ORIGINAL ARTICLE

Prognostic factors for progression of early- and late-stage calcific aortic valve disease in Japanese: The Japanese Aortic Stenosis Study (JASS) Retrospective Analysis

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Calcific aortic valve disease (CAVD) is the most common etiology of acquired valvular heart disease, and hypertension is a principal underlying disease. The Japanese Aortic Stenosis Study (JASS) Retrospective Analysis is a retrospective observational study to clarify the prognostic factors for progression of CAVD in Japanese. Data from 556 subjects who met the following criteria were analyzed: (1) ≥ 50 years old; (2) calcification in any aortic valve leaflet or peak aortic jet velocity $\geq 2 \text{ m s}^{-1}$ on an echocardiographic study performed between July 2004 and June 2007; and (3) availability of earlier echocardiographic data from within the previous 2–5 years to assess the progression of CAVD. The subjects were divided into two groups according to CAVD severity on the preceding echocardiographic examination. In early-stage subjects with calcification in one or zero leaflets who were without aortic stenosis on the preceding echocardiographic study ($n=157$), the prognostic factors for progression were the following: (1) no use of angiotensin receptor blockers (ARB) and (2) use of warfarin. In late-stage subjects with calcification in two or three leaflets and/or aortic stenosis on the preceding echocardiographic study ($n=399$), progression was observed in females and in subjects with low hemoglobin and a concentric left ventricle. There was no relation between medications and changes in CAVD. Prognostic factors for the progression of CAVD were different between the early and late stages. Initiation of ARB treatment during the early stage may be effective, and we should be vigilant about progression of CAVD in patients treated with warfarin.

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INTRODUCTION

The prevalence of calcific aortic valve disease (CAVD) increases with aging,¹ and CAVD is the most common etiology of acquired valvular heart disease in developed countries.² Hypertension is a principal underlying disease,^{3–6} and previous studies in Western countries have shown an association between several clinical factors and the presence and/or progression of CAVD.^{3,6,7} The Cardiovascular Health Study showed that African-American ethnicity was associated with lower risk of CAVD progression.⁶ Although several risk factors are shared between atherosclerotic diseases and CAVD, discrepancies in their

pathogenesis have also been identified.^{8–10} These results highlight the necessity of investigating prognostic factors for incidence and progression of CAVD in Asian populations.

The Japanese Aortic Stenosis Study (JASS) is a multicenter, hospital-based observational study that includes retrospective and prospective studies. The JASS Retrospective Analysis is a retrospective study to investigate the prognostic factors for progression of CAVD in Japanese subjects. As previous studies in Western countries suggest that prognostic factors differ according to CAVD severity,^{4,6,11} the study subjects were divided on the basis of the presence of early- vs. late-stage diseases.

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METHODS

Subjects

The JASS Retrospective Analysis enrolled 775 Japanese subjects who met the following criteria: (1) age ≥ 50 years old; (2) markedly increased reflectivity (calcification) of any aortic valve leaflet or peak aortic jet velocity of at least 2 m s^{-1} on an echocardiographic recording performed between July 2004 and June 2007; and (3) availability of a report or recording from an echocardiographic study performed 2–5 years back. Subjects with rheumatic valvular disease or who had undergone aortic valve replacement were excluded. In 556 of the 775 subjects, we were able to assess whether CAVD had progressed or not compared with the previous echocardiographic study. Mean follow-up duration was 2.8 years. In these 556 subjects, laboratory data from the time of the preceding echocardiographic examination were collected from the medical records. Phlebotomy was performed in the fasting or non-fasting state. The glomerular filtration rate (eGFR) was calculated using an equation modified for the Japanese: $\text{eGFR (ml min per } 1.73 \text{ m}^2) = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094}$ (if female, $\times 0.739$).¹²

This retrospective study conforms to the guiding principles for epidemiologic studies of the Ministry of Health, Labour and Welfare, Japan, and was approved by all relevant institutional ethical committees.

