Outcomes of surgical aortic valve replacement for severe aortic stenosis: Incorporation of left ventricular systolic function and stroke volume index

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ABSTRACT

Objectives: We sought to assess predictors of mortality in consecutive patients with severe aortic stenosis undergoing aortic valve replacement and to determine whether there are differences in mortality, separated on the basis of different aortic stenosis subtypes and left ventricular stroke volume index.

Methods: We studied 875 patients (aged 69 ± 12 years, 67% were men) with severe aortic stenosis (aortic valve area ≤ 1 cm²) who underwent aortic valve replacement between January 2007 and December 2008 (excluding other severe valve disease, balloon aortic valvuloplasty, and transcatheter aortic valve replacement). Clinical and echocardiographic data were recorded. Left ventricular stroke volume index was measured as left ventricular outflow tract velocity time integral $\times$ left ventricular outflow tract area/body surface area. Patients were classified into the following subtypes: (1) standard severe (n = 536, left ventricular ejection fraction $\geq 50\%$ and mean gradient ≥ 40 mm Hg); (2) paradoxical severe (n = 152, left ventricular ejection fraction $\geq 50\%$, mean gradient < 40 mm Hg and left ventricular stroke volume index < 35 mL/m²); and (3) low left ventricular ejection fraction severe (n = 187, ejection fraction $< 50\%$). Society of Thoracic Surgeons score and all-cause mortality were recorded.

Results: At 4.8 ± 2 years, 153 patients (18%) died (30-day mortality 1.8%). On multivariable Cox analysis, age (hazard ratio [HR], 1.49), New York Heart Association class (HR, 1.52), prior cardiac surgery (HR, 1.41), aortic stenosis subtypes (standard severe reference HR, 1; paradoxical severe HR, 1.48; and low left ventricular ejection fraction severe HR, 2.03), and reduced glomerular filtration rate (HR, 1.17) were associated with higher long-term mortality ($P < .05$).

Conclusions: In patients with severe aortic stenosis undergoing aortic valve replacement, patients with standard severe aortic stenosis had better long-term survival than those with paradoxical severe or low left ventricular ejection fraction severe aortic stenosis. (J Thorac Cardiovasc Surg 2015;149:1558-66)

Kaplan-Meier survival curves of the study population are shown, divided on the basis of AS subtypes (standard severe, paradoxical severe, and low EF severe).

Central Message

In a contemporary study of patients with AS undergoing AVR, we demonstrate that despite low 30-day mortality, approximately 20% patients are dead at the 5-year follow-up. Patients with paradoxical severe and low LVEF severe AS had significantly worse outcomes than those with standard severe AS.

Perspective

In a contemporary study of patients with AS undergoing AVR, despite a low 30-day mortality, approximately 1 in 5 patients are dead at the 5-year follow-up. Along with expected predictors, such as increasing age, low glomerular filtration rate (GFR), and history of cardiac surgery, different AS subtypes and LV flow impairment were independently associated with mortality. Patients with paradoxical severe and low LVEF severe AS had significantly worse outcomes than those with standard severe AS. In patients with severe AS, a thorough clinical and imaging assessment needs to be performed to identify and characterize patients early, before the occurrence of advanced symptoms or LV flow impairment.

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Abbreviations and Acronyms

AS	= aortic stenosis
AVA	= aortic valve area
AVR	= aortic valve replacement
CABG	= coronary artery bypass grafting
EF	= ejection fraction
EOA	= effective orifice area
GFR	= glomerular filtration rate
LV	= left ventricular
LVOT	= left ventricular outflow tract
LV-SVI	= left ventricular stroke volume index
NYHA	= New York Heart Association
STS	= Society of Thoracic Surgeons

Supplemental material is available online.

Over the years, numerous studies have demonstrated that aortic valve replacement (AVR) significantly improves survival in patients with severe aortic stenosis (AS).¹⁻¹² As a result, the current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines designate a class I indication for AVR in patients with severe AS who present with symptoms or who demonstrate signs of cardiac dysfunction, defined as resting left ventricular ejection fraction (LVEF) of 50% or less.^{13,14}

However, AS is a complex hemodynamic process, and determination of its true severity is frequently challenging. Although severe AS has been traditionally defined on the basis of echocardiographic aortic valve area (AVA) 1 cm² or less and a mean AV gradient of 40 mm Hg or more,¹⁵ it is increasingly recognized that not all patients with severe AS have severely elevated transvalvular gradients. Indeed, recent work has shown that the traditional definition of severe AS can fail to classify up to 15% to 30% of patients with reduced transvalvular flow gradients resulting from decreased LVEF or in those with normal LVEF because of diminished forward stroke volume related to myocardial remodeling, reduced left ventricular (LV) cavity size, or impaired LV compliance.¹⁶⁻¹⁸

