Impact of Valve Replacement on Long-Term Survival in Asymptomatic Patients With Severe Aortic Stenosis

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Aortic valve (AV) replacement (AVR) is the only effective treatment for severe aortic stenosis (AS). However, survival benefits by performing AVR in asymptomatic AS patients with preserved left ventricular (LV) function remains controversial. This study included 468 patients (aged 64.2 ± 13.0 years, 232 women) with preserved LV function (≥50%) and severe AS (AV area ≤1.0 cm^2, peak trans-AV velocity [V_{max}] ≥4.0 m/s, or mean AV pressure gradient ≥40 mm Hg) between 2000 and 2015. AVR was performed in 221 (47.2%) patients early (within 3 months; n = 130, 27.8%) or during follow-up (n = 91, 19.4%), whereas the remainder (n = 247) received medical treatment. Time-dependent Cox regression analyses were performed to determine the impact of AVR on long-term survival outcomes. During a median follow-up of 60.9 months (quartile 1 to 3, 29.9 to 107.0 months), 72 (15.4%) patients developed AS-related symptoms and 146 (31.2%) died. On time-dependent Cox models, AVR was associated with a significant risk reduction in all-cause death (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.40 to 0.97; p = 0.036) and cardiac death (HR, 0.59; 95% CI, 0.35 to 0.995; p = 0.048) after adjusting for significant contributors to mortality. Survival benefits by performing AVR were manifested in most risk subgroups. In conclusion, AVR in asymptomatic severe AS patients with preserved LV function resulted in significant survival benefits, suggesting that early recruitment for AVR may be warranted before ventricular dysfunction or symptom development. **(Am J Cardiol 2019;123:1321−1328)**

Aortic stenosis (AS) is the most frequent type of valvular heart disease in the elderly.[1,2,3] Current guidelines recommend aortic valve replacement (AVR) (class 1) for symptomatic severe AS patients or those with decreased left ventricular (LV) ejection fraction (EF) (<50%), whereas advocating watchful waiting for asymptomatic severe AS patients until symptom onset.[4] The recommendation on watchful waiting, however, is largely based on evidences extrapolated from small-sized retrospective studies.[5,6] In contrast, recent large-scale cohort studies[7,8] have questioned the benign natural courses of asymptomatic severe AS and argued the need for earlier intervention. Also, the optimal timing of AVR in asymptomatic severe AS patients is hard to pinpoint due to (1) the difficulty in detecting subtle symptoms in elderly sedentary patients, (2) increased operative risks with aging and deterioration of LV function during watchful waiting, (3) unpredictable progression of severe AS, and (4) advent of less-invasive transcatheter techniques.[9−13] When comparing AVR with medical management in treating asymptomatic severe AS patients, the duration from initial severe AS diagnosis to AVR needs to be incorporated into the risk analysis to better address the occurrence of mortality or cardiac events before AVR.[14] Thus, we evaluated the impact of AVR on long-term survival and the development of major adverse cardiac events (MACEs) in asymptomatic patients with severe AS and preserved LV function, with consideration of surgical timing.

Methods

This study was approved by the institutional review board of Asan Medical Center in Seoul, South Korea, which waived the need for informed consent due to its retrospective nature. For data collection, we used the Institutional Electronic Database of Asan Medical Center, which maintains all longitudinal clinical information of individuals since January 2000. We identified patients who were assigned the International Classification of Disease codes, designated as rheumatic or nonrheumatic AS (I35.0, I35.2, I06.0, and I06.2) between January 2000 and August 2015, yielding 4972 consecutive adult patients (age ≥17 years). For symptomatology, a detailed retrospective review was

