Significance of Coronary Artery Disease and Left Ventricular Afterload in Unoperated Asymptomatic Aortic Stenosis

Kentaro Shibayama, MD; Masao Daimon, MD; Hiroyuki Watanabe, MD; Takayuki Kawata, MD; Sakiko Miyazaki, MD; Ryoko Morimoto-Ichikawa, MD; Masaki Maruyama, MD; Shuo-Ju Chiang, MD; Katsumi Miyauchi, MD; Hiroyuki Daida, MD

Background: Because the covariates of cardiovascular events in unoperated patients with asymptomatic aortic stenosis (AS) have not been adequately evaluated, we aimed to identify them.

Methods and Results: A total of 230 patients with asymptomatic severe AS were retrospectively enrolled. The patients were divided into 2 groups based on aortic valve replacement (AVR) after enrollment: a non-AVR group (n=112), and an AVR group (n=118). The primary clinical endpoint was cardiovascular events, which were defined as cardiovascular death or hospitalization. Coronary artery disease [hazard ratio (HR): 3.62, 95% confidence interval (CI): 1.585–8.245, $P<0.01$] and high valvulo-arterial impedance (HR: 3.08, 95% CI: 1.261–7.532, $P<0.05$) were identified as independent covariates of cardiovascular events in the non-AVR group. The relative risk of cardiovascular events rose with an increase in the number of risk factors ($P<0.0001$).

Conclusions: In unoperated patients with asymptomatic AS, the presence of coronary artery disease and increased global left ventricular afterload may be associated with a poor prognosis. (*Circ J* 2016; **80**: 519–525)

Key Words: Aortic stenosis; Coronary artery disease; Echocardiography; Valve disease surgery; Valvular heart disease

It is known that patients with symptomatic aortic stenosis (AS) have a high mortality rate and require prompt aortic valve replacement (AVR).¹ In contrast, patients with asymptomatic AS have a benign prognosis and cardiovascular events are generally preceded by the development of significant symptoms.^{2–4} Although management of asymptomatic AS remains controversial,^{5,6} previous reports showed that selected patients with asymptomatic AS may benefit from AVR.^{7–11} Therefore, the current ACC/AHA guideline published in 2014 considers surgery as a reasonable strategy in asymptomatic patients with left ventricular ejection fraction (LVEF) $<50\%$, very severe AS, abnormal exercise stress testing and rapid disease progression; and in patients undergoing other cardiac surgery.¹ However, the covariates of cardiovascular events in unoperated patients with asymptomatic AS have not been adequately evaluated. In addition, despite the fact that an ethnic influence on the risk of AS has been proposed,¹² there is a paucity of Japanese studies regarding the clinical outcomes of unoperated asymptomatic patients with severe AS.

The present study aimed to identify these covariates in a Japanese population of unoperated patients with asymptomatic severe AS.

Methods

Study Population

In this retrospective study, a total of 230 patients with asymptomatic severe AS recorded in an echocardiographic database at Juntendo University Hospital were consecutively enrolled between August 2000 and August 2012. Severe AS was defined as a peak transaortic velocity (V_p) of >4.0 m/s or an aortic valve area (AVA) <1.0 cm² with normal LV function (LVEF $\geq 50\%$).¹ When AVA was <1.0 cm² and there was LV dysfunction (LVEF $<50\%$), severe AS was determined by the presence of severe leaflet calcification or congenital stenosis.¹ All patients met the following specific inclusion criteria: age ≥ 20 years, absence of symptoms, and no more than mild associated cardiac valve lesions. Symptoms of AS were defined as a

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Department of Cardiology, Juntendo University School of Medicine, Tokyo (K.S., M.D., T.K., S.M., R.M.-I., M.M., S.-J.C., K.M., H.D.); Heart Center, Tokyo Bay Urayasu/Ichikawa Medical Center, Urayasu (K.S., H.W.), Japan; and Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei (S.-J.C.), Taiwan

Mailing address: Masao Daimon, MD, Department of Cardiology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: daimon@muf.biglobe.ne.jp

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Table 1. Baseline Characteristics of Patients With Asymptomatic AS