Echocardiography and assessment of the progression of CAVD

Doppler echocardiography was conducted using commercially available echocardiographic machines as described previously.^{13,14} In the routine echocardiographic examination, measurements were conducted on-line. Ejection fraction was calculated using a modification of the method of Quinones *et al.*¹⁵ as described previously.^{13,14} In subjects with regional wall motion abnormalities, the biplane Simpsons' method was used.^{13,14} Left ventricular (LV) mass was calculated following a formula derived from data compiled by the American Society of Echocardiography¹⁶ as described previously.^{13,14} LV mass index was calculated as a ratio of LV mass to height^{2.7,14}. The number of aortic valve leaflets with calcification was evaluated by an experienced cardiologist and/or sonographer.

The 556 subjects were divided into two groups according to the degree of CAVD at the preceding echocardiography. The group with early-stage CAVD comprised subjects with calcification on one or no leaflet and peak aortic transvalvular flow velocity $< 2 \text{ m s}^{-1}$ ($n=157$).^{6,17–19} The late-stage CAVD group comprised subjects with two or three calcified aortic valves and/or with peak aortic transvalvular flow velocity of $\geq 2 \text{ m s}^{-1}$ ($n=399$). Eleven patients had bicuspid aortic valve, and all met the criteria for late-stage CAVD. As of their small number, their data were analyzed with other late-stage subjects.

Progression in the late-stage group was defined as a $\geq 0.3 \text{ m s}^{-1}$ per year rate of increase in peak aortic transvalvular flow velocity at follow-up, as described previously.^{17,20} In the early-stage group, progression was defined as the appearance of two or three newly calcified leaflets or the onset of aortic stenosis (peak aortic transvalvular flow velocity of $\geq 2 \text{ m s}^{-1}$) at follow-up.

Statistical analysis

Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC, USA). Continuous data are summarized as mean $\pm$ s.d. Categorical data are presented as percentages. The Student's *t*-test was used for normally distributed data, especially demographic data, and the Wilcoxon rank sum test was used for non-normally distributed data (for example, laboratory data). The χ^2 test was used for binary data (for example, use of concomitant medication). The Mantel test was applied for ordered categorical data, that is, the degree of aortic and mitral regurgitation. The significance level was fixed at 5%.

RESULTS

Subject characteristics

Baseline characteristics are listed in Table 1. Age and prevalence of hypertension, diabetes mellitus, dyslipidemia and renal insufficiency were increased in subjects with late-stage CAVD. Systolic blood pressure was higher, but diastolic blood pressure was lower in late- vs. early-stage subjects. The prescription rate of angiotensin-converting

Table 1 Subject characteristics

	All	Early stage	Late stage
<i>n</i>	556	157	399
Age (years)	73.7 $\pm$ 9.0	71.1 $\pm$ 8.0	74.7 $\pm$ 9.2*
Male (%)	52.3	55.4	51.1
Body mass index (kg m^{-2})	22.5 $\pm$ 3.4	23.0 $\pm$ 3.2	22.3 $\pm$ 3.4
Systolic blood pressure (mm Hg)	135 $\pm$ 18	133 $\pm$ 16	137 $\pm$ 19*
Diastolic blood pressure (mm Hg)	74 $\pm$ 11	77 $\pm$ 12	73 $\pm$ 11*
<i>Comorbidity (%)</i>			
Hypertension	72.8	65.6	75.7*
Diabetes mellitus	29.0	22.9	31.3*
Dyslipidemia	49.1	40.1	52.6*
Renal insufficiency	23.4	12.1	27.8*
<i>Medications (%)</i>			
Angiotensin converting enzyme inhibitor	20.5	33.8	15.3*
Angiotensin receptor blocker	30.9	23.6	33.8*
β -blocker	21.8	28.0	19.3*
Calcium channel blocker	41.7	49.0	38.9*
Warfarin	18.9	17.2	19.6
Statins	27.5	24.8	28.6
Oral hypoglycemic medications	10.8	9.6	11.3
Insulin	4.5	6.4	3.8

* $P < 0.05$ vs. early stage.