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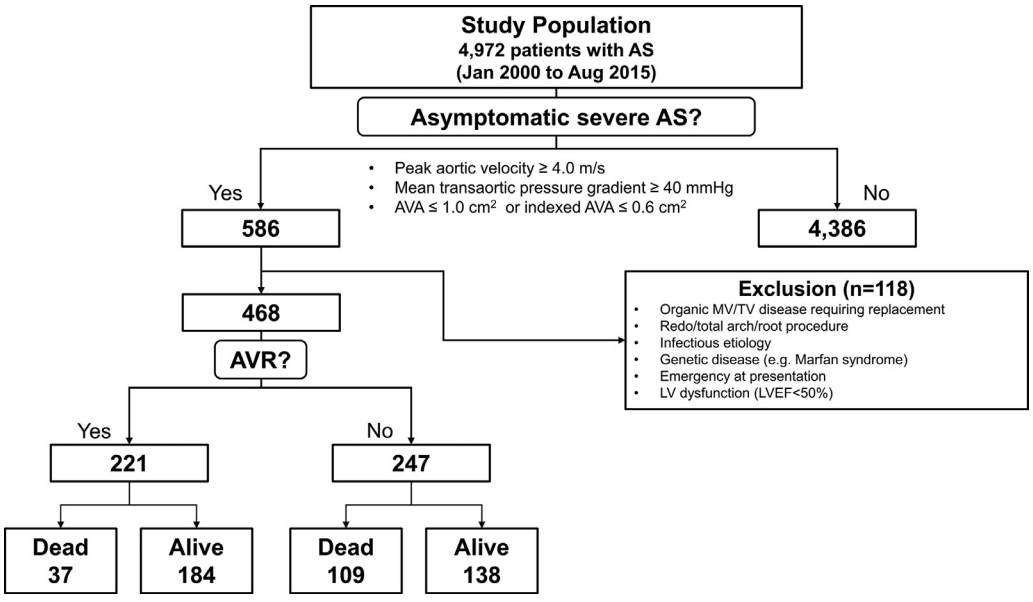

Figure 1. Flow diagram of the study cohort.

undertaken to identify patients staged as C (asymptomatic severe AS; n = 586) in accordance with the 2014 American College of Cardiology/American Heart Association guidelines.[4] Exclusion criteria were patients (n = 118) who had (1) previous AV or aortic root surgery, (2) an infectious etiology, (3) concomitant organic mitral valve or tricuspid valve disease requiring surgical replacement, (4) aortic disease requiring concomitant aortic replacement by total circulatory arrest, (5) overt genetic aortopathy (e.g., Marfan syndrome), (6) requirements for emergency surgery at initial presentation, and (7) LV dysfunction (LVEF<50%) (stage C2). Finally, 468 consecutive asymptomatic severe AS patients with preserved LV function (LVEF ≥50%) were enrolled; AVR was performed in 221 (47.2%) patients, whereas 247 (52.8%) received medical treatment (Figure 1).

The decision to perform AVR was made by the patient and the family members after consultation with the heart team composed of cardiac surgeons and cardiologists in our institution; considering the patient's risk and hemodynamic profiles, optimal treatment strategies were discussed at the weekly team meetings. Thereafter, the heart team provided balanced opinions on the potential benefits of AVR against the estimated operative risks and prosthesis-related complications.

Details of the echocardiographic evaluations were described in a previous study.[15] In brief, comprehensive 2-dimensional and Doppler echocardiographic examinations were performed in all patients at initial presentation to our institution and annually thereafter. A peak aortic velocity was measured with the maximal velocity signal in the apical, right parasternal, or suprasternal view. Additionally, the mean trans-aortic pressure gradient was calculated with the modified Bernoulli equation. The aortic valve area was estimated using the continuity equation and indexed to the body surface area.

Surgical AVR was performed through either median full-sternotomy (n = 201) or minimally invasive approach (n = 20) depending on the surgeon's preference or the necessity of concomitant procedures. Cardiopulmonary bypass was instituted in a standardized fashion for each approach as previously described.[16] Myocardial protection was achieved with the anterograde administration of cardioplegic solution (tepid blood cardioplegia, cold crystalloid cardioplegia, or del Nido cardioplegia) under mild systemic hypothermia or normothermia. The suture technique was left at the discretion of the operating surgeons.

The outcomes of interest were all-cause death, cardiac death, and MACEs, including nonfatal myocardial infarction, stroke, infective endocarditis, hospitalization owing to heart failure, and AV reoperation. Clinical follow-up data were obtained every 3 to 6 months during outpatient clinic visits, and all visits to our institution until the end of June 2016 were included.

Categorical variables, summarized as frequencies and percentages, were compared with the chi-square test. Continuous variables, summarized as mean ± standard deviation or median with interquartile range, were compared using the Student's *t* test. To address time-dependent effects of AVR from the initial diagnosis of severe AS on overall mortality, the date of diagnosis was set as the index date when severe AS was first diagnosed using echocardiographic evaluation or clinical presentations. Therefore, considering the time interval between the index date and the time of AVR, time-dependent Cox regression analyses were performed.[14] Risk variables (Table 1) were analyzed in the univariable Cox models, and those with p value ≤0.1 were used in the multivariable Cox models by involving a stepwise backward elimination technique, to retain those with p values <0.1 in the final model. The variables that remained significant in the final model were fitted into the time-dependent Cox models with the incorporation of "time-varying AVR" factor to determine the