Therefore, cardiologists increasingly are recognizing various subtypes of AS based not only on transvalvular gradient, valve area, and ejection fraction (EF) but also on LV stroke volume index (LV-SVI). Accurate characterization of patients as having standard severe, paradoxical severe, and low LVEF low gradient severe AS, based on AVA, LVEF, transvalvular gradients, and LV-SVI, is likely

important, because these groups of patients may have varying outcomes as demonstrated in prior moderately sized studies.^{2,3,17,19-24} Many prior studies have confined their attention to patients undergoing isolated AVR. Although this may make analysis of outcomes simpler, it fails to recognize that many of the patients currently undergoing operation for AS have concomitant coronary disease or disease of the aorta that significantly affects their operative and subsequent course and is an inherent part of the disease spectrum of AS in the current era. In the current study, we sought to (1) assess predictors of mortality in a consecutive contemporary group of patients with severe AS undergoing AVR and (2) determine whether there are differences in mortality, separated on the basis of different AS subtypes and preserved versus impaired LV-SVI.

MATERIALS AND METHODS**Study Population**

This was an observational cohort study of 875 consecutive patients with severe AS (AVA $\leq$ 1 cm²) who had an echocardiogram at our tertiary care center between January 2007 and December 2008 followed by AVR at Cleveland Clinic. We excluded the following patients: those with other valvular disease (ie, mitral/tricuspid valve disease or prosthetic AS) and those who underwent transcatheter AVR or balloon aortic valvuloplasty (because, at the time, these therapies were performed in individuals who were deemed high risk or inoperable).

Clinical Data

Data were assembled by analysis of electronic medical records after appropriate approval by the institutional review board was obtained. Demographics and clinical data were extracted from the electronic health record at the time of the initial visit. The presence of angina, syncope, and New York Heart Association (NYHA) class was extracted from the electronic medical record to assess the symptomatic status of each patient. The decision to operate was made after a careful evaluation by the cardiologist and cardiothoracic surgeon at the time of initial presentation. No patient went directly for AVR without being evaluated by a cardiologist at our center. In patients who were perceived to be asymptomatic at the initial evaluation, the decision to operate was made on the basis of the following potential high-risk factors: LV systolic dysfunction, abnormal blood pressure response, excessive LV hypertrophy, and AVA less than 0.6 cm². On the basis of the available preoperative data, Society of Thoracic Surgeons (STS) score was calculated.

Preoperative Echocardiography

All patients underwent a comprehensive echocardiogram with commercially available instruments (Philips Medical Systems, NA, Bothell, Wash; General Electric Medical Systems, Milwaukee, Wis; and Siemens Medical Solutions USA, Inc, Malvern, Pa) as part of a standard clinical diagnostic evaluation. Measurements and recordings were obtained according to current recommendations.^{15,25} LV dimensions (end systolic and end diastolic), LV mass, and left atrial dimensions were measured from 2-dimensional images and indexed to body surface area. LVEF was calculated using the Simpson's biplane method. Diastolic function was graded using the current grading recommendations for this assessment.²⁶ We used a semiquantitative 5-point scale (with grades of none, mild, moderate, moderately severe, and severe) to stratify aortic regurgitation, mitral regurgitation, and tricuspid regurgitation assessed by color 2-dimensional Doppler echocardiography clips obtained in multiple standard views. Right ventricular systolic pressure was estimated in a standard fashion.²⁷

For quantification of AS severity, LV outflow tract diameter was measured in a standard fashion on parasternal long-axis views.¹⁵ The AVA was calculated using the continuity equation. Dimensionless index was calculated as left ventricular outflow tract (LVOT)_{VTI}/AV_{VTI}. LV-SVI was measured using the following formula: $LVOT_{VTI} \times LVOT_{area} / \text{body surface area}$. A cutoff of 35 mL/m² or greater was considered as preserved LV-SVI.¹⁵⁻¹⁸ On the basis of these calculations, severe AS was defined as AVA 1 cm² or less and dimensionless index less than 0.25. The patients in the study population were further classified as having (1) standard severe AS (AVA ≤1 cm², LVEF ≥50%, dimensionless index <0.25, and mean gradient ≥40 mm Hg); (2) paradoxical severe AS (AVA ≤1 cm², LVEF ≥50%, mean gradient <40 mm Hg, dimensionless index <0.25, and LV-SVI <35 mL/m²); and (3) low EF severe AS (AVA ≤1 cm², mean gradient <40 mm Hg, dimensionless index <0.25, and EF <50%).^{16,19}

Surgery

The details of various surgical therapies for the management of AS were recorded and categorized as follows: (1) AVR; (2) AVR and coronary artery bypass grafting (CABG); (3) AVR and concomitant other valve repair/replacement (which is standard practice if the other valvular lesion is moderate) ± CABG; and (4) AVR and ascending aorta repair or replacement ± CABG. In patients with moderate disease of other valves (mitral or tricuspid), in addition to severe AS, additional valve surgery (most commonly mitral or tricuspid valve repair ± CABG) was also performed at the time of operation. The final decision regarding the specific operative technique was made by the attending cardiothoracic surgeon.