Table 2 Preceding echocardiographic data

	All	Early stage	Late stage
Left atrial dimension (mm)	41 $\pm$ 8	40 $\pm$ 9	41 $\pm$ 8*
Left ventricular end-diastolic dimension (mm)	48 $\pm$ 7	49 $\pm$ 7	48 $\pm$ 7
Left ventricular end-systolic dimension (mm)	31 $\pm$ 7	31 $\pm$ 8	30 $\pm$ 7
Ejection fraction (%)	66 $\pm$ 11	65 $\pm$ 12	66 $\pm$ 10
Left ventricular mass index ($\text{g m}^{-2.7}$)	55.3 $\pm$ 17.2	51.2 $\pm$ 15.7	57.0 $\pm$ 17.6*
<i>The degree of aortic regurgitation (%)</i>			
0	37.8	52.2	32.1
I	34.4	28.7	36.6
II	21.6	16.6	23.6
III	5.8	2.6	7.0
IV	0	0	0
$P < 0.0001$ vs. early stage			
<i>The degree of mitral regurgitation (%)</i>			
0	28.2	31.9	26.8
I	50.4	47.8	51.4
II	17.3	15.9	17.8
III	3.6	3.8	3.5
IV	0.2	0.6	0
$P = 0.5567$ vs. early stage			

* $P < 0.05$ vs. early stage.

enzyme (ACE) inhibitors, β -blockers and calcium channel blockers was lower, and angiotensin receptor blocker (ARB) use was higher in subjects with late- vs. early-stage CAVD.

Data from the previous echocardiographic studies are shown in Table 2. Average left atrial dimension and LV mass index were higher

Table 3 Laboratory data at the preceding echocardiography

	All	Early stage	Late stage
Hemoglobin (g per 100 ml)	12.5 ± 2.1	13.3 ± 1.8	12.2 ± 2.2*
White blood cell count (μl ⁻¹)	5885 ± 1943	5880 ± 1486	5887 ± 2102
Platelet (10 ⁴ per μl)	19.8 ± 7.6	20.8 ± 5.5	19.4 ± 8.3*
Serum glucose (mg per 100 ml)	114 ± 32	107 ± 26	117 ± 33*
Total cholesterol (mg per 100 ml)	193 ± 38	197 ± 35	192 ± 39
Triglyceride (mg per 100 ml)	123 ± 61	117 ± 49	126 ± 66
Creatinine (mg per 100 ml)	1.7 ± 2.4	1.3 ± 2.0	1.8 ± 2.6
eGFR (ml min ⁻¹ per 1.73 m ²)	56.9 ± 27.3	60.8 ± 22.4	55.3 ± 28.8*

Abbreviation: eGFR, glomerular filtration rate.
**P* < 0.05 vs. early stage.

in subjects with late- vs. early-stage disease. Aortic regurgitation was observed in more than half of subjects with late-stage CAVD, but in less than half of subjects with early-stage disease.

Laboratory data measured at the time of the preceding echocardiographic examination are shown in Table 3. Hemoglobin and platelet levels and eGFR were lower, whereas serum glucose level was higher in subjects with late- vs. early-stage CAVD.

Prognostic factors for progression of CAVD at the early and late stages

Of the 157 subjects with early-stage CAVD on the preceding echocardiographic study, progression during the follow-up period was observed in 75 subjects and was associated with the use of warfarin and nonuse of ARBs. About half of the subjects without progression were free of mitral regurgitation, but more than 80% of those with progression did have mitral regurgitation. There was no significant difference in the prevalence of atrial fibrillation between subjects with and without progression (17.8 and 22.0%, respectively). There was no association between progression and any other factors listed in Tables 1–3 (Tables 4 and 5).

Of 399 subjects with late-stage CAVD on the preceding echocardiographic study, progression during the follow-up period was observed in 73 subjects. Those with disease progression were more likely to be female, with smaller LV end-diastolic and end-systolic dimensions and lower hemoglobin levels than those without progression (Tables 4 and 6). There was no significant difference in the prescription rates of any medications listed in Table 4.

Hypertension, diabetes mellitus, dyslipidemia and renal insufficiency were not associated with progression in subjects in either early or late stages of CAVD.

DISCUSSION

Previous studies have shown that factors such as aging, male gender, high low-density lipoprotein (LDL) levels and a history of hypertension were related to the progression of CAVD.^{4,6,20} However, prognostic factors are likely to differ between the early and late stages, and moreover, the Cardiovascular Health Study has shown the effects of ethnicity on CAVD pathogenesis.⁶ This retrospective study analyzed data from Japanese patients and showed that early-stage subjects with mitral regurgitation, nonuse of ARBs or warfarin use tended to undergo progression of CAVD. In late-stage subjects, progression was associated with female gender, small LV cavity and low level of hemoglobin. Although the prevalence of hypertension, diabetes mellitus, dyslipidemia and renal insufficiency was higher in subjects with late- vs. early-stage disease, none of these comorbidities affected CAVD progression in early- or late-stage disease.