Table 1
Baseline characteristics according to the performance of aortic valve replacement

Variable	Entire cohort (n = 468)	Treatment		p value
		Medical (n = 247)	AVR (n = 221)	
Age (years)	64.2 ± 13.0	67.1 ± 13.1	61.0 ± 12.3	<0.001
Women	232 (49.6%)	121 (49.0%)	111 (50.2%)	0.861
Body mass index (kg/m^2)	24.1 ± 3.2	23.6 ± 3.2	24.6 ± 3.2	0.001
Hypertension	214 (45.7%)	122 (49.4%)	92 (41.6%)	0.112
Diabetes mellitus	103 (22.0%)	66 (26.7%)	37 (16.7%)	0.013
Insulin therapy	16 (3.4%)	11 (4.5%)	5 (2.3%)	0.295
Hyperlipidemia	120 (25.6%)	61 (24.7%)	59 (26.7%)	0.697
Chronic obstructive pulmonary disease	58 (12.4%)	24 (9.7%)	34 (15.4%)	0.086
Serum hemoglobin level (g/dL)	12.9 ± 1.8	12.5 ± 1.9	13.4 ± 1.6	<0.001
Anemia	146 (31.2%)	98 (39.7%)	48 (21.7%)	< 0.001
Serum total bilirubin level (mg/dL)	1.0 ± 1.9	1.2 ± 2.6	0.9 ± 0.5	0.098
Serum creatinine level (mg/dL)	1.0 ± 0.8	1.1 ± 1.1	0.9 ± 0.3	0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)	89.9 ± 37.2	88.3 ± 41.4	91.6 ± 31.9	0.349
Severe chronic kidney disease	16 (3.4%)	15 (6.1%)	1 (0.5%)	0.002
Dialysis	10 (2.1%)	10 (4.0%)	0 (0.0%)	0.007
Atrial fibrillation	53 (11.3%)	34 (13.8%)	19 (8.6%)	0.106
Peripheral arterial disease	6 (1.3%)	4 (1.6%)	2 (0.9%)	0.784
Previous stroke	43 (9.2%)	34 (13.8%)	9 (4.1%)	0.001
Coronary artery disease	49 (10.5%)	17 (6.9%)	32 (14.5%)	0.011
Previous acute myocardial infarction	9 (1.9%)	5 (2.0%)	4 (1.8%)	0.356
Previous malignancy	85 (18.2%)	56 (22.7%)	29 (13.1%)	0.011
Previous cardiac surgery	13 (2.8%)	9 (3.6%)	4 (1.8%)	0.356
Previous percutaneous coronary intervention	20 (4.3%)	13 (5.3%)	7 (3.2%)	0.373
Etiology				
Rheumatic fever	67 (14.3%)	42 (17.0%)	25 (11.3%)	0.105
Bicuspid aortic valve	189 (40.4%)	63 (25.5%)	126 (57.0%)	<0.001
Echocardiographic data				
Left ventricular ejection fraction (%)	63.4 ± 5.0	63.1 ± 5.1	63.7 ± 5.0	0.180
Left ventricular end-systolic dimension (mm)	30.0 ± 6.0	30.0 ± 6.1	30.0 ± 5.9	0.916
Left ventricular end-diastolic dimension (mm)	49.2 ± 6.7	49.3 ± 6.5	49.2 ± 6.9	0.953
Left atrium diameter (mm)	40.9 ± 7.9	42.0 ± 8.5	39.7 ± 6.8	0.001
Left ventricular mass index (g/m^2)	138.7 ± 47.5	136.8 ± 40.3	140.8 ± 54.4	0.364
Peak aortic valve velocity (m/s)	4.6 ± 0.7	4.5 ± 0.6	4.7 ± 0.7	<0.001
Aortic valve area (cm^2)	0.77 ± 0.20	0.80 ± 0.19	0.74 ± 0.21	0.001
Mean aortic valve pressure gradient (mm Hg)	51.6 ± 16.8	48.6 ± 15.9	55.0 ± 17.2	<0.001
Functional mitral regurgitation >mild	8 (1.7%)	7 (2.8%)	1 (0.5%)	0.104
Concomitant aortic regurgitation >mild	100 (21.4%)	54 (21.9%)	46 (20.8%)	0.870
Functional tricuspid regurgitation >mild	12 (2.6%)	11 (4.5%)	1 (0.5%)	0.015
Peak tricuspid regurgitation pressure gradient (mmHg)	26.2 ± 9.9	27.7 ± 11.0	24.6 ± 8.2	0.001
Very severe aortic stenosis	135 (28.8%)	52 (21.1%)	83 (37.6%)	<0.001

Values are presented as n (%) or a mean ± standard deviation, unless otherwise indicated.

impact of AVR on all-cause death and cardiac death. Extended Kaplan-Meier plots were delineated to illustrate the impact of a time-varying AVR on long-term survival.[17] All p values were two-tailed, and those <0.05 were considered statistically significant. SPSS software v21.0 (IBM Corp., Armonk, New York) and R software v3.4.0 (R foundation, Vienna, Austria) were used for statistical analyses.