Postoperative Echocardiography

We evaluated postoperative follow-up echocardiograms for LVEF and AV gradients. In addition, we recorded different types and sizes of AV prostheses, including bioprostheses, mechanical prostheses, and homografts. Subsequently, to determine the presence of patient–prosthesis mismatch, we recorded the effective orifice areas (EOAs) of the prosthetic AV (stroke volume/prosthetic valve_{VTI}) in each patient and indexed it to body surface area.²⁸ Normal indexed EOA values are greater than 0.85 cm²/m². Patient–prosthesis mismatch was categorized as severe if indexed EOA was less than 0.65 cm²/m² and moderate if indexed EOA was between 0.65 and 0.85 cm²/m².²⁸

Outcomes Assessment

All-cause mortality was considered to be the primary outcome. Death notification was confirmed by observation of death certificate or verified with a family member. The duration of follow-up ranged between time of AVR and June 2013. In addition, we also recorded postoperative stroke, defined as a neurologic impairment lasting more than 24 hours because of cerebral ischemia or hemorrhage confirmed by radiographic studies. Transient ischemic attack was similarly defined as neurologic impairment lasting less than 24 hours.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median and compared using Student *t* test or analysis of variance (for normally distributed variables) or Mann–Whitney test (for non-normally distributed variables). Categorical data are expressed as percentage and compared using the chi-square test. To assess outcomes, Cox proportional hazards analysis was used. Initially, univariable analysis was performed for individual potential predictors of mortality. Subsequently, forward stepwise multivariable survival analysis was performed incorporating only selected and relevant variables, known to be associated with outcomes in patients with AS. For the stepwise analysis, a *P* value threshold less than .1 was used as a model entry cutoff. Hazard ratios with 95% confidence

intervals were calculated. The proportional hazards assumption was examined using inspection of Schoenfeld residuals plotted against time. Also, to test the linearity of the relationship between STS score and survival in the Cox proportional hazards model, we performed polynomial transformations of STS score. Survival, as a function over time, was analyzed using the Kaplan–Meier method, and event curves were analyzed using a log-rank test in which proportional hazards were not violated and a generalized Wilcoxon (Breslow's) test in which the survival curves clearly crossed and violated the proportional hazards. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc, Chicago, Ill), Stata version 10.0 (StataCorp, LP, College Station, Tex), and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria).

RESULTS

The baseline and clinical data in the study population as a whole and divided into various AS subgroups are shown in [Table 1](#). This was an older population with an expected distribution of cardiovascular risk factors. However, because this was a contemporary study population, the majority of the patients were taking optimal cardioprotective medications, with expected differences between subgroups that had preserved versus low LVEF. No patient had active endocarditis at the time of AVR. The echocardiographic data in the study population as a whole and divided into various AS subgroups are shown in [Table 2](#). As expected, the LV size parameters were abnormal in the subgroup with low LVEF severe AS and normal in the other 2 subgroups. AV gradients were the highest in the standard severe AS subgroup, whereas patients with low LVEF severe AS had the highest proportion of moderate mitral and tricuspid regurgitation.

The distribution of cardiac surgeries in the study population as a whole and divided into various AS subgroups is shown in [Table 3](#). The highest proportion of isolated AVR was performed in the standard severe AS subgroup, and the highest proportion of concomitant CABG was performed in the low EF severe AS subgroup. Distribution of different valve types was as follows: bioprosthesis (92%), mechanical prosthesis (6%), and homograft (1%), with no differences between subgroups.

