

Early Surgery vs. Surgery After Watchful Waiting for Asymptomatic Severe Aortic Stenosis

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on behalf of the CURRENT AS Registry Investigators

Background: There is no large-scale study comparing postoperative mortality after aortic valve replacement (AVR) for asymptomatic severe aortic stenosis (AS) between initial treatment with AVR vs. eventual AVR after conservative management.

Methods and Results: We analyzed data from a multicenter registry enrolling 3,815 consecutive patients with severe AS. Of 1,808 asymptomatic patients, 286 patients initially underwent AVR (initial AVR group), and 377 patients were initially managed conservatively and eventually underwent AVR (AVR after watchful waiting group). Mortality after AVR was compared between the 2 groups. Subgroup analysis according to peak aortic jet velocity (V_{max}) at diagnosis was also conducted. There was no significant difference between the 2 groups in 5-year overall survival (OS; 86.0% vs. 84.1%, $P=0.34$) or cardiovascular death-free survival (DFS; 91.3% vs. 91.1%, $P=0.61$), but on subgroup analysis of patients with $V_{max} \geq 4.5$ m/s at diagnosis, the initial AVR group was superior to the AVR after watchful waiting group in both 5-year OS (88.4% vs. 70.6%, $P=0.003$) and cardiovascular DFS (91.9% vs. 81.7%, $P=0.023$).

Conclusions: Asymptomatic severe AS patients who underwent AVR after watchful waiting had a postoperative survival rate similar to those who initially underwent AVR. In a subgroup of patients with $V_{max} \geq 4.5$ m/s at diagnosis, however, the AVR after watchful waiting group had worse postoperative survival rate than the initial AVR group.

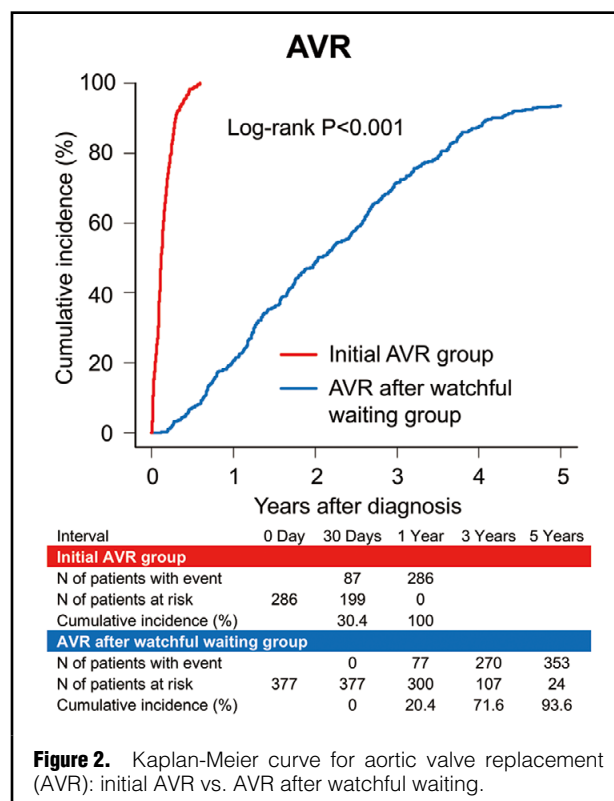
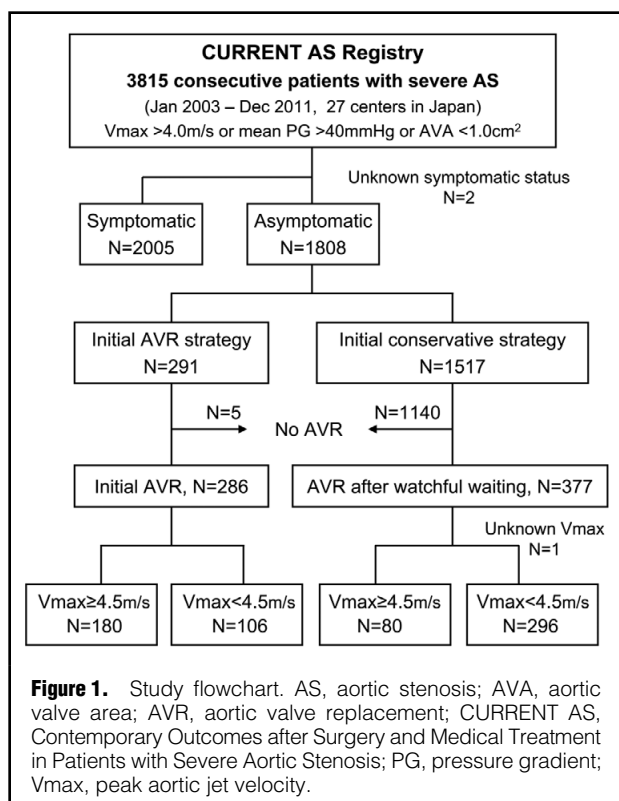
Key Words: Aortic stenosis; Aortic valve replacement; Echocardiography; Survival; Watchful waiting