	Total
n	230
Age (years)	72±11
Female (n, %)	131 (57)
BSA (m ²)	1.5±0.2
BMI (kg/m ²)	23±4
Systolic blood pressure (mmHg)	130±20
Diastolic blood pressure (mmHg)	70±13
Hypertension (n, %)	145 (63)
Diabetes (n, %)	58 (25)
Dyslipidemia (n, %)	105 (46)
Smoking (n, %)	68 (30)
Atrial fibrillation (n, %)	17 (7)
Chronic renal failure (n, %)	27 (12)
Coronary artery disease (n, %)	71 (31)
Cerebral vascular disease (n, %)	27 (12)
Peripheral artery disease (n, %)	5 (2)
Pacemaker implantation (n, %)	4 (2)
BNP (pg/dl)	258±521
Transthoracic echocardiography	
LV end-diastolic diameter (cm)	4.6±0.5
LV end-systolic diameter (cm)	2.9±0.6
LVEF (%)	67±10
Stroke volume (ml)	65±17
LV mass (g)	206±58
Peak transaortic velocity (m/s)	4.4±0.8
Mean pressure gradient (mmHg)	45±17
AVA (cm ²)	0.77±0.13
AVA index (cm ² /m ²)	0.50±0.10
Very severe AS	50 (22%)
E/e'	17±7
Zva (mmHg×m ² /ml)	4.3±1.2
High Zva	64 (28%)
Etiology (n, %)	
Bicuspid aortic valve	19 (8)
Rheumatic change	9 (4)
Degenerative change	202 (88)

*P<0.05 vs. AVR group. AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BSA, body surface area; BMI, body mass index; BNP, B-type natriuretic peptide; LV, left ventricular; Zva, valvulo-arterial impedance.

history of angina, dyspnea, syncope, presyncope or congestive heart failure reported at the time of the initial clinical and echocardiographic evaluations.⁴ Patients with fatigue or mild dyspnea occurring with maximal exertion were not excluded because of the lack of specificity of these symptoms.⁴ Patients with a past history of myocardial infarction and surgical AVR were also excluded. At study entry, clinical data, including coronary artery disease (CAD), which was defined as at least 1 epicardial artery with at least 50% stenosis or a history of percutaneous coronary intervention,¹³ were retrieved from the hospital database. This study was approved by the institutional review boards and all patients gave written informed consent.

Echocardiographic Study

All patients underwent comprehensive transthoracic echocardiography (TTE) that included 2D and Doppler echocardiog-

raphy performed by an experienced sonographer or cardiologist using commercially available equipment. Follow-up TTE was performed at 1, 3 and 5 years after baseline TTE. Vp and mean transaortic pressure gradient (MPG) were derived from transaortic flow recorded with continuous-wave Doppler using a multi-window approach. AVA was calculated by the continuity equation, and the AVA index was calculated as AVA divided by body surface area (BSA). Both Vp and AVA were measured in all the patients. Very severe AS was defined as Vp >5.0 m/s, MPG >60 mmHg, and AVA <0.60 cm².¹⁴ The LV end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume were measured by Simpson's biplane method using 2D images obtained from both the apical 4- and 2-chamber views. LVEF was calculated by the following equation: 100×(LVEDV–LVESV)/LVEDV. LV mass was calculated using diastolic measurements of LV internal diameter (ID) and posterior wall thickness (PWT) on 2D echocardiography according to the formula recommended by the American Society of Echocardiography: LV mass (g)=0.8×{1.04×[(IVST+LVID+LVPWT)³–(LVID)³]}+6 g (where IVST is interventricular septal wall thickness).¹⁵ For assessing diastolic function, pulsed-wave Doppler examination of mitral inflow and tissue Doppler imaging of mitral annular motion at the septum were also performed. Peak velocity of early diastolic flow (E) was measured from pulsed-wave Doppler examination of mitral inflow. Early diastolic velocities at the septal mitral annulus (e') were measured from tissue Doppler imaging. The ratio of mitral E to e' (E/e') was calculated as an index of LV filling pressure.¹⁶

Valvulo-Arterial Impedance (Zva)

To estimate a global LV hemodynamic afterload, we calculated the valvulo-arterial impedance (Zva): Zva=(SAP+MPG)/SVi, where SAP is the systolic arterial pressure and SVi is the stroke volume index (stroke volume divided by BSA).^{9,17,18} Hence, Zva theoretically accounts for the effects of both AS and systemic arterial compliance that oppose ventricular ejection.¹⁷ Zva was considered to be high if ≥4.9 mmHg×m²/ml, according to previous reports.^{19,20}