Outcomes and Survival Assessment

During a mean follow up of 4.8 ± 2 years, 153 patients (18%) died. At 30 days postoperatively, 16 patients (1.8%) died, of whom 9 were undergoing redo cardiac surgery (4 patients [1%] in standard severe, 6 patients [4%] in paradoxical severe, and 6 patients [3%] in low LVEF severe AS subgroups). Only 2 patients undergoing isolated AVR died at 30 days, whereas the remainder of deaths occurred in those undergoing a combination procedure (AVR in addition to other surgery). In addition, 44 patients (5%) died at 1 year and 66 patients (8%) died at 2 years, with no differences in mortality between different surgeries or AS subtypes. Stroke within 30 days postoperatively was observed in 12 patients (1.3%). There

TABLE 1. Baseline characteristics of the study population

	Total population (n = 875)	Normal EF, high gradient (n = 536)	Normal EF, low gradient paradoxical (n = 152)	Low EF, low gradient (n = 187)	P value
Age (y)	69 ± 12	69 ± 12	69 ± 12	72 ± 11	.004
Male gender	584 (67%)	337 (63%)	96 (63%)	151 (81%)	<.001
BSA (m ²)	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	2.1 ± 0.3	.5
Angina	296 (34%)	187 (35%)	50 (33%)	59 (32%)	.2
Syncope	61 (7%)	36 (7%)	7 (5%)	18 (10%)	.13
NYHA class					<.001
I	164 (19%)	111 (21%)	31 (20%)	22 (12%)	
II	402 (46%)	266 (50%)	60 (40%)	76 (41%)	
III	264 (30%)	143 (27%)	54 (36%)	67 (36%)	
IV	45 (5%)	16 (3%)	7 (4%)	22 (12%)	
Hypertension	664 (76%)	423 (79%)	124 (82%)	117 (63%)	<.001
Hyperlipidemia	737 (83%)	448 (84%)	131 (86%)	158 (85%)	.7
Diabetes mellitus	210 (24%)	115 (22%)	39 (26%)	56 (30%)	.06
Prior stroke	66 (8%)	41 (8%)	15 (10%)	10 (5%)	.29
Smoking history	444 (51%)	271 (51%)	86 (54%)	87 (47%)	.3
Obstructive CAD	512 (59%)	283 (53%)	104 (68%)	125 (67%)	<.001
Atrial fibrillation	182 (21%)	102 (19%)	30 (20%)	50 (27%)	.07
Dialysis	22 (3%)	8 (2%)	5 (3%)	9 (5%)	.04
Prior open surgery	179 (20%)	85 (16%)	28 (18%)	66 (35%)	<.001
ICD	51 (6%)	14 (3%)	4 (3%)	33 (18%)	<.001
Pacemaker	431 (49%)	257 (48%)	73 (48%)	101 (54%)	.3
STS score (%)	5.4 ± 6	4.6 ± 6	5.1 ± 6	8.0 ± 8	<.001
Beta-blockers	810 (93%)	494 (92%)	139 (91%)	177 (95%)	.45
ACE inhibitors	421 (48%)	215 (40%)	79 (52%)	127 (68%)	<.001
Aspirin	819 (94%)	501 (94%)	141 (93%)	177 (95%)	.76
Statins	700 (80%)	426 (80%)	125 (82%)	149 (80%)	.7
Diuretics	825 (94%)	505 (94%)	141 (93%)	179 (96%)	.002
Aldosterone receptor blocker	93 (11%)	39 (7%)	10 (7%)	44 (24%)	<.001
Hemoglobin (mg/dL)	13 ± 2	14 ± 2	13 ± 2	13 ± 2	.1
GFR (mL/min/1.73 m ²)	69 ± 22	70 ± 20	68 ± 23	64 ± 24	.001
LDL (mg/dL)	98 ± 37	100 ± 34	100 ± 46	94 ± 40	.1
HDL (mg/dL)	50 ± 16	51 ± 16	52 ± 15	45 ± 15	.001

P values reflect comparison between AS subtypes. EF, Ejection fraction; BSA, body surface area; NYHA, New York Heart Association; CAD, coronary artery disease; ICD, internal cardioverter defibrillator; STS, Society of Thoracic Surgery; ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

were an additional 14 strokes (1.6%) and 6 transient ischemic attacks (0.7%) during follow-up. Transient atrial fibrillation (within 30 days postoperatively) was observed in 123 patients (14%). Postoperative pacemaker and implantable cardioverter defibrillators were implanted in 35 patients (4%) and 9 patients (1%), respectively.

