

Initial Surgical versus Conservative Strategies in Patients with Asymptomatic Severe Aortic Stenosis

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ABSTRACT

BACKGROUND Current guidelines generally recommend the strategy of watchful waiting for aortic valve replacement (AVR) until symptoms emerge in asymptomatic patients with severe aortic stenosis (AS). However, there is no previous large-scale multicenter study comparing the initial AVR strategy with the conservative strategy in this population.

OBJECTIVES This study sought to compare the long-term outcomes of initial AVR versus conservative strategies following the diagnosis of asymptomatic severe AS.

METHODS The CURRENT AS registry is a multicenter registry enrolling 3815 consecutive patients with severe AS (peak aortic jet velocity >4.0 m/s, or mean aortic pressure gradient >40 mmHg, or aortic valve area <1.0 cm²) between January 2003 and December 2011. Among 1808 asymptomatic patients, the initial AVR and conservative strategies were chosen in 291 patients, and 1517 patients, respectively. The median duration of follow-up was 1361 days with 90% follow-up rate at 2-year. The propensity-score matched cohort of 582 patients (initial AVR group: 291 patients and conservative group: 291 patients) was developed as the main analysis set for the current report.

RESULTS Baseline characteristics of the 2 groups in the propensity-score matched cohort were largely comparable, except for the slightly younger age and the greater aortic stenosis severity in the initial AVR group. In the conservative group, AVR was performed in 41% of patients during follow-up. The cumulative 5-year incidences of all-cause death and heart failure hospitalization were significantly lower in the initial AVR group than in the conservative group (15.4% versus 26.4%, $p=0.009$, and 3.8% versus 19.9%, $p<0.001$, respectively). The results from the multivariable Cox models in the entire cohort were consistent with those from the propensity-score matched analysis.

CONCLUSIONS The long-term outcome of asymptomatic patients with severe AS was dismal when managed conservatively in the real clinical practice, which might be substantially improved by the initial AVR strategy.

Clinical trial: UMIN 000012140

KEY WORDS: aortic stenosis, aortic valve replacement, asymptomatic

Abbreviations list

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CI = confidence interval

HF = heart failure

HR = hazard ratio

LV = left ventricular

PG = pressure gradient

TAVI = transcatheter aortic valve implantation

VARC = Valve Academic Research Consortium

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Introduction

Aortic stenosis (AS) is a slowly progressive disease and survival during the asymptomatic phase of AS was reported to be similar to age-matched controls with a low risk of sudden death when patients are followed prospectively and promptly report symptom onset (1-3). The potential benefits of aortic valve replacement (AVR) in asymptomatic patients with severe AS were not considered to outweigh the operative mortality of AVR (4,5). Therefore, the current guidelines generally recommend a strategy of watchful waiting for AVR until symptoms emerge in asymptomatic patients with severe AS (6). However, the recommendation was based on previous small single-center studies that sought to evaluate symptoms and/or AVR, but not mortality as the outcome measures (1-3,7). Multicenter study design seemed to be crucial for extrapolating the study results into real clinical practice, because the quality of echocardiographic examination, the ways of patient follow-up, and the operative mortality of AVR might be variable among centers. Furthermore, there is no large-scale study comparing the initial AVR strategy with the conservative strategy in asymptomatic patients with severe AS except for one small single center observational study in patients with very severe AS (8) Also, the patient demographics, age, and operative mortality of AVR in the contemporary clinical practice might be different from those reported in the previous studies (1-3,9-13). There is an

obvious clinical need to evaluate the balance between risks and benefits of AVR in asymptomatic patients with severe AS in the contemporary clinical practice.

Therefore, we sought to compare the initial AVR strategy with the conservative strategy for the long-term outcomes of asymptomatic patients in a large Japanese multicenter registry of consecutive patients with severe AS.

Methods

Study Population

The CURRENT AS (Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis) registry is a retrospective, multicenter registry enrolling consecutive patients with severe AS among 27 centers (on-site surgical facility in 20 centers) in Japan between January 2003 and December 2011. We searched the hospital database of transthoracic echocardiography, and enrolled consecutive patients who met the definition of severe AS (peak aortic jet velocity [V_{\max}] $>4.0\text{m/s}$, mean aortic pressure gradient [PG] $>40\text{mmHg}$, or aortic valve area [AVA] $<1.0\text{cm}^2$) for the first time during the study period.⁽⁶⁾ We excluded those patients who had a history of aortic valve repair/replacement/plasty or percutaneous aortic balloon valvuloplasty. The institutional review boards in all 27 participating centers (Online Appendix) approved the protocol. Written informed consent from each patient was waived in this retrospective study, because we used clinical information obtained in the

routine clinical practice, and no patients refused to participate in the study when contacted for follow-up.