Table 4 Association of each factor with the progression of CAVD

	Early stage P-value	Late stage P-value
Age	0.8944	0.6187
Gender	0.1427	0.0311*
Body mass index	0.5917	0.4317
Systolic blood pressure	0.7145	0.5081
Diastolic blood pressure	0.8594	0.4913
<i>Comorbidity</i>		
Hypertension	0.3331	0.4744
Diabetes mellitus	0.2416	0.5502
Dyslipidemia	0.5380	0.8114
Renal insufficiency	0.6284	0.9579
<i>Medications</i>		
Angiotensin-converting enzyme inhibitor	0.5699	0.4971
Angiotensin receptor blocker	0.0326*	0.4604
β-Blocker	0.4810	0.0521
Calcium channel blocker	0.6974	0.6043
Warfarin	0.0308*	0.3148
Statins	0.8156	0.4776
Oral hypoglycemic medications	0.6502	0.9641
Insulin	0.0692	0.8388
Left atrial dimension	0.1437	0.7268
Left ventricular end-diastolic dimension	0.6562	0.0144*
Left ventricular end-systolic dimension	0.4471	0.0120*
Ejection fraction	0.3298	0.3087
Left ventricular mass index	0.1241	0.9572
The degree of aortic regurgitation	0.4532	0.1558
The degree of mitral regurgitation	0.0001*	0.8057
Hemoglobin	0.3684	0.0166*
White blood cell count	0.7898	0.6567
Platelet	0.3102	0.8894
Serum glucose	0.6124	0.9110
Total cholesterol	0.6096	0.3299
Triglyceride	0.1737	0.0630
Creatinine	0.6067	0.2260
eGFR	0.8014	0.3299

Abbreviations: CAVD, calcific aortic valve disease; eGFR, glomerular filtration rate.

Prognostic factors for progression of early-stage CAVD

We have shown that the prognostic factors for progression of CAVD in Japanese subjects differ between the early and late stages, a conclusion that is compatible with previous studies of Caucasian subjects.^{4,6,11,17}

In this study, nonuse of ARBs was associated with progression in early-stage subjects. Previous studies showed that ACE and angiotensin II type 1 receptor were upregulated when angiotensin II was expressed in the calcified human aortic valve compared with the normal valve.^{21,22} An experimental study showed that in hypercholesterolemic rabbits, ARBs prevented lesion formation in the aortic valve, specifically preventing the accumulation of macrophages, myofibroblasts and osteoblasts, upregulation of osteopontin and ACE, and disruption of endothelial integrity.²³ Findings from these earlier studies and this study suggest that ARBs prevent progression of CAVD during the early stage. However, use of ACE inhibitors did not affect CAVD progression in this study. This may be partly explained by upregulation of chymase and ACE in the calcified aortic valve²² and by

Table 5 Prognostic factors for the progression of CAVD in subjects at the early stage

	Progression	
	+	–
1. Angiotensin receptor blocker		
Use	16.0%	30.5%
No use	84.0%	69.5%
Odds ratio 0.434 (95% CI; 0.200, 0.944), $P=0.0326$		
2. Warfarin		
Use	24.0%	11.0%
No use	76.0%	89.0%
Odds ratio 2.561 (95% CI; 1.071, 6.126), $P=0.0308$		
3. Mitral regurgitation		
0	13.3%	48.8%
I	61.3%	35.4%
II	17.3%	14.6%
III	8.0%	0.0%
IV	0.0%	1.2%
$P=0.0001$		

Abbreviations: CAVD, calcific aortic valve disease; CI, confidence interval.