Subsequently, univariable and forward stepwise multivariable Cox proportional hazard analysis was performed for the primary end point of long-term all-cause mortality. Neither quadratic nor cubic transformations of STS score were significant predictors of long-term mortality when forced into the Cox model that already included nontransformed STS score. Initially, individual predictors, potentially associated with mortality in patients with AS, were tested in a univariable fashion. The results are shown in Table E1. Subsequently, only selected relevant predictors were entered into a forward

multivariable stepwise model, the results of which are shown in Table 4. Atrial fibrillation, coronary artery disease, LV mass index, and patient–prosthesis mismatch were associated with long-term all-cause mortality on univariable analysis; however, they did not remain independently significant on multivariable survival analysis. Also, the type of cardiac surgery performed was not associated with long-term outcomes. When STS score was entered into the multivariable model (instead of its individual predictors), the results were similar (Table 4, model B). The proportion of long-term all-cause deaths in the various AS subtypes were as follows: 65 of 536 (12%) in the standard severe AS subgroup, 32 of 152 (21%) in the paradoxical severe AS subgroup, and 56 of 187 (30%) in the low LVEF severe AS subgroup. Kaplan–Meier survival curves, demonstrating the mortality in the study population, separated on the basis of different

TABLE 2. Baseline and follow-up echocardiographic characteristics of the study population

	Total population (n = 875)	Normal EF, high gradient (n = 536)	Normal EF, low gradient paradoxical (n = 152)	Low EF, low gradient (n = 187)	P value
Preoperative echocardiography					
LVEF (%)	59 ± 5	59 ± 5	57 ± 4	34 ± 10	<.001
Indexed LVEDD (cm/m ²)	2.4 ± 0.4	2.3 ± 0.4	2.3 ± 0.4	2.7 ± 0.4	<.001
Indexed LVESD (cm/m ²)	1.6 ± 0.5	1.4 ± 0.3	1.4 ± 0.3	2.0 ± 0.6	<.001
Indexed LA dimension (cm/m ²)	2.1 ± 0.4	2.1 ± 0.4	2.1 ± 0.4	2.3 ± 0.4	<.001
Indexed LV mass (g/m ²)	126 ± 43	129 ± 42	128 ± 41	149 ± 46	<.001
Diastolic dysfunction					<.001
Abnormal relaxation	735 (84%)	461 (86%)	134 (88%)	140 (74%)	
Pseudo-normal	123 (14%)	70 (13%)	18 (12%)	35 (20%)	
Restrictive filling	17 (2%)	5 (1%)	0	2 (6%)	
LVOT diameter (cm)	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	.3
AV gradient					
Peak (mm Hg)	81 ± 27	94 ± 22	56 ± 13	64 ± 24	<.001
Mean (mm Hg)	47 ± 16	55 ± 13	31 ± 7	37 ± 15	<.001
Calculated AV area (continuity equation)	0.70 ± 0.2	0.67 ± 0.2	0.76 ± 0.1	0.75 ± 0.2	<.001
LV-SVI (mL/m ²)	37 ± 10	40 ± 10	29 ± 4	32 ± 9	<.001
Aortic dimension at mid-ascending segment (cm)	3.4 ± 0.6	3.4 ± 0.6	3.3 ± 0.6	3.4 ± 0.6	.3
Aortic regurgitation					.5
None	162 (19%)	100 (19%)	30 (20%)	32 (17%)	
Mild	495 (56%)	307 (57%)	88 (55%)	100 (53%)	
Moderate	155 (18%)	94 (18%)	22 (15%)	39 (21%)	
Moderate-severe	49 (6%)	26 (5%)	10 (7%)	13 (7%)	
Severe	14 (2%)	9 (2%)	2 (2%)	3 (2%)	
Mitral regurgitation					<.001
None	101 (12%)	64 (12%)	23 (15%)	14 (7%)	
Mild	625 (72%)	413 (77%)	108 (71%)	104 (59%)	
Moderate	149 (17%)	59 (12%)	21 (14%)	69 (35%)	
Tricuspid regurgitation					<.001
None	105 (12%)	64 (12%)	20 (13%)	21 (10%)	
Mild	691 (79%)	434 (81%)	117 (77%)	140 (71%)	
Moderate	79 (9%)	38 (7%)	15 (10%)	26 (14%)	
RVSP (mm Hg)	36 ± 11	35 ± 11	34 ± 11	41 ± 16	<.001
Postoperative echocardiography					
LVEF (%)	51 ± 11	53 ± 7	54 ± 7	38 ± 13	<.001
AV gradient					
Peak (mm Hg)	25 ± 11	27 ± 12	24 ± 9	23 ± 10	<.001
Mean (mm Hg)	14 ± 6	15 ± 7	13 ± 5	13 ± 6	<.001
Indexed EOA of prosthetic valve (cm ² /m ²)	0.88 ± 0.14	0.88 ± 0.11	0.86 ± 0.12	0.92 ± 0.14	.005
Patient prosthesis mismatch					.02
None	59%	304 (58%)	77 (52%)	124 (68%)	
Moderate	336 (40%)	213 (41%)	66 (45%)	57 (31%)	
Severe	10 (1%)	5 (1%)	4 (3%)	1 (0.5%)	

P values reflect comparison between AS subtypes. EF, Ejection fraction; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LA, left atrium; LV, left ventricular; LVOT, left ventricular outflow tract; AV, aortic valve; LV-SVI, left ventricular stroke volume index; RVSP, right ventricular systolic pressure; EOA, effective orifice area.