Follow-up and Clinical Outcomes

Follow-up information about the development of symptoms, subsequent AVR, hospitalization because of cardiovascular events, and cardiovascular death was obtained by reviewing inpatient records, records at outpatient clinics, interviews with patients, and questionnaires mailed to all patients. Deaths were classified as either cardiovascular or noncardiovascular. Death occurring without explanation was considered as cardiovascular. The primary clinical endpoint for the present study was a cardiovascular event, which was defined as cardiovascular death or cardiovascular hospitalization. The secondary clinical endpoint was AVR.

Statistical Analysis

Data are presented as mean±standard deviation for continuous variables, or as number with percentage for categorical variables. Differences between groups were analyzed by t-test or Mann-Whitney U test for continuous variables, and by chi-square test or Fisher's exact probability test for categorical variables, as appropriate. To identify covariates of cardiovascular events, multivariate Cox proportional hazards regression analysis was used to identify the covariates of clinical endpoints among the baseline clinical and echocardiographic variables. Any variable with a P value <0.10 in the univariate analysis was included in the multivariate analysis. The

Kaplan-Meier method was used for cumulative survival analysis, with the log-rank test for assessing statistical differences between curves. Two-tailed P-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 21.0 software (SPSS Inc, Chicago, IL, USA).

Results

Patients Characteristics

Baseline characteristics and echocardiographic data are outlined in [Table 1](#). The mean age of the patients was 72 ± 11 years (range, 20–95 years). The mean LVEF, Vp and AVA were $67 \pm 10\%$, 4.4 ± 0.8 m/s and 0.77 ± 0.13 cm², respectively; 57% (n=131) of the patients were females. The study population included patients with CAD (31%, n=71), very severe AS (22%, n=50) and high Zva (28%, n=64).

Clinical Outcomes

Follow-up information was available for all 230 patients. The mean follow-up time was 33 ± 31 months (range: 0–144 months). Among the 230 patients enrolled, total clinical events (cardiovascular event and AVR) occurred in 143 patients. A cardiovascular event occurred in 25 patients, comprising 4 cardiovascular deaths and 21 cardiovascular hospitalizations. The deaths were 3 from congestive heart failure and 1 from multiple embolism caused by atrial fibrillation. Hospitalization was for congestive heart failure (n=15) and ischemic heart attack (n=6). A total of 118 patients underwent AVR during follow-up because of the development of symptoms, LV dysfunction, or a rapid decrease in AVA; 2 patients developed AS symptoms but did not undergo subsequent AVR. In the multivariate analysis, the following significant covariates of total clinical events remained in the final model: MPG [hazard ratio (HR): 1.04, 95% confidence interval (CI): 1.006–1.074, $P < 0.05$] and AVA (HR: 0.11, 95% CI: 0.014–0.929, $P < 0.05$).

The study patients were divided into 2 groups based on AVR after study enrollment: non-AVR (n=112), and AVR (n=118) ([Figure 1](#)). The non-AVR group served as the unoperated patients in this study as in previous studies.^{21,22} In the non-AVR group, 85 patients (76%) remained free of a clinical event after a follow-up of 31 ± 26 months. The 1-year, 3-year, and 5-year event-free survival in the unoperated patients with asymptomatic AS was $87 \pm 3\%$, $77 \pm 5\%$, and $60 \pm 9\%$, respectively.

Covariates of Cardiovascular Events in the Non-AVR Group

[Table 2](#) compares the baseline characteristics of the non-AVR group with and without cardiovascular events. In the multivariate analysis, systolic blood pressure, CAD, AVA, and high Zva (all $P < 0.10$) were included in the initial step of the model-building process. Only the following significant covariates remained in the final model: CAD (HR: 3.62, 95% CI: 1.585–8.245, $P < 0.01$) and high Zva (HR: 3.08, 95% CI: 1.261–7.532, $P < 0.05$) ([Table 3](#)).