Among 3815 patients enrolled in the registry, there were 2005 patients with and 1808 patients without symptoms related to AS at the time of the index echocardiography, excluding 2 patients whose symptomatic status were not available. In this primary report from the CURRENT AS registry, 1808 asymptomatic patients were subdivided into the initial AVR group (291 patients) and the conservative group (1517 patients) according to the treatment strategies selected after the index echocardiography (**Figure 1**). Baseline characteristics and 5-year clinical outcomes were compared between the initial AVR and conservative groups. Because the selection of initial AVR was determined by physicians, and the characteristics were supposed to be highly different between groups, we had chosen to develop the propensity-score matched cohort of 582 patients (initial AVR group: 291 patients and conservative group: 291 patients) as the main analysis set for the current report (**Figure 1** and Online Figure 1). We also analyzed the entire cohort of asymptomatic AS patients to explore the robustness of our analyses. Initial AVR and initial conservative strategies were compared by the intention-to-treat principle regardless of the actual performance of AVR. The follow-up was commenced on the day of the index echocardiography.

Echocardiography

All patients underwent a comprehensive 2-dimensional and Doppler echocardiographic evaluation in each participating center. V_{\max} and mean aortic PG were obtained with the use of the simplified Bernoulli equation. AVA was calculated with the use of the standard continuity equation, and was indexed to body surface area (14).

Data Collections and Definitions

Collection of baseline clinical information was conducted through review of the hospital charts or database. Angina, syncope, or congestive heart failure including dyspnea were regarded as symptoms related to AS. Follow-up information was mainly collected through review of the hospital charts and additional information was collected through contact with patients, relatives, and/or referring physicians by sending mail with questions regarding survival, symptoms and subsequent hospitalizations.

The primary outcome measures for the current analysis were all-cause death and heart failure (HF) hospitalization. The causes of death were classified according to the Valve Academic Research Consortium (VARC) definitions, and were adjudicated by a clinical event committee (Online Appendix) (15,16). Sudden death was defined as unexplained death in previous stable patients. Aortic valve-related death included aortic procedure-related death, sudden death, and death due to HF possibly related to aortic valve. HF hospitalization was defined as hospitalization due to worsening HF requiring intravenous drug therapy. Other

definitions of the clinical events were described in the Online Appendix.

Statistical Analysis

Categorical variables were presented as numbers and percentages, and were compared with the chi-square test or the Fisher's exact test. Continuous variables were expressed as the mean and SD or median and interquartile range (IQR). Based on their distributions, continuous variables were compared using the Student's t test or Wilcoxon rank sum test. We used the Kaplan-Meier method to estimate the cumulative incidence and assessed the differences with the log-rank test.

We used logistic regression model to develop propensity-score for the choice of initial AVR with 15 independent variables relevant to the choice of initial AVR listed in **Table 1**. The c-statistics was 0.783 and the coefficients of the independent variables are shown in Online Table 1. We then calculated the propensity score by summing up all coefficients multiplies corresponding variables. To make propensity-score matched cohort, patients in the conservative group were matched to those in the initial AVR group using a 1:1 greedy matching technique (17). We then calculated the cumulative incidence using the propensity-score matched cohort. Not all relevant variables were well matched, probably due to many patients in the conservative group. Therefore, we conducted an adjusted analysis using the Cox proportional hazard models with the following risk adjusting variables; age, dyslipidemia, malignancy currently under

treatment, EuroSCORE II, and STS score (PROM), as a sensitivity analysis in the propensity-score matched cohort. For the secondary analysis among the entire cohort of 1808 asymptomatic patients, the 21 clinically relevant factors listed in **Table 1** were included in the Cox proportional hazard models as the risk adjusting variables and the centers were incorporated as the stratification variable. The continuous variables other than age were dichotomized by median values or clinically meaningful reference values. Because the difference in age between the 2 groups was too large to allow the dichotomous approach, we treated age as a continuous variable in the Cox proportional hazard models. Proportional hazard assumptions for the risk-adjusting variables including the categorized age in quartile were assessed on the plots of log (time) versus log [- log (survival)] stratified by the variable, and were verified to be acceptable. The risks of initial AVR strategy relative to conservative strategy for the clinical endpoints were expressed as hazard ratios and their 95% confidence intervals.