AS subtypes are shown in Figure 1 (generalized Wilcoxon statistic 34, $P < .001$). Likewise, the proportion of all-cause deaths in the population, separated on the basis of preserved (≥ 35 mL/m²) versus impaired (< 35 mL/m²) LV-SVI were as follows: 62 of 439 (14%) in those with preserved LV-SVI versus 91 of 436 (21%) in those with impaired LV-SVI. Kaplan–Meier survival curves, demonstrating the mortality in the study population,

separated on the basis of preserved versus impaired LV-SVI, are shown in Figure 2 (log-rank statistic 7, $P = .007$).

DISCUSSION

In the current contemporary study of patients with severe AS undergoing AVR (isolated or in combination with other surgical procedures), we divided the population into various

TABLE 3. Distribution of cardiac surgeries in the total study population and various aortic stenosis subgroups

	Total population (n = 875)	Normal EF, high gradient (n = 536)	Normal EF, low gradient paradoxical (n = 152)	Low EF, low gradient (n = 187)	P value
Isolated AVR	390 (45%)	279 (52%)	55 (36%)	56 (30%)	<.001
AVR + CABG	312 (36%)	163 (30%)	67 (44%)	82 (44%)	
AVR + other valve repair or replacement ± CABG	95 (11%)	37 (7%)	19 (13%)	39 (21%)	
AVR + ascending aorta repair or replacement ± CABG	78 (9%)	57 (11%)	11 (7%)	10 (5%)	

P values reflect comparison between AS subtypes. EF, Ejection fraction; AVR, aortic valve replacement; CABG, coronary artery bypass grafting.

subtypes (standard severe, paradoxical severe, and low EF severe AS) on the basis of AV gradients, LVEF, and LV-SVI, excluding those with low AV gradients and preserved LV-SVI. To the best of our knowledge, this is one of the largest studies evaluating predictors of outcomes of such patients, incorporating different AS subtypes and LV-SVI. As expected, this was an older population with an expected distribution of cardiovascular risk factors among different AS subtypes. Because this was a contemporary study population, the majority of the patients were taking optimal cardioprotective medications. Only 45% of patients underwent isolated AVR; the rest underwent a combination procedure, with coronary bypass

grafting being the most common concomitant surgery performed. Postoperative echocardiography revealed successful reduction in AV gradients and a low incidence of severe patient–prosthesis mismatch, with no significant differences between AS subtypes.

In the current study, despite a low 30-day postoperative mortality, approximately 1 in 5 patients have died during 4.8 ± 2 years of follow-up, suggesting that patients with severe AS represent a sick cohort. As expected, long-term mortality was independently associated with increasing age, worsening NYHA class, reduced renal function, and need for redo cardiac surgery (or STS score, which is a composite of multiple risk factors). In addition, we also demonstrate that patients with different AS subtypes have significant differences in mortality after AVR. Those with standard severe AS had significantly better outcomes compared with those with paradoxical or low LVEF severe AS. Incorporating AS subtypes or LV-SVI resulted in significant improvement in predicting long-term survival over and above STS score (or standard individual clinical predictors such as NYHA class and age). Although other potential variables, such as atrial fibrillation, coronary artery disease, indexed LV mass (a surrogate of LV hypertrophy), and patient–prosthesis mismatch, were significantly associated with mortality on univariable analysis, they did not remain independently predictive on

TABLE 4. Forward stepwise multivariable Cox proportional hazards analysis for the primary end point of long-term mortality

Variable	Hazard ratio	P value
Model A		
Age (10-y increase)	1.49 (1.27-1.75)	<.001
NYHA class	1.52 (1.22-1.90)	<.001
GFR (for every 10-unit decrease)	1.17 (1.08-1.27)	<.001
Prior cardiac surgery	1.41 (1.05-1.96)	.03
AS subcategories		
Standard severe	1	
Paradoxical severe	1.48 (1.15-1.88)	<.001
Low EF severe	2.03 (1.41-2.93)	<.001
Chi-square for the model = 97, P < .0001		
Model B		
STS score (for every 1% increase)	1.35 (1.15-1.58)	<.001
AS subcategories		
Standard severe	1	
Paradoxical severe	1.46 (1.15-1.86)	<.001
Low EF severe	2.26 (1.70-3.36)	<.001
Chi-square for the model 53, P < .001		