Symptomatic severe aortic stenosis (AS) has an extremely poor prognosis unless treated with aortic valve replacement (AVR).^{1–4} Therefore, the current guidelines strongly recommend AVR for symptomatic severe AS patients.^{5,6} Conversely, management of asymptomatic severe AS remains controversial. The prognosis of

asymptomatic severe AS has been reported to be favorable, and thus, current guidelines generally recommend a conservative strategy of watchful waiting for asymptomatic severe AS.^{5,6} Nevertheless, in clinical practice, some cardiologists refer a substantial proportion of asymptomatic severe AS patients for AVR shortly after diagnosis without

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waiting for symptoms to develop. One reason for early surgical referral is the risk of cardiac events during watchful waiting. Furthermore, asymptomatic severe AS patients who are conservatively managed until the development of symptoms might potentially have increased operative and long-term postoperative mortality due to progression of the disease to a later stage. It is unknown, however, whether mortality is increased with late AVR, because there has been no large-scale study comparing early vs. late AVR in asymptomatic severe AS patients.

In addition, it is also unknown whether mortality after late AVR is increased in more severe AS. Current guidelines recommend AVR for very severe AS (peak aortic jet velocity [$V_{\max}$] $\geq 5.0 \text{ m/s}$ in the USA⁵ or $\geq 5.5 \text{ m/s}$ in Europe⁶) regardless of symptom status. In some previous studies from high-volume centers, however, higher likelihood of cardiac death and of developing symptoms during conservative management was noted in asymptomatic severe AS with $V_{\max} \geq 4.5 \text{ m/s}$.^{7,8} We hypothesized that operative and long-term mortality after late AVR would also be increased compared with those after early AVR in a subgroup of patients with $V_{\max} \geq 4.5 \text{ m/s}$.

The purpose of the present study was to evaluate operative and long-term mortality after AVR in asymptomatic severe AS patients, comparing initial treatment with AVR vs. eventual AVR after watchful waiting in a large Japanese observational database of consecutive patients with severe AS.

Methods

Study Design

The study design and primary results of the Contemporary Outcomes after Surgery and Medical Treatment in Patients with Severe Aortic Stenosis (CURRENT AS) registry have been previously reported.⁹ In brief, the CURRENT AS registry is a retrospective, multicenter registry that enrolled 3,815 consecutive patients with severe AS from 27 centers in Japan between January 2003 and December 2011. Severe AS was defined on Doppler echocardiography as $V_{\max} > 4.0 \text{ m/s}$, mean aortic pressure gradient (PG) $> 40 \text{ mmHg}$, or aortic valve area $< 1.0 \text{ cm}^2$. Patients with a history of aortic valve surgery were excluded. In asymptomatic severe AS patients, AVR was indicated in patients with left

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ventricular ejection fraction (LVEF) <50%, patients undergoing other heart surgery, or patients with very severe AS. Taking account patient age, comorbidity, and preference, the clinical decision regarding initial AVR or conservative management was made by an attending cardiologist after index echocardiography. The protocol was independently approved by the institutional review board or ethics committee at each participating center. Written informed consent was waived because of the retrospective nature of the study, and no patients refused to participate in the study when contacted for follow-up.

The entire cohort consisted of 2,005 patients with and 1,808 patients without AS-related symptoms at diagnosis, excluding 2 patients whose symptom status was not available. In the asymptomatic patients, initial AVR and conservative strategies were chosen in 291 patients and in 1,517 patients, respectively (Figure 1). In patients managed with initial AVR, 286 patients underwent surgical AVR (initial AVR group). In patients managed with a conservative strategy, 377 patients eventually underwent surgical AVR during follow-up (AVR after watchful waiting group; Figure 1). In the present study, we compared the perioperative and long-term clinical outcomes after AVR between these 2 groups.

Furthermore, we conducted a subgroup analysis according to whether Vmax was ≥ 4.5 m/s (n=260; initial AVR, n=180; AVR after watchful waiting, n=80) or <4.5 m/s (n=402; initial AVR, n=106; AVR after watchful waiting, n=296) at diagnosis.

Data Collection and Endpoints

Baseline data were collected from medical records or

echocardiography databases at each hospital. Angina, syncope, or heart failure (HF) symptoms including dyspnea were regarded as AS-related symptoms. Follow-up data were collected from medical records or through contact with patients, relatives, or referring physicians using mailed questionnaires or telephone interviews.