Results

Baseline demographic and clinical characteristics of the entire cohort are shown in Table 1. Patients receiving medical treatment (Medical group) were older and presented with several morbidities more frequently than did those undergoing AVR (AVR group) in general. Patients in the AVR group presented with a history of coronary artery disease more frequently than did those in the Medical group. As for echocardiographic profiles, the Medical group had a larger left atrium, whereas the AVR group had a higher AV velocity and mean AV pressure gradient. Bicuspid AV and very severe AS, defined by a peak velocity ≥5.0 m/s or a mean transaortic pressure gradient ≥60 mm Hg,[4] were more common in the AVR group.

During follow-up, 72 (15.4%) patients developed valve-related symptoms: chest pain (n = 17, 3.6%), dyspnea (n = 49, 10.5%), syncope (n = 2, 0.4%) and combined chest pain and dyspnea (n = 4, 0.9%). Censored at the time of death and surgical intervention, the cumulative incidence

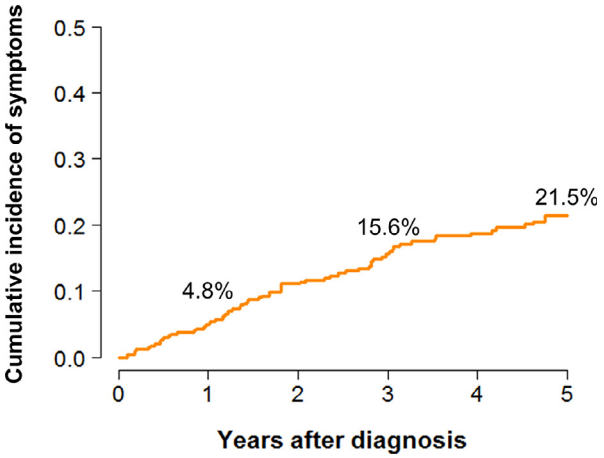

Figure 2. Cumulative incidence of valve-related symptoms in the study population.

rates of valve-related symptoms were 4.8%, 15.6%, and 21.5% at 1-, 3-, and 5-years after the initial diagnosis, respectively (Figure 2).

In the AVR group, the median time from the index date to AVR was 49 days (quartile 1 to 3, 12 to 581 days); AVR was performed in 130 (58.8%) patients within 3 months after the index date. Concomitant aorta and coronary bypass surgery were performed at the time of AVR in 52 (23.5%) and 24 (10.9%) patients, respectively. Early mortality (death within 30 days of AVR) occurred in 2 (0.9%) patients after AVR (Table 2). During a median follow-up of 60.9 months (quartile 1 to 3, 29.9 to 107.0 months; 2755 patient-years [PY]), 109 of 247 (9.1%/PY) patients in the Medical group and 37 of 221 (2.4%/PY) in the AVR group died. Of these, the incidence of cardiac death was 74 (6.2%/PY) in the Medical group and 26 (1.7%/PY) patients in the AVR group (Table 3). MACEs occurred in 9 (0.8%/PY) patients in the Medical group and 20 (1.3%/PY) in the AVR group. In the AVR group, incidences of the individual component of MACEs before and after AVR were as follows: myocardial infarction, 0.3%/PY versus 0.2%/PY; stroke, 1.0%/PY versus 0.3%/PY; and hospitalization due to heart failure, 1.7%/PY versus 0.2%/PY (Table 3).

On time-dependent Cox analyses, AVR was associated with reduced risk of all-cause mortality (hazard ratio [HR], 0.62; 95% confidence interval [CI] 0.40 to 0.97; p = 0.036; Table 4 and Figure 3-A) as well as cardiac death (HR, 0.59; 95% CI 0.35 to 0.995; p = 0.048; Supplementary Table 1 and Figure 3-B). For further verification, when the impact of AVR was evaluated after censoring patients at symptom onset, AVR was consistently associated with a reduced risk for all-cause mortality (HR, 0.63; 95% CI 0.40 to 0.99; p = 0.048; Figure 3-C). The risk reduction for all-cause mortality by AVR tended to be predominant in several risk subgroups of patients with hypertension, hyperlipidemia, anemia, and very severe AS (Figure 4).