In the non-AVR group, 44 patients (39%) had 1 risk factor (CAD: n=22; high Zva: n=22) and 11 patients (10%) had 2 risk factors. The relative risk of cardiovascular events rose with an increase in the number of risk factors ($P < 0.0001$) ([Figure 2](#)). At 3 years, the probability of remaining free of cardiovascular events was $93 \pm 4\%$ in the patients with no risk factors, $75 \pm 10\%$ in the patients with high Zva as their only risk factor, $72 \pm 11\%$ in the patients with CAD as their only risk factor and $20 \pm 17\%$ in the patients with both risk factors.

Serial TTE Data

Of the 112 unoperated patients with asymptomatic AS, 1-year, 3-year, and 5-year follow-up TTE data were available for 52 patients (46%), 37 patients (33%) and 16 patients (14%), respectively ([Table 4](#)). There were no significant differences in LVEF, LVESV, LV mass and LV mass index at 1, 3 and 5 years of follow-up compared with baseline values. The mean Vp and mean MPG were significantly increased at 1-year ($P < 0.01$), 3-year ($P < 0.001$) and 5-year follow-up ($P < 0.001$). AVA at 5 years of follow-up ($P < 0.05$) was significantly less than the baseline value, although the mean AVA at 1 and 3 years of follow-up did not change.

Discussion

The main achievement of the present study was the successful identification of the independent covariates of cardiovascular events in unoperated patients with asymptomatic AS: CAD (HR: 3.62, 95% CI: 1.585–8.245, $P < 0.01$) and high Zva (HR: 3.08, 95% CI: 1.261–7.532, $P < 0.05$). The relative risk of cardiovascular events rose with an increase in the number of risk factors ($P < 0.0001$).

Table 2. Baseline Characteristics of Patients in the No-AVR Group (n=112) With and Without Cardiovascular Events

	Cardiovascular event (n=25)	No cardiovascular event (n=87)	P value
Follow-up period (m)	20±21	31±26	
Age (years)	73±9	72±13	0.7
Female (n, %)	8 (32)	51 (59)	0.2
BSA (m ²)	1.6±0.2	1.5±0.2	0.3
BMI (kg/m ²)	23±3	23±4	0.6
Systolic blood pressure (mmHg)	140±25	128±18	<0.05
Hypertension (n, %)	18 (72)	55 (63)	0.5
Diabetes (n, %)	7 (28)	27 (31)	0.9
Dyslipidemia (n, %)	12 (48)	39 (45)	0.8
Smoking (n, %)	11 (44)	22 (25)	0.12
Atrial fibrillation (n, %)	4 (16)	6 (7)	0.2
Chronic renal failure (n, %)	4 (16)	10 (11)	0.5
Coronary artery disease (n, %)	13 (52)	20 (23)	<0.05
Cerebral vascular disease (n, %)	5 (20)	13 (15)	0.5
Peripheral artery disease (n, %)	2 (8)	1 (1)	0.13
Pacemaker implantation (n, %)	0 (0)	2 (2)	0.9
BNP (pg/dl)	143±124	234±543	0.4
LV end-diastolic diameter (cm)	4.6±0.7	4.6±0.5	0.9
LV end-systolic diameter (cm)	3.0±0.7	2.8±0.5	0.4
LV ejection fraction (%)	64±12	69±8	0.2
Stroke volume (ml)	63±17	68±18	0.18
LV mass (g)	204±62	198±53	0.8
Peak transaortic velocity (m/s)	4.0±0.9	4.1±0.6	0.9
Mean pressure gradient (mmHg)	39±14	39±13	0.9
AVA (cm ²)	0.78±0.11	0.83±0.10	<0.05
AVA index (cm ² /m ²)	0.50±0.09	0.55±0.08	<0.05
Very severe AS	3 (12%)	7 (8%)	0.5
E/e'	17±7	17±8	0.8
Zva (mmHg×m ² /ml)	4.8±1.2	4.0±1.3	<0.05
High Zva	14 (56%)	19 (22%)	<0.01
Etiology (n, %)			0.4
Bicuspid aortic valve	0 (0)	5 (6)	
Rheumatic disease	1 (4)	5 (6)	
Degenerative disease	24 (96)	77 (88)	

*P<0.05 vs. AVR group. Abbreviations as in Table 1.