Table 1. Reasons for AVR in the AVR After Watchful Waiting Group

	AVR after watchful waiting (n=377)
Development of symptoms	222 (59)
Angina	60
Syncope	18
Heart failure	162
Requiring hospitalization	50
Progression of AS	137 (36)
Progression to very severe AS	37
Planned CV surgery for indications other than AS	10 (2.7)
Decrease in LVEF	3 (0.8)
Infective endocarditis	2 (0.5)
Before high-risk non-cardiac surgery	2 (0.5)
Without any reasons described here (simply due to severe AS)	48 (13)

Data given as n (%). The total exceeds 100% because some patients had multiple reasons for AVR. AS, aortic stenosis; AVR, aortic valve replacement; CV, cardiovascular; LVEF, left ventricular ejection fraction.

HF hospitalization during watchful waiting

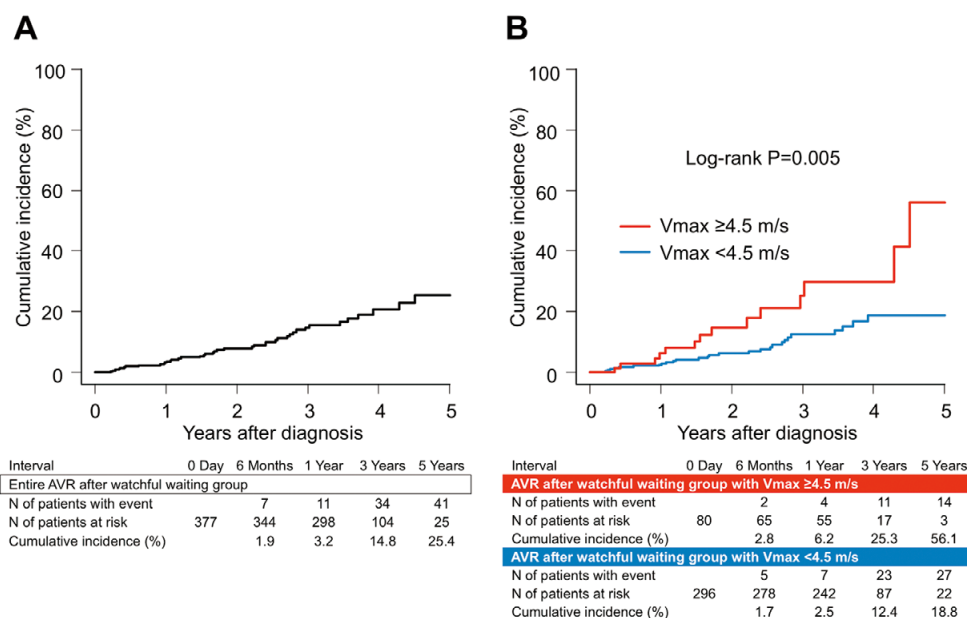


Figure 3. Kaplan-Meier curve for heart failure (HF) hospitalization before aortic valve replacement (AVR) in the (A) AVR after watchful waiting group, and (B) AVR after watchful waiting group according to peak aortic jet velocity (Vmax) $\geq$ or <4.5 m/s. Patients were censored at AVR.

The primary outcome measures in the present analysis were all-cause death and cardiovascular death. Causes of death were classified according to the Valve Academic Research Consortium definitions.^{10,11} HF hospitalization was defined as hospitalization due to worsening HF requiring i.v. drug therapy.

Echocardiography

All echocardiography was performed by experienced sonographers using commercially available echocardiographic imaging systems equipped with M-mode, 2-D, pulsed, continuous, and color-flow Doppler capabilities. Vmax was recorded from multiple transducer positions with continuous wave Doppler, and aortic valve area was calculated using the continuity equation.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and compared using the chi-squared test or Fisher's exact test. Continuous variables are expressed as mean±SD or median (IQR), and compared using Student's

t-test or Wilcoxon rank sum test based on distribution. Changes in continuous variables were assessed with paired t-test. Cumulative incidence was estimated using the Kaplan-Meier method, and differences between groups were assessed with log-rank test. To clarify whether the effect of initial AVR was different between subgroups, treatment-subgroup interactions were assessed with the Cox proportional hazards model. The date of AVR was regarded as time zero on the Kaplan-Meier curves for overall survival (OS) and cardiovascular death-free survival (DFS) after AVR. We also evaluated the cumulative incidence of HF hospitalization during watchful waiting in the AVR after watchful waiting group, in which the date of the index echocardiography was regarded as time zero, and patients were censored when they underwent AVR. All statistical analysis was conducted with JMP 10.0.2 (SAS Institute, Cary, NC, USA) or SPSS 22.0 (IBM, Armonk, NY, USA). All reported P-values are 2-tailed, and P<0.05 was considered statistically significant.