Table 2
Operative profiles

Variable	N = 221
Diagnosis to operation (quartile 1-3) (days)	49 (12-581)
Early vs late surgery	
Early surgery (≤ 3 months)	130 (58.8%)
Late surgery (> 3 months)	91 (41.2%)
Concomitant procedures	
Coronary bypass	24 (10.9%)
Aorta	52 (23.5%)
Mitral valve repair	7 (3.2%)
Tricuspid valve repair	4 (1.8%)
Maze	7 (3.2%)
Early mortality	2 (0.9%)

Table 3
Clinical outcomes

Variable	Treatment received	
	Medical (n = 247)	AVR (n = 221)
All-cause mortality, n (%/patient-years [PY])	109 (9.1%/PY)	37 (2.4%/PY)
Cardiac death	74 (6.2%/PY)	26 (1.7%/PY)
Non-cardiac death	35 (2.9%/PY)	11 (0.7%/PY)
MACE, n (%/patient-years [PY])	9 (0.8%/PY)	20 (1.3%/PY)
Myocardial infarction	4 (0.3%/PY)	3 (0.2%/PY)
Before AVR	-	1 (0.3%/PY)
After AVR	-	2 (0.2%/PY)
Stroke	2 (0.2%/PY)	7 (0.4%/PY)
Before AVR	-	3 (1.0%/PY)
After AVR	-	4 (0.3%/PY)
Infective endocarditis	0 (0.0%/PY)	4 (0.3%/PY)
Before AVR	-	0 (0.0%/PY)
After AVR	-	4 (0.3%/PY)
Hospitalization due to heart failure	3 (0.3%/PY)	7 (0.4%/PY)
Before AVR	-	5 (1.7%/PY)
After AVR	-	2 (0.2%/PY)
Reoperation*	Not applicable	1 (0.1%/PY)
Composite outcomes, n (%/patient-years [PY])		
All-cause mortality + MACE	110 (9.2%/PY)	51 (3.3%/PY)

AVR, aortic valve replacement; MACE, major adverse cardiac event.
* AVR group only.

Discussion

The present study demonstrated that AVR is significantly associated with the reduced risk of all-cause and cardiac mortality in asymptomatic severe AS patients with preserved LV function. These survival benefits tended to be demonstrated in most risk subgroups. A time-varying statistical methodology was used to adequately reflect a time lag from the diagnosis of AS to the time of AVR in the survival analysis.

Ross and Braunwald asserted that the risk of sudden death in severe AS patients greatly increased upon development of valve-related symptoms.[3] Since then, the estimated life expectancies of asymptomatic patients with severe AS have been deemed similar to those of general populations without severe AS.[6,18–20] Thus, conservative medical treatment has been advocated in these patients, whereas surgical treatment has been recommended in highly select group of patients after weighing the anticipated survival benefits

Table 4
Univariate and multivariate analysis for all-cause mortality (time-dependent Cox regression analysis)

	Univariate analysis			Multivariate analysis*		
Risk factors	Hazard ratio	95% Confidence interval	p value	Hazard ratio	95% Confidence interval	p value
Aortic valve replacement	0.49	0.34-0.72	< 0.001	0.62	0.40-0.97	0.036
Age (by 1-year increment)	1.07	1.06-1.09	< 0.001	1.06	1.04-1.07	< 0.001
Body mass index (by 1 kg/m^2 increment)	0.94	0.89-0.99	0.011	0.96	0.91-1.01	0.083
Hypertension	2.02	1.45-2.82	< 0.001			
Diabetes mellitus	2.38	1.69-3.34	< 0.001			
Anemia	3.47	2.50-4.82	< 0.001	1.41	0.95-2.08	0.086
Severe chronic kidney disease	5.47	3.08-9.70	< 0.001	3.78	2.03-7.04	< 0.001
Atrial fibrillation	2.09	1.35-3.22	0.001			
Peripheral arterial disease	4.01	1.64-9.81	0.002			
Previous stroke	2.63	1.69-4.09	< 0.001	1.75	1.10-2.80	0.019
Coronary artery disease	1.88	1.20-2.93	0.006	2.22	1.39-3.54	0.001
Previous percutaneous coronary intervention	2.27	1.15-4.47	0.018			
Previous malignancy	4.46	3.18-6.24	< 0.001	3.36	2.36-4.78	< 0.001
Rheumatic etiology	0.60	0.35-1.02	0.058			
Left atrium diameter (by 1 mm increment)	1.05	1.03-1.07	< 0.001	1.02	0.99-1.05	0.059
Left ventricular mass index (by 1 g/m^2 increment)	1.004	1.001-1.007	0.003	1.003	1.000-1.007	0.040
Significant mitral regurgitation	4.05	1.89-8.67	<0.001			
Significant tricuspid regurgitation	2.89	1.41-5.90	0.004			
Peak tricuspid regurgitation pressure gradient (by 1 mm Hg increment)	1.03	1.02-1.04	<0.001	1.02	1.002-1.032	0.031