Table 6 Prognostic factors for the progression of CAVD in subjects at the late stage

	Progression	
	+	–
1. Gender		
Male	39.7%	53.7%
Female	60.3%	46.3%
Odds ratio 0.569 (95% CI; 0.339, 0.954), $P=0.0311$		
2. Left ventricular end-diastolic dimension (mm)		
	46 ± 6	48 ± 7
$P=0.0144$		
3. Left ventricular end-systolic dimension (mm)		
	28 ± 5	31 ± 9
$P=0.0120$		
4. Hemoglobin (g per 100 ml)		
	11.6 ± 2.1	12.3 ± 2.2
$P=0.0166$		

Abbreviations: CAVD, calcific aortic valve disease; CI, confidence interval.

the inadequate suppression of angiotensin II production in the aortic valve by ACE inhibitors.

Warfarin use was also associated with CAVD progression. Matrix γ -carboxyglutamic acid protein is a mineral-binding extracellular matrix protein and a potent inhibitor of tissue calcification. Vitamin K antagonists such as warfarin induce the incomplete γ -carboxylation of matrix γ -carboxyglutamic acid protein and attenuate the synthesis and function of matrix γ -carboxyglutamic acid protein.²⁴ Previous observational studies in Western countries showed that aortic valve

calcifications were significantly larger in patients treated with oral anticoagulants,^{25,26} a finding that is compatible with our current data from Japanese patients. In a society with many elderly, such as in Western countries and Japan, the use of oral anticoagulants to prevent thromboembolic events has increased correspondingly with the rising prevalence of atrial fibrillation, but the effects of warfarin on the progression of CAVD were independent of the presence of atrial fibrillation in this study. We should be aware of this potential adverse effect of warfarin.

Subjects with progression of CAVD had a higher prevalence of mitral regurgitation. Jassal *et al.*²⁷ reported the close relationship between mitral annular calcification and aortic valve calcification in patients with aortic stenosis. We did not assess the effects of mitral annular calcification, but the relationship between mitral regurgitation and progression of early-stage CAVD may be partly explained by the previous finding.

Prognostic factors for progression of late-stage CAVD

This study showed that more subjects with progression of late-stage CAVD were female. A valvular origin of heart failure, such as aortic stenosis, was more common in women than in men.^{28,29} However, some studies of Caucasian patients found that male gender was a prognostic factor for the development of aortic stenosis,^{6,7} whereas others found no influence of gender.^{11,20} The effects of gender on coronary artery calcification differed even between patient cohorts from the Western countries.³⁰ It is plausible that gender influence on the incidence and progression of CAVD differs among racial groups.

The subjects with CAVD progression had a smaller LV cavity than those without progression. There was no difference in LV mass index, and our results therefore indicate that the LV cavity was more concentric in subjects with progression. Aortic valve area is altered by transvalvular flow and increases during exercise. However, exercise-induced increases are small in subjects with stiff aortic valves leading to excessive pressure overload and concentric remodeling of the LV cavity. Thus, the aortic valve of subjects with concentric LV cavity might have already been more severely injured at the time of the preceding echocardiographic study. Subjects with CAVD progression also had lower hemoglobin levels than those without progression. The enhanced shear stress associated with stenosis of the native aortic valve can theoretically induce intravascular hemolysis.^{31–33} Aortic stenosis is sometimes associated with loss of high molecular von Willebrand multimers and with a greater tendency to bleed.^{34,35} Although these issues are of clinical significance only in cases of severe anemia requiring transfusion, mild anemia in our subjects may exist in part because of these mechanisms. If so, the low hemoglobin level may also indicate that aortic valve injury was more severe at the earlier echocardiographic examination in subjects with progression. Although renal insufficiency is closely related to anemia in patients with cardiovascular diseases, there was no significant difference in serum creatinine or eGFR levels between subjects with vs. without progression. These results suggest that CAVD progression is closely related to its severity at baseline in the late-stage subjects, a conclusion that is compatible with findings from previous studies.^{4,11,20} However, the mechanisms of this relationship cannot be explained by this study, and future studies are required.

Differences in comorbidities between subjects with early- and late-stage CAVD. The prevalence of hypertension, diabetes mellitus, dyslipidemia and renal insufficiency was higher in subjects with late- vs. early-stage CAVD (Table 1). This suggests that the presence of these comorbidities is related to the progression of CAVD; however, none

were found to be prognostic factors for progression in subjects in either early- or late-stage disease. This discrepancy was also observed in the Cardiovascular Health Study.^{3,6} The follow-up duration was only 2.8 years in this study, and each comorbidity may require a much longer time to affect the aortic valve. Treatment for each comorbidity during the study follow-up period might have masked its effects. In addition, although the data concerning cholesterol fractions were available for less than 70% of our study subjects, high-density lipoprotein levels tended to be high in subjects without CAVD progression compared with those with progression in both the early- and late-stage groups. This study does not necessarily rule out the effects of comorbidities, particularly those that are untreated, on incidence and/or progression of CAVD.