	Initial AVR (n=286)	AVR after watchful waiting (n=377)	P-value
Clinical characteristics			
Age (years)	71.6±8.8	72.0±8.2	0.57
Age ≥80 years	49 (17)	62 (16)	0.81
Male	123 (43)	165 (44)	0.85
BMI (kg/m ²)	22.0±3.1	22.9±3.6	0.001
BMI <22 kg/m ²	145 (51)	161 (43)	0.041
BSA (m ²)	1.51±0.17	1.52±0.17	0.28
Hypertension	183 (64)	256 (68)	0.29
Current smoking	21 (7)	24 (6)	0.62
History of smoking	72 (25)	105 (28)	0.44
Dyslipidemia	113 (40)	167 (44)	0.22
Statin therapy	69 (24)	132 (35)	0.003
Diabetes mellitus	58 (20)	99 (26)	0.07
Insulin therapy	10 (4)	21 (6)	0.21
Coronary artery disease	60 (21)	118 (31)	0.003
Prior myocardial infarction	4 (1)	31 (8)	<0.001
Prior PCI	21 (7)	68 (18)	<0.001
Prior CABG	6 (2)	17 (5)	0.09
Prior symptomatic stroke	25 (9)	37 (10)	0.64
Prior AF or AFI	38 (13)	58 (15)	0.45
Aortic/peripheral vascular disease	37 (13)	48 (13)	0.94
Serum creatinine (mg/dL)	1.6±2.5	1.6±2.3	0.96
Creatinine >2 mg/dL	33 (12)	41 (11)	0.79
Hemodialysis	32 (11)	36 (10)	0.49
Anemia	128 (45)	133 (35)	0.013
Liver cirrhosis (Child-Pugh B or C)	1 (0.3)	0 (0)	0.43
Malignancy	33 (12)	45 (12)	0.88
Malignancy currently under treatment	7 (2)	11 (3)	0.71
Immunosuppressive therapy	4 (1)	9 (2)	0.41
CLD	25 (9)	44 (12)	0.22
CLD (moderate or severe)	2 (0.7)	9 (2)	0.13
Logistic EuroSCORE (%)	5.5 (3.7–8.1)	6.2 (3.7–9.0)	0.15
STS score (PROM) (%)	2.0 (1.4–3.3)	2.6 (1.6–3.7)	0.011

(Table 2 continued the next page.)

	Initial AVR (n=286)	AVR after watchful waiting (n=377)	P-value
Etiology of AS			
Degenerative	215 (75)	291 (77)	
Congenital (unicuspid, bicuspid, or quadricuspid)	52 (18)	53 (14)	
Rheumatic	9 (3)	28 (7)	0.016
Infective endocarditis	3 (1)	0 (0)	
Others	7 (2)	5 (1)	
Echocardiographic variables			
Vmax (m/s)	4.8±0.8	4.0±0.6	<0.001
Vmax ≥5 m/s	113 (40)	24 (6)	<0.001
Vmax ≥4.5 m/s	180 (63)	80 (21)	<0.001
Vmax ≥4 m/s	241 (84)	197 (52)	<0.001
Peak aortic PG (mmHg)	93±32	66±20	<0.001
Mean aortic PG (mmHg)	55±20	38±12	<0.001
AVA (equation of continuity) (cm ²)	0.67±0.16	0.80±0.15	<0.001
AVA index (cm ² /m ²)	0.45±0.11	0.53±0.11	<0.001
LVEDD (mm)	45±6	46±6	0.050
LVESD (mm)	28±6	29±6	0.15
LVEF (%)	66.8±9.9	67.2±9.0	0.59
IVST in diastole (mm)	12±2	11±2	<0.001
PWT in diastole (mm)	12±2	11±2	<0.001
Any combined valvular disease (moderate or severe)	81 (28)	107 (28)	0.99
Moderate or severe AR	55 (19)	69 (18)	0.76
Moderate or severe MS	7 (2)	12 (3)	0.57
Moderate or severe MR	26 (9)	28 (7)	0.44
Moderate or severe TR	22 (8)	34 (9)	0.54
TR PG ≥40 mmHg	21 (7)	22 (6)	0.44

Data given as mean±SD, n (%), or median (IQR). AF, atrial fibrillation; AFL, atrial flutter; AR, aortic regurgitation; AVA, aortic valve area; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CLD, chronic lung disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IVST, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MS, mitral stenosis; PCI, percutaneous coronary intervention; PG, pressure gradient; PROM, predicted risk of mortality; PWT, posterior wall thickness; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation; Vmax, peak aortic jet velocity. Other abbreviations as in Table 1.