* Only variables with a p value ≤0.10 in univariate analysis were included in the multivariate analysis.

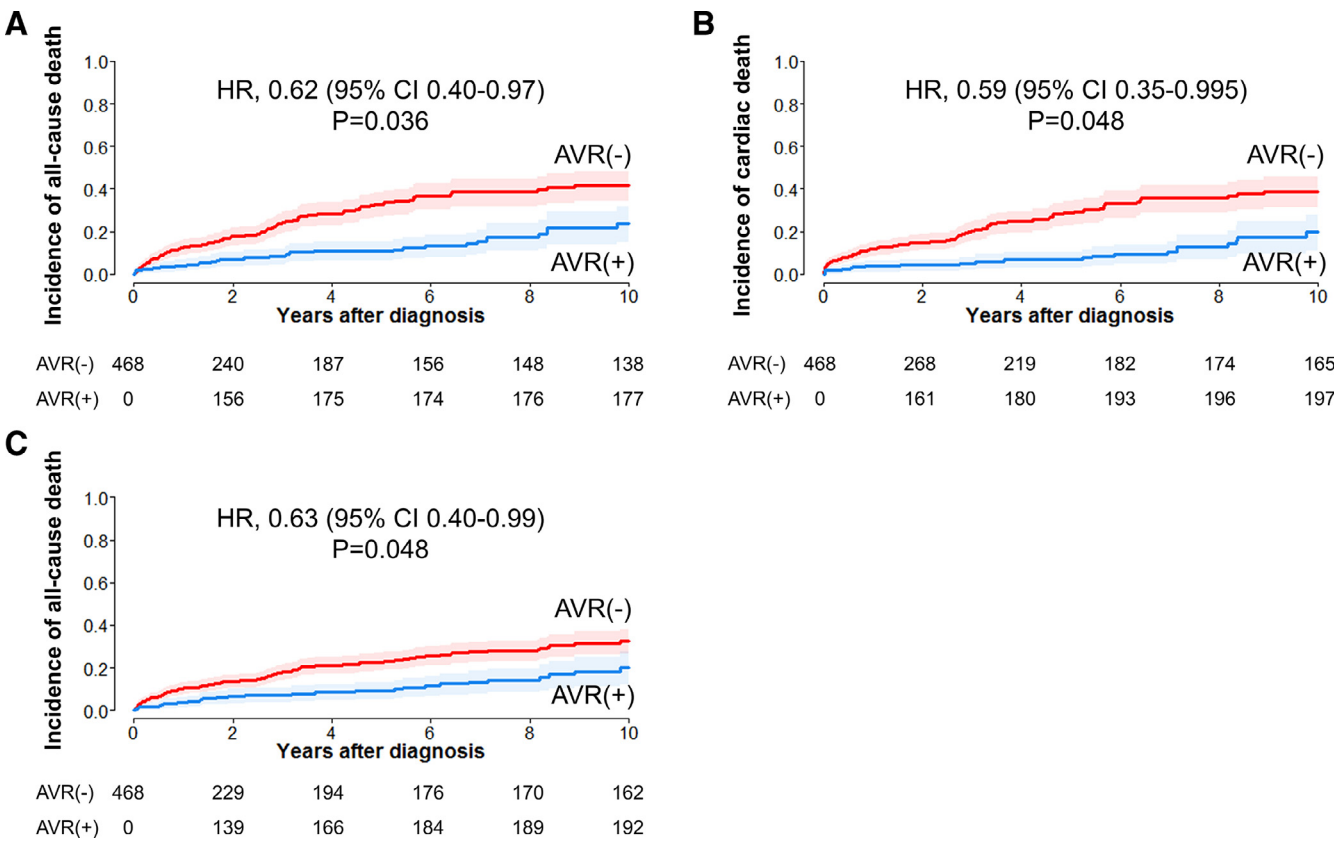

Figure 3. Extended Kaplan-Meier plots delineating the incidence of (A) all-cause mortality (B) cardiac mortality and (C) all-cause mortality (censored at the time of symptoms).