Study limitations

There are several limitations of this study. First, this is a retrospective and hospital-based study, and thus, the selection of study subjects might be biased. The results presented here should be confirmed by prospective studies such as JASS Prospective Analysis (<https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000842&type=summary&language=E>). Second, it is well known that the prevalence of CAVD is high in patients with chronic kidney disease, particularly those requiring hemodialysis,³⁶ but renal insufficiency and eGFR were not identified as predictive factors for progression in this study. This may be because very few hemodialysis patients participated in this study, and the follow-up period was not long enough for the renal insufficiency to exacerbate CAVD. Third, the severity of CAVD at baseline was varied even within each group, and analysis of data from the late-stage subjects suggests that whether or not CAVD progresses is closely related to its severity at baseline. If subjects were divided into more groups, the effects of the baseline severity might have been omitted, and other prognostic factors might have been unmasked. However, the number of patients with severe CAVD (peak aortic transvalvular flow velocity $>4\text{ m s}^{-1}$) was too small in this study to identify prognostic factors. To exclude the effects of baseline disease severity and to unmask other prognostic factors, future studies with larger number of subjects are required. Fourth, the follow-up period was not the same between subjects with and without progression in either groups. In the late-stage group, the follow-up period in subjects with progression was shorter than in those without progression. CAVD gradually progresses in general, and thus, even if the follow-up period were lengthened for subjects with progression, the classification of each subject might not be affected. In the early-stage group, the difference in the follow-up period was only 0.39 year, and thus, the effects of a difference in follow-up period were probably small even if present. Fifth, phlebotomy was not necessarily performed in the fasting state, and data concerning cholesterol fractions were unavailable in more than 30% of our study subjects. Thus, this study might not be able to make conclusive statements about the relationship between CAVD progression and dyslipidemia.

Clinical implications

Moura *et al.*³⁷ reported the attenuated progression of aortic stenosis in patients who received rosuvastatin because their low-density lipoprotein levels were $>130\text{ mg per }100\text{ ml}$ at baseline, compared with those who did not receive rosuvastatin because their baseline low-density lipoprotein was $<130\text{ mg per }100\text{ ml}$; in addition, the greater decrease in low-density lipoprotein was associated with less progression of aortic stenosis in the rosuvastatin-treated patients. Recent clinical trials failed to find beneficial effects of pharmacological lipid-lowering therapy in preventing progression of aortic stenosis in patients for

whom lipid-lowering therapy is not indicated according to current guidelines.^{19,38,39} In this study, the subset of patients with aortic stenosis fell into the cohort of subjects with late-stage CAVD, and as in the previous studies, results from this group found that use of statins or other medications had no effect on the progression of disease in the late stage. Use of statins may attenuate the progression of late-stage CAVD in patients for whom lipid-lowering therapy is indicated according to the current guidelines; however, administering statins beyond these guidelines in an effort to prevent progression of late-stage CAVD through their non-lipid-lowering effects is likely to be unjustified. Currently, there is no pharmacological therapy that is specific for late-stage CAVD.

In contrast, use of ARBs during early-stage CAVD was associated with lack of progression in this study. The prevalence of aortic stenosis is because of high CAVD in developed countries, and the only established therapeutic strategy is aortic valve replacement. This finding suggests that initiation of ARBs during early-stage disease may prevent progression of CAVD and avoid aortic valve replacement. To clarify the effects of ARBs, randomized trials should be performed.

CONCLUSIONS

Prognostic factors for progression of CAVD differed between early- and late-stage disease in a Japanese patient cohort. This study suggests that initiation of ARB treatment during the early stage is effective in preventing disease progression, and that caution is indicated in patients treated with oral anticoagulants. Female gender is predictive for disease progression during the late stage, and progression may be more rapid in patients who have a more severe aortic valve injury.

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