Results

Subjects

Of the 1,808 patients who were asymptomatic at diagnosis, 663 underwent AVR. The median follow-up period was 1452 days (IQR, 1,085–1,926 days). The median interval from diagnosis to AVR was 44 days (IQR, 24–76 days) in the initial AVR group (n=286), and 744 days (IQR, 427–1,169 days) in the AVR after watchful waiting group (n=377; **Figure 2**). The reasons for AVR after watchful waiting were development of symptoms in 222 patients (59%), and progression of AS in 137 patients (36%) including progression to very severe AS in 37 patients (**Table 1**). In a subgroup analysis of the reasons for AVR after watchful waiting, the proportion of patients who underwent AVR due to HF hospitalization and progression to very severe AS was higher in patients with Vmax ≥4.5 m/s than in those with Vmax <4.5 m/s at diagnosis (**Table S1**). In the AVR after watchful waiting group, the cumulative incidence of HF hospitalization before AVR was 25.4% at 5 years (**Figure 3A**). Cumulative incidence of HF hospitalization before AVR was higher in patients with Vmax ≥4.5 m/s than in those with Vmax <4.5 m/s at diagnosis (56.1% vs. 18.8% at 5 years, P=0.005; **Figure 3B**).

Baseline Characteristics and Echocardiography

In the entire analyzed cohort, the mean age at diagnosis was 71.8±8.5 years, and 288 (43%) were male. Mean Vmax was 4.3±0.8 m/s, mean PG was 44±18 mmHg, and mean aortic valve area was 0.74±0.17 cm². The initial AVR group had a lower prevalence of coronary artery disease and a higher prevalence of anemia than the AVR after watchful waiting group (**Table 2**). At index echocardiography, the initial AVR group had a greater Vmax and mean PG, smaller aortic valve area, and thicker LV wall than the AVR after watchful waiting group (**Table 2**).

In the subgroup of patients with Vmax ≥4.5 m/s, the initial AVR group had a lower prevalence of chronic lung disease than the AVR after watchful waiting group (**Table S2**). In the subgroup of patients with Vmax <4.5 m/s, the initial AVR group had a lower prevalence of prior myocardial infarction and a higher prevalence of renal failure than the AVR after watchful waiting group (**Table S3**). In both subgroups, the initial AVR group had a greater Vmax and mean PG, and smaller aortic valve area than the AVR after watchful waiting group at index echocardiography (**Tables S2,S3**).

Progression of Aortic Stenosis

Preoperative echocardiographic data (≤60 days before AVR)

Table 3. Echocardiography Changes in the AVR After Watchful Waiting Group

Variables	At diagnosis (n=190)	Just before AVR (n=190) [†]	P-value
Vmax (m/s)	4.0±0.6	4.6±0.8	<0.001
AVA (cm ²)	0.78±0.16	0.67±0.15	<0.001
LVEDD (mm)	46.5±5.4	47.1±6.4	0.07
LVESD (mm)	29.4±5.5	31.0±7.5	<0.001
LVEF (%)	66.5±9.5	62.4±12.8	<0.001
IVST (mm)	11.2±2.1	11.7±2.3	<0.001
PWT (mm)	10.8±1.8	11.2±2.1	0.007
Progression rate of AS			
ΔVmax per year (m/s)		0.36±0.56	
ΔAVA per year (cm ²)		−0.06±0.16	

Data given as mean±SD. [†]Median time from diagnosis to AVR in the 190 patients with paired data, 697 days (IQR, 401–1,085 days). ΔAVA, change in a AVA; ΔVmax, change in peak aortic jet velocity. Other abbreviations as in Tables 1,2.