In model A, the following predictors were considered for analysis: age, gender, symptoms, coronary artery disease, atrial fibrillation, prior cardiac surgery, GFR, indexed LV mass, aortic regurgitation, right ventricular systolic pressure, type of cardiac surgery performed, time to cardiac surgery, type of aortic valve prosthesis implanted, and patient–prosthesis mismatch. Because of collinearity with AS subtypes, LV-SVI and LVEF were not included in the analysis. However, if they were substituted for AS subtypes, LV-SVI and LVEF were significant. Patient–prosthesis mismatch (and not indexed EOA) was included in the multivariable analysis. Results were similar if indexed EOA was substituted for patient–prosthesis mismatch. In model B, predictors that constituted part of STS score were not considered for analysis. Other predictors were similar to model A. NYHA, New York Heart Association; GFR, glomerular filtration rate; AS, aortic stenosis; EF, ejection fraction; STS, Society of Thoracic Surgeons.

FIGURE 1. Kaplan–Meier survival curves of the study population, divided on the basis of AS subtypes. EF, Ejection fraction.

FIGURE 2. Kaplan-Meier survival curves of the study population, divided on the basis of preserved versus impaired LV-SVI. SVI, Stroke volume index.

multivariable analysis. The results were similar when documented noncardiac causes of mortality (eg, cancer, neurologic etiologies, advanced renal/liver diseases) were excluded from survival analysis. These data suggest that in patients with severe AS, a thorough clinical and imaging assessment needs to be performed to identify patients early, before occurrence of advanced symptoms or LV flow impairment. In such patients, early AVR could be associated with improved survival. However, this observation requires further prospective validation.

Similar to our study, multiple previous studies have reported that AVR results in improved survival in patients with severe AS, along with its potential predictors.¹⁻¹² However, unlike the current study, many of these studies are older, had relatively small sample sizes, or only reported outcomes of isolated AVR. Because we included only patients from 2007 and 2008, the current study took into account only modern surgical techniques, and the majority of the patients were receiving appropriate cardioprotective medications known to be associated with improved survival. Furthermore, unlike the other studies, the current study used Doppler echocardiography to distinguish between various AS subtypes and flow characteristics based on AVA, dimensionless index, AV gradients, LVEF, and LV-SVI. Indeed, previous studies have reported that assessment of transvalvular flow is an important determinant of outcome, and patients with a reduced gradient, despite preserved LVEF, had poor outcomes with medical therapy compared with AVR.¹⁶⁻¹⁹ However, unlike those previous reports, all patients in the current study underwent AVR, and we demonstrate that patients with paradoxical severe AS have a higher mortality when compared with those with standard severe AS. As expected, increasing age, history of cardiac surgery, and low GFR were associated with worse outcomes. However, unlike previous reports that have suggested that patient-prosthesis mismatch and LV hypertrophy predicted

increased mortality,^{8,29} in the current study, these variables did not remain independently predictive on multivariable analysis. This is most likely because of a low incidence of severe patient-prosthesis mismatch in the current study, likely due to a more modern population. Another possibility is that LV flow and systolic function are stronger predictors of outcomes than these variables.

Clinical Implications

In a contemporary study of patients with AS undergoing AVR, we demonstrate that despite low 30-day mortality, approximately 1 in 5 patients are dead at the 5-year follow-up. Along with the expected predictors such as increasing age, low GFR, and a history of cardiac surgery, different AS subtypes (and LV flow impairment) were also independently associated with mortality. Patients with paradoxical severe and low LVEF severe AS had significantly worse outcomes compared with those with standard severe AS. In patients with severe AS, a thorough clinical and imaging assessment needs to be performed to identify and characterize patients early, before occurrence of advanced symptoms or LV flow impairment. Early AVR (eg, before development of advanced symptoms) could be associated with improved outcomes in this high-risk population.

Study Strengths and Limitations

This is an observational study from a single tertiary care center, and thus is not free from selection bias. In addition, some of the higher-risk patients undergoing evaluation for surgical AVR could have been diverted to transcatheter AVR. We can only report associations, not causality. We only selected patients who were initially evaluated (clinically and by echocardiography) in 2007 and 2008. This inherently allowed us to focus on a contemporary population with a high proportion of cardioprotective medications, in whom surgery was performed over a narrow time frame using similar, modern surgical techniques. Unlike in previous reports, our study population was heterogeneous and did not just consist of patients who underwent isolated AVR. Although this may make analysis of outcomes simpler, many of the patients currently undergoing operation for AS have concomitant coronary disease or disease of the aorta that significantly affects their operative and subsequent course and is an inherent part of the disease spectrum of AS in the current era. Because echocardiographic measurements of LVOT diameter and AV gradients are operator-dependent, there is the likelihood that some patients with moderate AS were misclassified as having paradoxical severe AS. However, despite that possibility, the outcomes were significantly worse in the paradoxical AS subtype compared with the standard severe AS subtype. That is likely the reason why incorporating flow assessment (ie, LV-SVI) in the workup of the patient