All statistical analyses were conducted by a physician (Taniguchi T) and a statistician (Morimoto T) with the use of JMP 10.0.2 (SAS Institute Inc., Cary, NC, USA) or SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All reported p values were 2 tailed, and p values <0.05 were considered statistically significant.

Results

Baseline Characteristics in the Entire Cohort and in the Propensity-Score Matched Cohort

Baseline characteristics were significantly different between the initial AVR and conservative groups before matching (**Table 1**). Patients in the conservative group as compared with those in the initial AVR group were much older (77.8 ± 9.4 versus 71.6 ± 8.7 years, $p<0.001$) and more often had prior symptomatic stroke, atrial fibrillation or flutter, malignancy currently under treatment, chronic lung disease and coronary artery disease. Patients in the initial AVR group had greater AS severity than those in the conservative group. There were 247 patients who were regarded as ineligible for AVR by the attending physicians, although the decision regarding the ineligibility for AVR was not uniform in this retrospective study. They had one or more reasons for the ineligibility; extreme old age in 170 patients; reduced cognitive function in 53 patients; serious comorbid conditions other than heart that limit life expectancy in 43 patients; renal failure in 26 patients; muscle weakness in 26 patients; anatomic factors that preclude or increase the risk of cardiac surgery, such as a porcelain aorta, prior radiation, or an arterial bypass graft in 22 patients; reduced pulmonary function in 14 patients; malnutrition in 10 patients; severe liver cirrhosis in 2 patients.

Among 291 patients who were referred to AVR despite absence of symptoms related to AS, 184 (63%) patients had one or more formal indications for AVR; very severe AS ($V_{\max} \geq 5.0\text{m/s}$ or mean aortic PG $\geq 60\text{mmHg}$) in 118 patients (41%), left ventricular dysfunction (left ventricular ejection fraction [LVEF] $<50\%$) in 19 patients (7%), candidates for other cardiac

surgery in 24 patients (8%), a rapid hemodynamic progression in 32 patients (11%), and active infective endocarditis in 1 patient (0.3%).

Baseline characteristics of the initial AVR and conservative groups in the propensity-score matched cohort were much more comparable than those in the entire cohort except for the slightly younger age, the slightly lower Society of Thoracic Surgeons (STS) score and the greater AS severity in the initial AVR group (**Table 1**). Patients in the matched cohort had mean age of early 70s, and had relatively low STS predicted risk of mortality. Regarding the eligibility for severe AS, 43 patients (15%) in the initial AVR group and 111 patients (38%) in the conservative group were included on the basis of AVA $<1.0 \text{ cm}^2$ alone (LVEF $\geq 50\%$) with less severe Vmax and mean aortic PG (**Table 1**).

Clinical Outcomes in the Propensity-Score Matched Cohort

In the initial AVR group, surgical AVR was actually performed in 286 (98%) patients and 1 patient underwent transcatheter aortic valve implantation with median interval of 44 days from the index echocardiography (**Table 2** and **Central Illustration**). In the remaining 4 patients, 2 patients died suddenly, 1 patient died of respiratory failure while waiting for AVR, and 1 patient was lost to follow-up on day 15. The 30-day mortality rate after AVR was 1.4% in the initial AVR group.

Among 291 patients in the conservative group, AVR was performed in 118 patients

(41%) during follow-up with the median interval of 780 days from the index echocardiography (**Central Illustration**). Among 116 patients (40%) with emerging symptoms related to AS during follow-up in the conservative group, AVR was performed in 80 patients (69%) with median interval of 72 (IQR: 42-121) days after onset of symptoms. AVR was performed in 30 patients (67%) out of 45 patients presenting with NYHA class-3 or -4 HF (Online Table 2).

The cumulative 5-year incidence of all-cause death was significantly lower in the initial AVR group than in the conservative group (15.4% versus 26.4%, $p=0.009$) (Table 2, and Central Illustration). The cumulative 5-year incidences of cardiovascular death and aortic valve-related death were also significantly lower in the initial AVR group than in the conservative group (9.9% versus 18.6%, $p=0.01$, and 5.3% versus 13.5%, $p=0.003$, respectively). The cumulative 5-year incidence of sudden death trended to be lower in the initial AVR group than in the conservative group (3.6% versus 5.8%, $p=0.06$). Among 46 patients with cardiovascular death in the conservative group, heart failure (9 patients who did not undergo AVR despite symptoms) and sudden death (8 patients who did not undergo AVR despite symptoms, and 10 patients without symptoms) were the dominant causes of cardiovascular death (Online Table 3). The initial AVR strategy as compared with the conservative strategy was also associated with markedly lower cumulative 5-year incidences of emerging symptoms related to AS and HF hospitalization (3.2% versus 46.3%, $p<0.001$, and 3.8% versus 19.9%, $p<0.001$, respectively) (**Table 2, Central**

Illustration and Figure 2). The results from the adjusted analysis conducted as a sensitivity analysis were fully consistent with those from the unadjusted analysis (**Table 2**).