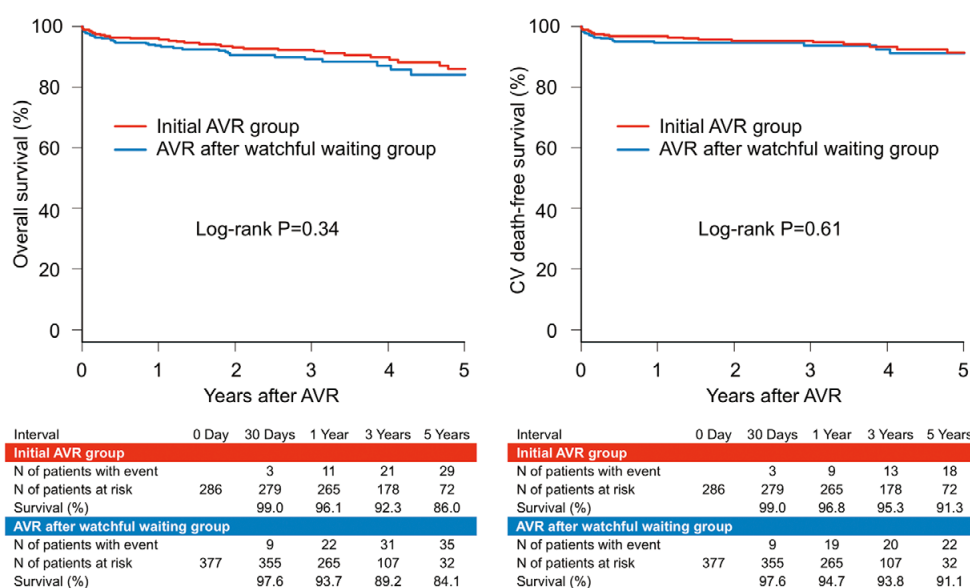


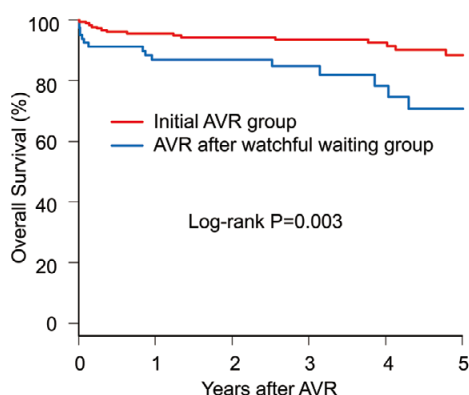
Figure 4. Kaplan-Meier curves for (Left) overall survival and (Right) cardiovascular (CV) death-free survival after aortic valve replacement (AVR) vs. timing of AVR.

was available in 190 of 377 patients in the AVR after watchful waiting group (Table 3). Vmax increased from 4.0±0.6m/s at diagnosis to 4.6±0.8m/s just before AVR, and aortic valve area decreased from 0.78±0.16cm² to 0.67±0.15cm², similar to the preoperative values in the initial AVR group. The progression rates of Vmax and aortic valve area were 0.36±0.56m/s per year and −0.06±0.16cm² per year, respectively. Echocardiographic changes in each subgroup are listed in Table S4.

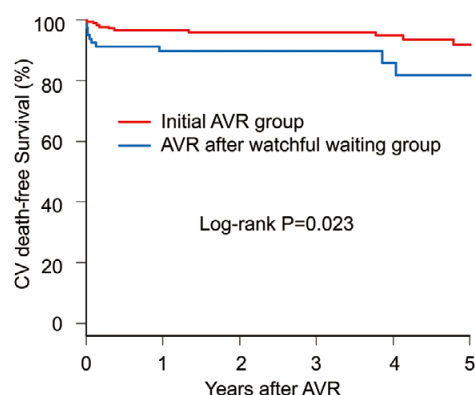
Operative Mortality

The operative mortality (≤30 days after AVR) in all 663 patients was 1.9%. There were 3 operative deaths (1.1%) in the initial AVR group, and 9 operative deaths (2.7%) in the AVR after watchful waiting group (P=0.25). The causes of

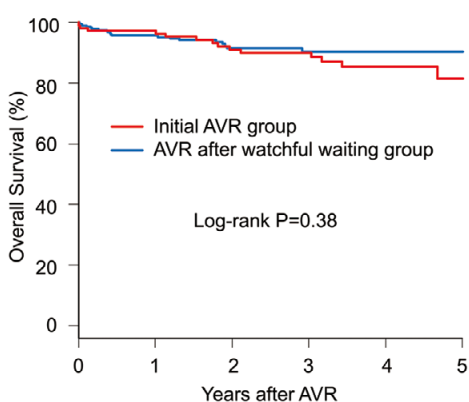
death in the initial AVR group were cardiac rupture in 1 patient, cerebral infarction in 1 patient, and mesenteric ischemia in 1 patient. The causes of death in the AVR after watchful waiting group were mesenteric ischemia in 3 patients, HF in 2 patients, sudden cardiac arrest in 1 patient, pneumonia in 1 patient, cerebral hemorrhage in 1 patient, and unknown in 1 patient. In the subgroup of patients with Vmax ≥4.5m/s at diagnosis, operative mortality was lower in the initial AVR group than in the AVR after watchful waiting group (0.6% vs. 7.5%, P=0.004), whereas in the subgroup of patients with Vmax <4.5m/s at diagnosis, the operative mortality was not different between the 2 groups (1.9% vs. 1.0%, P=0.61).

A Patients with Vmax ≥ 4.5 m/s

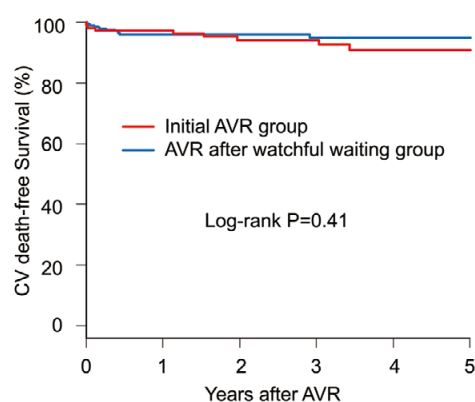
Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Initial AVR group					
N of patients with event		1	8	11	15
N of patients at risk	180	176	164	112	52
Survival (%)		99.4	95.5	93.6	88.4
AVR after watchful waiting group					
N of patients with event		6	10	11	15
N of patients at risk	80	73	60	33	13
Survival (%)		92.5	86.9	84.6	70.6



Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Initial AVR group					
N of patients with event		1	6	7	10
N of patients at risk	180	176	164	112	52
Survival (%)		99.4	96.6	96.0	91.9
AVR after watchful waiting group					
N of patients with event		6	8	8	10
N of patients at risk	80	73	60	33	13
Survival (%)		92.5	89.7	89.7	81.7

B Patients with Vmax <4.5 m/s

Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Initial AVR group					
N of patients with event		2	3	10	14
N of patients at risk	106	103	101	66	20
Survival (%)		98.1	97.2	90.0	81.6
AVR after watchful waiting group					
N of patients with event		3	12	20	20
N of patients at risk	296	281	204	73	19
Survival (%)		99.0	95.6	90.3	90.3



Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Initial AVR group					
N of patients with event		2	3	6	8
N of patients at risk	106	103	101	66	20
Survival (%)		98.1	97.2	94.1	90.8
AVR after watchful waiting group					
N of patients with event		3	11	12	12
N of patients at risk	296	281	204	73	19
Survival (%)		99.0	96.0	94.8	94.8

Figure 5. Kaplan-Meier curves for (Left) overall survival and (Right) cardiovascular (CV) death-free survival after aortic valve replacement (AVR) vs. timing of AVR in patients with (A) peak aortic jet velocity (Vmax) ≥ 4.5 m/s and (B) Vmax <4.5 m/s.

Long-Term Outcomes

The median follow-up interval after AVR was 977 days (IQR, 478–1,511 days). Mean age at AVR in the AVR after watchful waiting group was 74.3 ± 8.1 years. Five-year OS and cardiovascular DFS after AVR in all 663 patients were 84.9% and 91.0%, respectively. There were no significant differences between the initial AVR group and the AVR after watchful waiting group in 5-year OS and cardiovascular DFS after AVR (86.0% vs. 84.1%, $P=0.34$; and 91.3% vs. 91.1%, $P=0.61$, respectively; **Figure 4**). The initial AVR group as compared with the AVR after watchful waiting

group, however, had significantly better 5-year OS and cardiovascular DFS after AVR in the subgroup of patients with Vmax ≥ 4.5 m/s at diagnosis (88.4% vs. 70.6%, $P=0.003$, and 91.9% vs. 81.7%, $P=0.023$, respectively; **Figure 5A**), but not in the subgroup of patients with Vmax <4.5 m/s (81.6% vs. 90.3%, $P=0.38$, and 90.8% vs. 94.8%, $P=0.41$, respectively; **Figure 5B**). There were significant interactions between the effects of initial AVR and the subgroups (interaction $P=0.006$ for OS and interaction $P=0.031$ for cardiovascular DFS).

Discussion

The main findings of the present study were as follows: (1) in asymptomatic severe AS patients, the operative and long-term mortality after AVR were not different between the 2 group of patients who underwent early AVR vs. late AVR after watchful waiting; (2) in the subgroup of patients with $V_{\max} \geq 4.5$ m/s at diagnosis, however, patients who underwent late AVR after watchful waiting had higher operative and long-term mortality than patients who underwent early AVR.

In clinical practice, some cardiologists are reluctant to postpone AVR in asymptomatic severe AS patients until the development of symptoms, because sudden death during asymptomatic follow-up is of great concern. In previous prospective studies, however, sudden death without preceding symptoms is uncommon, with an incidence $<1\%$ per year.^{12–14} Thus, watchful waiting in cases in which AVR is planned once symptoms develop has been considered a reasonable strategy and is widely accepted in the management of asymptomatic severe AS.^{15–17}

In addition to sudden death, there is another concern in conservative management: the patients who are initially managed conservatively might have increased operative and long-term mortality after AVR due to the later stage of disease at the time of surgery. In the AVR after watchful waiting group, AS was found to progress and LVEF to decrease during watchful waiting. LVEF decreased from 67% at diagnosis to 62% at AVR. The latter was still in the normal range, but there is a possibility that subclinical LV contractile dysfunction had already begun during watchful waiting because LVEF in the hypertrophied heart is usually higher than in normal heart. Nevertheless, the present study demonstrated no significant differences between the initial AVR group and the AVR after watchful waiting group in operative and long-term mortality after AVR, suggesting that the strategy of AVR after watchful waiting for asymptomatic severe AS does not have negative effects on operative and long-term mortality after AVR.