could help further refine the classification of these patients. Another limitation arises when continuous variables such as AV gradient and LV-SVI are dichotomized. However, the cutpoints used are standard values used in routine clinical decision making. Advanced parameters of LV function assessment (E/e' and strain) were not uniformly available and thus not incorporated into the analysis. We report all-cause mortality as the primary end point, as opposed to cardiac mortality. However, it has been demonstrated that all-cause mortality is more objective and unbiased than cardiac mortality.^{30,31}

CONCLUSIONS

In a contemporary study of patients with AS who undergo AVR, we demonstrate that despite low 30-day mortality, approximately 20% of patients are dead at the 5-year follow-up. Along with the expected predictors such as increasing age, low GFR, and a history of cardiac surgery, different AS subtypes (and LV flow impairment) were independently associated with mortality. Patients with paradoxical severe and low LVEF severe AS had significantly worse outcomes than patients with standard severe AS. In such patients, a thorough clinical and imaging assessment needs to be performed to identify and characterize patients early, before the occurrence of advanced symptoms or LV flow impairment. Early AVR could be associated with improved outcomes in this high-risk population, although this awaits prospective determination.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: aortic stenosis, aortic valve replacement, echocardiography, outcomes

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TABLE E1. Univariable Cox proportional hazard survival analysis in the study population for the primary end point of all-cause mortality

Variable	Hazard ratio	P value
Age (for 10-y increase)	1.65 (1.40-1.93)	<.001
Male gender	1.17 (0.82-1.68)	.35
Angina	1.27 (0.89-1.82)	.18
Syncope	1.43 (0.70-2.94)	.32
NYHA class	1.84 (1.51-2.25)	<.001
Hypertension	1.31 (0.91-1.88)	.13
Hyperlipidemia	1.06 (0.67-1.68)	.78
Diabetes mellitus	1.16 (0.81-1.67)	.41
Obstructive coronary artery disease	1.62 (1.15-2.27)	.006
Stroke	1.42 (0.71-2.95)	.38
Smoking	1.05 (0.76-1.45)	.76
Prior cardiac surgery	2.07 (1.48-2.92)	<.001
Atrial fibrillation	1.51 (1.05-2.16)	.02
Dialysis	3.97 (2.12-7.43)	<.001
Pacemaker	1.40 (1.02-1.93)	.04
Implantable defibrillator	1.04 (0.64-1.77)	.67
STS score (for every 1% increase)	1.45 (1.26-1.67)	<.001
Aspirin	1.34 (0.73-2.43)	.45
Beta-blockers	0.76 (0.44-1.34)	.34
ACE inhibitors	0.79 (0.57-1.08)	.14
Statins	0.94 (0.62-1.43)	.77
Diuretics	2.64 (0.85-6.55)	.09
GFR (for every 10-unit decrease)	1.22 (1.13-1.32)	<.001
Indexed left atrial area	1.03 (0.86-1.43)	.28
Indexed LV end-systolic dimension	1.37 (0.98-1.95)	.10
Indexed LV mass (for 10 g/m ² increase)	1.04 (1.01-1.08)	.03
LVEF	0.97 (0.96-0.98)	<.001
LV diastolic dysfunction	1.63 (0.80-2.70)	.35
AS subcategories		
Standard severe	1	
Paradoxical severe	1.53 (1.18-1.95)	<.001
Low EF severe	2.33 (1.48-3.03)	<.001
LV-SVI	0.97 (0.96-0.99)	.004
Aortic regurgitation	1.09 (0.95-1.26)	.23
Mitral regurgitation	1.03 (0.80-1.33)	.45
Right ventricular systolic pressure	1.03 (0.99-1.05)	.14
Indexed EOA of prosthetic valve	0.50 (0.20-0.98)	.03
Patient–prosthesis mismatch	1.34 (1.02-1.79)	.03
Time to cardiac surgery from initial visit	1.12 (1.01-1.30)	.04
Type of cardiac surgery performed	1.12 (0.95-1.39)	.25
Type of valve prosthesis implanted (bioprosthesis vs mechanical)	1.16 (0.66-2.03)	.58

ACE, Angiotensin-converting enzyme; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; AS, aortic stenosis; LV-SVI, left ventricular stroke volume index; EOA, effective orifice area.