Crude Clinical Outcomes in the Entire Cohort

Among 1808 asymptomatic patients with severe AS, median follow-up interval after the index echocardiography was 1361 (IQR: 1055-1697) days with 90% follow-up rate at 2-year.

Among 1517 patients in the conservative group, follow-up information was collected from the hospital chart of the participating centers in 1311 patients (86.4%). AVR was performed in 392 patients (26%) during follow-up with median interval of 788 days (**Table 3** and Online Figure 2).

The 30-day mortality rate after AVR was 2.6% in the conservative group, which tended to be higher than that in the initial AVR group, but without significant difference ($p=0.29$). Among 492 patients with emerging symptoms related to AS during follow-up in the conservative group, AVR was performed in 239 patients (49%) with median interval of 70 (IQR: 41-131) days after onset of symptoms. AVR was performed only in 74 patients (37%) out of 201 patients presenting with New York Heart Association (NYHA) class-3 or -4 HF. Among 127 patients who presented with NYHA class-3 or -4 HF, but did not undergo AVR, 96 patients (76%) died with median interval of 95 (IQR: 11-467) days after onset of symptoms (Online Table 2). Among 679 patients who underwent AVR in the present study, AVR after symptom development during follow-up (N=247 including 8 patients who became symptomatic at the time of AVR) was associated with higher

30-day operative mortality than AVR while asymptomatic (N=432) (3.7% versus 1.2%, $p=0.03$).

The cumulative 5-year incidence of all-cause death was significantly lower in the initial AVR group than in the conservative group (**Table 3** and Online Figure 2). Among 582 patients (32%) who died during follow-up, HF and sudden death were the dominant causes of death in the conservative group (101 patients and 82 patients, respectively), while those were rare as the causes of death in the initial AVR group (1 patient and 8 patients, respectively) (Online Table 4). The cumulative 5-year incidence of HF hospitalization was also significantly lower in the initial AVR group than in the conservative group (**Table 3** and Online Figure 2). The cumulative 5-year incidence of sudden death was 7.6% (1.5%/year) in the conservative group as compared with 3.6% (0.7%/year) in the initial AVR group. Among 82 patients who had sudden death in the conservative group, 57 patients (70%) died suddenly without preceding symptoms. In 32 of these 57 patients (56%), sudden death occurred within 3 months of the last clinical follow-up visit.

The lower cumulative incidences of all-cause death and HF hospitalization in the initial AVR group than in the conservative group were consistently seen in the 2 subgroups of patients with or without current recommendations for AVR such as very severe AS at low surgical risk or severe AS with left ventricular dysfunction (Online Figure 3).

Adjusted Clinical Outcomes in the Entire Cohort

The favorable effect of the initial AVR strategy relative to the conservative strategy for

the clinical outcomes was similarly seen in the adjusted analysis of the entire cohort as in the propensity-score matched analysis, although the effect size was smaller in the propensity-score matched cohort than in the entire cohort (**Table 3**). The lower risks of the initial AVR strategy relative to the conservative strategy for all-cause death and HF hospitalization were consistently seen in the 2 subgroups of patients with or without current recommendations for AVR (Online Figure 3).

Discussion

The main finding of this study was that the initial AVR strategy as compared with the conservative strategy was associated with lower risk for all-cause death as well as HF hospitalization in asymptomatic patients with severe AS in a propensity-score matched analysis.