Table 3. Results of Multivariate Analysis to Determine the Covariates of Cardiovascular Events in Unoperated Patients With Asymptomatic AS

Variable	HR	95% CI	P value
Systolic blood pressure	1.01	0.992–1.030	0.26
Coronary artery disease	3.62	1.585–8.245	<0.01
Aortic valve area	0.05	0.001–2.207	0.12
High Zva	3.08	1.261–7.532	<0.05

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Covariates of Cardiovascular Event in Unoperated Patients With Asymptomatic AS

It is well known that there is overlap in the clinical factors traditionally associated with atherosclerosis and AS.²³ Thus, CAD is the most common comorbidity that influences outcomes after AVR for symptomatic AS.^{13,24} In fact, according to a large-scale Swedish registry, 41% of patients aged 61–70

years, and 51% of patients aged ≥71 years had significant CAD at the time of surgical AVR.²⁴ In contrast, there is little information that identifies CAD as a covariate of cardiovascular events in unoperated patients with asymptomatic AS. Carstensen and colleagues demonstrated that subclinical CAD in asymptomatic AS was associated with global and regional longitudinal dysfunction.²⁵ Moreover, some previous studies

Figure 2. Kaplan-Meier event-free survival curves in the non-AVR group (n=112) according to the cumulative number of risk factors, such as a past history of coronary artery disease (CAD) and high valvulo-arterial impedance (Zva). AVR, aortic valve replacement.

	Baseline	1 year	3 years	5 years
n	112	52	37	16
Follow-up (months)		13±3	34±7	61±10
LV ejection fraction (%)	68±9	69±7	68±8	66±6
LV end-diastolic volume (ml)	98±27	94±22*	96±26*	97±22
LV end-systolic volume (ml)	31±16	30±11	30±14	39±26
LV mass (g)	199±55	187±51	186±54	211±67
LV mass index (g/m ²)	130±35	122±32	121±33	140±43
E/e'	17±8 (n=84)	15±6 (n=35)	15±7 (n=32)	18±10 (n=12)
Aortic valve area (cm ²)	0.82±0.20	0.88±0.20	0.82±0.18	0.71±0.14*
Peak transaortic velocity (m/s)	4.1±0.7	4.3±0.6**	4.5±0.7***	4.9±0.7***
Mean transaortic pressure gradient (mmHg)	39±13	41±14**	46±13***	56±16***

Comparison with baseline data: *P<0.05, **P<0.01, and ***P<0.001. Abbreviations as in Table 1.

reported that longitudinal deformation deteriorated with progressive AS.^{26–28} Therefore, myocardial damage caused by AS and CAD might lead to earlier cardiovascular events compared with isolated AS, even in asymptomatic patients. We also found first that Zva was an independent determinant of clinical outcome in unoperated, asymptomatic severe AS. Previous studies reported that Zva, a surrogate of global LV hemodynamic afterload, was associated with clinical outcome in asymptomatic AS, although the majority of events in those patients included death after AVR and a clinical need for AVR as well as the development of symptoms and cardiovascular death.^{9,17,19} Hachicha and colleagues reported that Zva >5.5 mmHg×m²/ml was associated with a 2.6-fold increase in

the risk of death in patients with symptomatic or asymptomatic AS.¹⁷ Additionally, a report by Lancellotti and colleagues demonstrated that Zva ≥4.9 mmHg×m²/ml was the best cut-off value to discriminate between asymptomatic AS patients with and without cardiovascular events.¹⁹ That same study also reported that prolonged high global LV afterload can exceed the limit of LV compensatory mechanisms and lead to an intrinsic impairment of myocardial function.¹⁹ Therefore, increased global LV afterload may be associated with early cardiovascular events, such as cardiovascular death and congestive heart failure, even in asymptomatic AS patients.

However, an earlier study by Dal-Bianco and colleagues²⁹ reported that referral for AVR might have been confounded

by the primary physician's treatment bias. Therefore, clinical outcome including AVR was an important limitation in previous studies.^{9,17,19} Furthermore, AVR that is performed on the basis of AS severity has a critical effect on the covariates of total clinical events, including AVR. Consequently, MPG and AVA were identified as the covariates of total clinical events in the present study. Thus, we also used objective clinical endpoints that excluded AVR in order to identify the risk factors that predict cardiovascular events in unoperated patients with asymptomatic AS.

