreated Aortic Stenosis. *J Am Coll Cardiol.* 2023 Nov 28;82(22):2101-09. <https://doi.org/10.1016/j.jacc.2023.09.796>
29. Coisne A, Scotti A, Latib A, Montaigne D, Ho EC, Ludwig S, et al. Impact of Moderate Aortic Stenosis on Long-Term Clinical Outcomes: A Systematic Review and Meta-Analysis. *JACC Cardiovasc Interv.* 2022 Aug 22;15(16):1664-74. <https://doi.org/10.1016/j.jcin.2022.06.022>