In the analysis, however, of more severe AS patients ($V_{\max} \geq 4.5$ m/s), the AVR after watchful waiting group had worse postoperative outcomes than the initial AVR group. Furthermore, the AVR after watchful waiting group with $V_{\max} \geq 4.5$ m/s had a higher incidence of HF hospitalization during watchful waiting than those with $V_{\max} < 4.5$ m/s. Current guidelines recommend AVR for patients with very severe AS ($V_{\max} \geq 5.0$ m/s in the USA⁵ or ≥ 5.5 m/s in Europe⁶) regardless of symptom status, which is based on previous studies in which very severe AS patients had poor prognosis with a high event rate despite asymptomatic status.^{18,19} In a previous study of 116 patients with very severe AS ($V_{\max} \geq 5.0$ m/s), 6 cardiac deaths occurred in patients confirmed to be asymptomatic at last examination, and patients with $V_{\max} \geq 5.5$ m/s had a higher likelihood of severe symptom onset than those with $V_{\max} 5.0$ – 5.5 m/s.¹⁸ In another study, very severe AS ($V_{\max} \geq 5.0$ m/s, mean PG ≥ 50 mmHg, or aortic valve area <0.6 cm²) had a poorer 3-year OS and valve-related event-free survival than severe AS.¹⁹

There are also previous studies that have used a lower $V_{\max}$ threshold to identify patients who are likely to benefit from early AVR. In a study of severe AS patients with aortic valve area ≤ 0.75 cm² and $V_{\max} \geq 4.5$ m/s or mean PG ≥ 50 mmHg, the operated group (n=102) had no cardiac deaths, while the conventional treatment group (n=95) had

18 cardiac deaths during follow-up, and the incidence of sudden death in the conventional treatment group reached up to 1.7% per year.⁷ Another study showed that asymptomatic patients with $V_{\max} \geq 4.5$ m/s had a greater likelihood of developing symptoms (relative risk [RR], 1.34), or having surgery or cardiac death (RR, 1.48).⁸ Although a $V_{\max}$ threshold of 4.5 m/s is not used in the current guidelines and is not generally accepted, we consider there may be potential benefits of using $V_{\max}$ 4.5 m/s based on these studies. Therefore, we used it as the cut-off in the present subgroup analysis.

The present study emphasizes that even if asymptomatic severe AS patients with $V_{\max} \geq 4.5$ m/s at diagnosis could survive to AVR without cardiac death during watchful waiting, operative and long-term mortality after AVR would be increased compared with those who underwent early AVR. Higher incidence of HF hospitalization during watchful waiting and higher prevalence of very severe AS at AVR may explain why postoperative outcomes after watchful waiting were worse in the subgroup of patients with $V_{\max} \geq 4.5$ m/s. Based on the aforementioned previous studies and the present results, the threshold of AS severity for surgical referral in asymptomatic patients might need to be lowered in the future.

Study Limitations

This study has several limitations. First, this study was retrospective and the initial treatment strategy was decided by an attending cardiologist. Given that patients were not randomized into the 2 groups, potential selection bias cannot be eliminated. Prevalence of prior percutaneous coronary intervention was higher in the AVR after watchful waiting group. These patients might be accustomed to being treated with catheter intervention and reluctant to undergo surgery. AS was significantly more severe in the initial AVR group than the AVR after watchful waiting group, as expected. Second, asymptomatic status was assessed from history taking, but not confirmed on exercise testing. Some elderly patients might be asymptomatic because of sedentary lifestyle or because of subconsciously decreasing activity to avoid symptoms. In addition, frailty was not assessed in the present study, although frailty has become increasingly recognized as an outcome predictor after AVR. Third, there was a median interval of approximately 2 years between the date of diagnosis and AVR in the AVR after watchful waiting group, although we assessed patient characteristics and echocardiography at diagnosis. Given that the survival analysis started at the time of AVR, preoperative data might be more appropriate for evaluation. In real-world practice, however, the initial treatment strategy for asymptomatic severe AS should be decided at initial diagnosis. Therefore, comparison using baseline clinical data seems to be reasonable and acceptable. Fourth, not all patients may have received regularly scheduled follow-up, because this was a retrospective study; therefore, conservative strategy before AVR may not strictly fulfill the criteria for watchful waiting. Fifth, the conclusion derived from the post-hoc subgroup analysis might be regarded as only hypothesis generating. Finally, the present study analyzed only patients who underwent AVR. Some patients who were planned to undergo AVR when symptoms developed could not undergo AVR because of cardiac events such as sudden death during watchful waiting. These patients were not assessed in the present study.

Conclusions

Asymptomatic severe AS patients who underwent AVR after watchful waiting had a survival rate similar to those who initially underwent AVR. In a subgroup of patients with $V_{\max} \geq 4.5$ m/s at diagnosis, however, the AVR after watchful waiting group had worse postoperative outcomes than the initial AVR group.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Table S1. Reasons for AVR in the AVR after watchful waiting group vs. $V_{\max}$

Table S2. Clinical characteristics and echocardiography at diagnosis in patients with $V_{\max} \geq 4.5$ m/s

Table S3. Clinical characteristics and echocardiography at diagnosis in patients with $V_{\max} < 4.5$ m/s

Table S4. Echocardiographic changes in the AVR after watchful waiting group vs. $V_{\max}$

Please find supplementary file(s);
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