Although AVR is strongly recommended in symptomatic patients with severe AS who are candidates for surgery, management of asymptomatic patients with severe AS remains controversial. The current guidelines recommend a strategy of watchful waiting for AVR until symptoms emerge in asymptomatic patients with severe AS except for patients with left ventricular dysfunction, very severe AS, candidates for other cardiac surgery or abnormal exercise test (6,18). However, the current large-scale multicenter propensity-score matched analysis clearly demonstrated the benefits of the initial AVR strategy in reducing mortality and HF hospitalization as compared with the conservative strategy. The extent of benefits appeared to

be similar regardless of the current indications for AVR such as left ventricular dysfunction or very severe AS. Several important issues should be considered regarding the clinical relevance of the watchful waiting for AVR strategy. First and most importantly, the current recommendations for AVR are mainly dependent on the patients' symptoms. However, many patients with severe AS who could potentially be benefited from AVR may not complain any symptoms because of their sedentary life style. It is often difficult to distinguish the non-specific symptoms such as fatigue and dyspnea on exertion from the true symptoms related to AS. In the asymptomatic patients with severe AS, exercise stress test is recommended to confirm both their asymptomatic status and hemodynamic response to exercise (6,19). However, exercise testing is not commonly performed in real clinical practice due to concerns on safety, and cannot be performed in many patients because of their advanced age, limited exercise capacities, and comorbidities. Second, prompt detection of symptoms during follow-up is not always possible in the real clinical practice (6). Patients may not always be compliant to the close clinical follow-up (20). Indeed, in the current study, severe HF was the initial symptom in a sizable proportion of patients in the conservative group, in whom AVR was less frequently performed than in patients without severe HF, and mortality was extremely high if AVR was not performed. It is noteworthy that the initial AVR strategy as compared with the conservative strategy was associated with markedly lower risk for HF hospitalization, which should be regarded as a very serious clinical event in patients

with severe AS. Third, the present study and a prior large scale surgical report suggested that AVR after symptom development was carrying higher operative risk than AVR during the asymptomatic phase, although M. L. Brown, et al. reported similar AVR operative mortality between symptomatic and asymptomatic patients from a single center study.(4,21) Fourth, the annual rate of sudden death in the conservative group was 1.5% in the current study, suggesting that the rate of sudden death during asymptomatic phase might be higher than the rate (<1.0%/year) reported previously (2,3,9). Finally, in the present study, 41% of patients managed conservatively required AVR within a median follow up of 2 years, suggesting that one does not gain much by waiting. Balancing the risks of the watchful waiting for AVR strategy and the improvement in operative mortality, AVR during the asymptomatic phase might be a viable treatment option in severe AS patients at low-risk for AVR.

Limitations

This study has several limitations. First, in this retrospective study, we could not exclude the possibility of ascertainment bias for symptoms related to AS at baseline. However, we thoroughly reviewed all the patients' charts and referred to the hospital database to evaluate the symptomatic status. Second, we could not deny the residual confounding and selection bias in the comparison between the initial AVR and conservative strategies, although the characteristics of the 2 groups were largely comparable after propensity-score matching. Actually in the present

analysis, propensity-score matching did not completely eliminate the impact of differences in age as well as EuroSCORE and STS score in the two populations. However, the results from the adjusted analysis conducted as a sensitivity analysis were fully consistent with those from the unadjusted analysis. Third, some patients were included in this study on the basis of AVA <1.0 cm² alone (LVEF ≥50%) with less severe Vmax and mean aortic PG. The imprecision of assessing AVA by echocardiography with overestimation of AS severity in some patients is a possible concern. However, the proportion of those patients included on the basis of AVA <1.0 cm² alone was greater in the conservative group than in the initial AVR group. Clinical outcomes were worse in the conservative group than in the initial AVR group despite more frequent inclusion of somewhat less severe AS in the former group. Finally, patient follow-up in this multicenter study might have been less close than in the previous single-center studies and therefore, the emerging symptoms related to AS might be underestimated. However, follow-up information in the conservative group was collected from the hospital chart of the participating centers in 86.4% of patients, suggesting that majority of patients were followed by the cardiologists. It is important to note that even with follow-up by the cardiologists, presentation with severe heart failure during follow-up was not uncommon in the real clinical practice.

Conclusions

The long-term outcome of asymptomatic patients with severe AS was dismal when

managed conservatively in the real clinical practice, which might be substantially improved by the initial AVR strategy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with asymptomatic severe aortic stenosis, the initial aortic valve replacement strategy as compared with the conservative strategy currently recommended by the guidelines was associated with lower long-term risk of all-cause death and heart failure hospitalization by the propensity-score matched analysis from the multicenter CURRENT AS registry.

TRANSLATIONAL OUTLOOK: Further studies, particularly randomized controlled trials, are needed to compare the initial aortic valve replacement strategy with the conservative strategy as the initial management of patients with asymptomatic severe aortic stenosis.