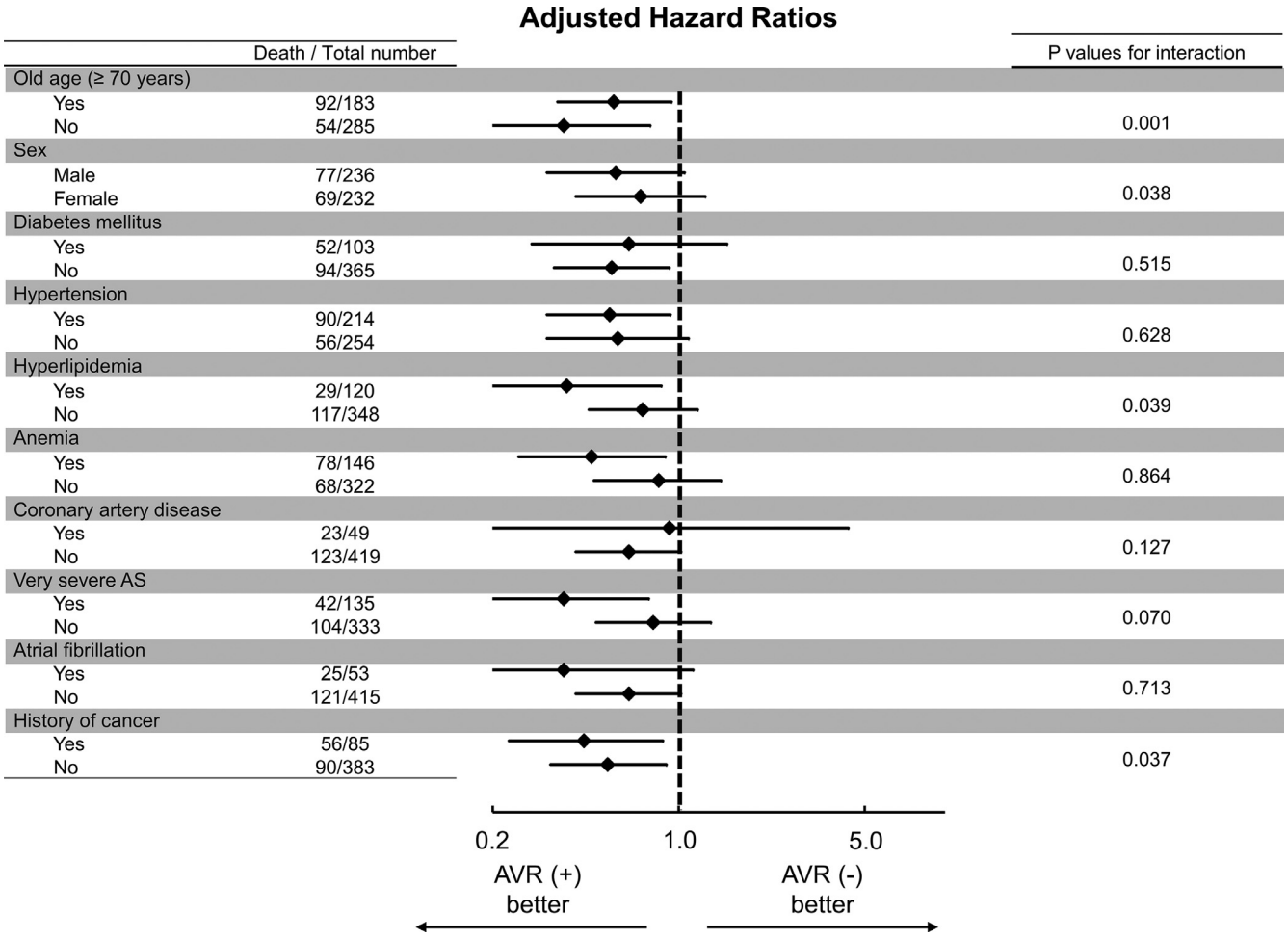

Figure 4. Adjusted HRs for all-cause mortality after AVR in the subgroups.