Clinical Outcome in Patients With Asymptomatic AS Without AVR

Brown and colleagues showed that the 10-year survival was only 33% in AS patients who remained asymptomatic and did not undergo AVR.⁸ Furthermore, a study by Pai and colleagues demonstrated that patients not undergoing AVR for asymptomatic AS had a 1-year, 2-year and 5-year survival of 67%, 56% and 38%, respectively.⁷ In contrast, the clinical outcomes in the present study, which included cardiovascular hospitalization as well as cardiovascular death, were better than those reported by Pai et al. Compared with the patients in that study (n=239, female 46%),⁷ the present patients (n=112, female 53%) had a larger mean AVA (0.82 cm² vs. 0.72 cm²) and a higher mean LVEF (68% vs. 57%). Therefore, the discrepancy in clinical outcomes might have been caused by differences in the study populations.

Serial TTE Changes in Unoperated Patients With Asymptomatic AS

The present study demonstrated significant progression of Vp and MPG in unoperated patients with asymptomatic AS. Although there were no significant differences in AVA between baseline and 1 or 3 years of follow-up, AVA at 5 years was smaller than at baseline. A study by Otto and colleagues² reported that the overall rate of increase in AS severity is predictable with an average annual increase in Vp of approximately 0.3 m/s and a decrease in AVA of approximately 0.1 cm². Nistri and colleagues demonstrated that the average increase in Vp was $0.26 \pm 0.32 \text{ m} \cdot \text{s}^{-1} \cdot \text{year}^{-1}$ with great individual variability in hemodynamic progression.³⁰ The present study results were consistent with those reports.^{2,30} There were few changes over time in LV geometry, mass, and systolic or diastolic function, which is also consistent with a previous study.²

Clinical Implications

A study by Beach and colleagues¹³ showed that patients with AS and CAD had worse short- and long-term prognoses and more postoperative morbidity than those with isolated AS. However, patients in that study who underwent AVR and coronary artery bypass graft for AS and CAD without evidence of myocardial damage had outcomes that were equivalent to propensity-matched isolated AS patients who underwent AVR.¹³ In addition, the present study demonstrated that CAD was an independent risk factor for cardiovascular events in unoperated patients with asymptomatic AS. Therefore, asymptomatic patients with severe AS and CAD may need to undergo an early aortic valve intervention before myocardial damage occurs. Similarly, asymptomatic patients with severe AS and increased Zva may potentially benefit from an early aortic valve intervention. Even if an early intervention is not indicated in patients with asymptomatic AS, medical therapy for LV ischemia and global LV afterload reduction may be beneficial.³¹

Study Limitations

First, patients who underwent AVR were excluded retrospectively in the present observational study of unoperated AS. Thus, selection bias may influence the clinical outcome of the unoperated patients. Further prospective study is required to clarify how Zva and CAD truly affect the natural history of unoperated AS. Second, the number of asymptomatic AS patients with cardiovascular events was low. However, the Cox proportional hazards model generated valid P values and CIs for the 2 significant risk factors because there were 25 cardiovascular events among 112 unoperated patients with asymptomatic AS. Third, we did not assess myocardial ischemia using stress echocardiography or nuclear imaging in asymptomatic patients with AS or CAD.^{19,22,29} We performed coronary angiography only in the patients who had suspected CAD by ECG or TTE. Fourth, stroke volume was calculated by the Simpson's biplane method. A previous report demonstrated no significant difference in stroke volume between by the LV outflow Doppler method and Simpson's biplane method ($P=1.000$).³² Fifth, the follow-up rates of TTE were low in this study. In particular, echocardiography might not be performed in patients with less severe AS, which might influence echocardiographic measurements during the follow-up period.

Our study patients with asymptomatic AS underwent echocardiography because they had a cardiac murmur on auscultation or abnormal ECG, or because they had been referred for suspected AS or other cardiovascular disease. These reasons why asymptomatic patients underwent echocardiography could be a selection bias of the study population. Unfortunately, details of this information were not available for all patients.

Conclusions

In unoperated patients with asymptomatic AS, the presence of CAD and the magnitude of global LV afterload may be associated with a poor prognosis. Furthermore, the relative risk of cardiovascular events rose with an increase in the number of risk factors.

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