against the surgical risks.[21] However, knowledge on the overall aspects of valvular heart disease changed in the last several decades; whereas Ross and Braunwald reported that AS-related death occurred at an average of 63 years,[3] 404 (73.9%) of 547 patients diagnosed as having AS were reported to be aged 65 years or older at the time of diagnosis in a recent, population-based study.[1] Also, because the elderly population is susceptible to degenerative calcific AS, the comparable survival between asymptomatic patients with severe AS and general elderly population without severe AS has been also questioned. Pellikka et al[8] reported their series of 622 asymptomatic patients with severe AS and demonstrated that the survival was comparable between asymptomatic patients with severe AS and a reference group matched for age and sex when the study cohorts were censored at the onset of symptoms or time of AVR; however, when they were censored only at the time of AVR, asymptomatic patients with severe AS demonstrated worse survival than the reference group, implying that severe AS patients who were initially asymptomatic but later developed AS-related symptoms may have died before having a chance to undergo AVR.

The poor prognosis of asymptomatic patients with severe AS and the potential benefit of early surgery were further advocated in the recent study by Taniguchi et al.[7] They evaluated 1808 asymptomatic patients with severe AS who were grouped according to the intention-to-treat basis: 291 patients with initial surgical treatment and 1517 with conservative management. They reported that the initial AVR strategy was associated with a lower risk of all-cause mortality in the entire cohort as well as in the propensity score-matched cohort. Consonant with the results of previous studies,[7,8,10] the survival benefits by performing AVR were also demonstrated in the present study. Analysis of our data revealed a significant risk reduction by AVR in all-cause mortality as well as in cardiac mortality. These results imply that some asymptomatic patients initially diagnosed as having severe AS may die or suffer from valve-related cardiac events before they undergo AVR. Thus, performing AVR after the diagnosis of severe AS may be beneficial in improving survival in this cohort, regardless of the onset of symptoms or LV deterioration.

With increasing evidences supporting initial interventional treatment in asymptomatic AS patients, the onset of symptoms (class I) as a key indicator for surgery in the current guidelines may need to be reconsidered.[22] As the patients affected by severe AS have become more aged, the

development of AS-related symptoms is likely to be underdiagnosed in these patients. Since valve-related symptoms may be sometimes insidious, nonspecific, and undistinguishable from aging-related symptoms, elderly patients may neglect these symptoms without conscious awareness, adapt to a sedentary lifestyle, or miss regular follow-up appointments with physicians.[5,9] Thus, lowering the threshold of valve-related symptom definition may become more important for recruiting such patients for timely interventional treatment. Otherwise, when patients present with intensive symptoms, they are very likely to already have advanced disease with deteriorated LV function, thus portending increased operative risks.

The poor prognosis of patients with very severe AS, though asymptomatic, has been reported in previous studies, and the benefit of early surgical treatment in this specific subgroup has been advocated.[10] The rate of hemodynamic deterioration of severe AS to a very severe status varies considerably among patients depending on their morbidities, such as hypertension, hyperlipidemia, and chronic kidney disease.[5] Thereby, some patients undergoing the unpredictable rapid progression of severe AS may be exempt from an opportunity to undergo AVR due to resultant heart failure.

Besides, the overall scheme in treating patients with severe AS is changing very rapidly by the advent of less invasive techniques, including TAVR. This less invasive transcatheter technique has been reported to yield comparable clinical outcomes to surgical AVR in high-risk patients as well as in intermediate-risk patients.[12,13] Technical advances of TAVR may lead to more widened interventional applications in patients with severe AS over the next decade; the application of an intervention, whether surgical or transcatheter, therefore, may become more common with an increasing elderly population.

Our study has the following limitations. Due to its retrospective design and observational data, the study may have residual selection bias despite using several adjustment models; particularly, mild symptomatic patients may have been included because exercise tests were not routinely performed at our center. Also, the cohort of severe asymptomatic AS patient with "preserved" LV function may have been altered by the introduction of a new method measuring LV systolic function.[23] In terms of clinical outcomes, although the decision to perform AVR was not based on the initial baseline risk profiles, the survival benefits in the AVR group may not be solely attributable to the impact of interventions considering the higher rates of several morbidities in the Medical group. Also, during the 15-year study period, treatment strategies and decision criteria for AVR may have gone through needed changes. Finally, because this study was performed at a high-volume center with a low operative mortality (0.9%), its results may lack generalizability. Thus, our results should be interpreted with caution, and randomized controlled trials are warranted to verify our findings.

In conclusion, AVR in asymptomatic severe AS patients with preserved LV function resulted in marked survival benefits, suggesting that early recruitment for AVR may be warranted for asymptomatic severe AS patients prior to ventricular deterioration or symptom development.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.035.

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