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Coronary Artery Disease and Outcomes of Aortic Valve Replacement for Severe Aortic Stenosis

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Objectives The study sought to contrast risk profiles and compare outcomes of patients with severe aortic stenosis (AS) and coronary artery disease (CAD) who underwent aortic valve replacement (AVR) and coronary artery bypass grafting (AS+CABG) with those of patients with isolated AS who underwent AVR alone.

Background In patients with severe AS, CAD is often an incidental finding with underappreciated survival implications.

Methods From October 1991 to July 2010, 2,286 patients underwent AVR+CABG and 1,637 AVR alone. A propensity score was developed and used for matched comparisons of outcomes (1,082 patient pairs). Analyses of long-term mortality were performed for each group, then combined to identify common and unique risk factors.

Results Patients with AS+CAD versus isolated AS were older, more symptomatic, and more likely to be hypertensive, and had lower ejection fraction and greater arteriosclerotic burden but less severe AS. Hospital morbidity and long-term survival were poorer (43% vs. 59% at 10 years). Both groups shared many mortality risk factors; however, early risk among AS+CAD patients reflected effects of CAD; late risk reflected diastolic left ventricular dysfunction expressed as ventricular hypertrophy and left atrial enlargement. Patients with isolated AS and few comorbidities had the best outcome, those with CAD without myocardial damage had intermediate outcome equivalent to propensity-matched isolated AS patients, and those with CAD, myocardial damage, and advanced comorbidities had the worst outcome.

Conclusions Cardiovascular risk factors and comorbidities must be considered in managing patients with severe AS. Patients with severe AS and CAD risk factors should undergo early diagnostics and AVR+CABG before ischemic myocardial damage occurs. (J Am Coll Cardiol 2013;61:837–48) © 2013 by the American College of Cardiology Foundation

Patients treated for severe aortic stenosis (AS) constitute a heterogeneous population ranging from young patients with isolated bicuspid valve disease to elderly patients with degenerative disease complicated by comorbidities. The most common comorbidity importantly influencing outcomes after aortic valve replacement (AVR), affecting a third of patients and half of those above age 70 years, is coronary artery disease (CAD) (1–3). Current guidelines recommend bypass of all significant stenoses at the time of AVR, with evidence level C (4); however, addition of coronary artery bypass grafting (CABG) to AVR is associated with elevated short- and long-term mortality (5–10). This association may be causal (e.g., by increasing myocardial ischemic time) (11) or simply a marker for a high-risk patient profile. Clarifying this may lead to more targeted diagnostics, therapy, and chronic disease management.

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To provide insight into severe AS with and without CAD and current treatment and patient outcomes, we contrasted risk profiles, compared outcomes, and identified risk factors for mortality. To accomplish these objectives, we studied a large group of patients who had routine pre-operative

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Abbreviations and Acronyms

AS = aortic stenosis
AVR = aortic valve replacement
CABG = coronary artery bypass grafting
CAD = coronary artery disease
LA = left atrial
LV = left ventricular
TTE = transthoracic echocardiography

coronary angiography before AVR and received the most common AVR device implanted at our institution, with or without CABG. We sought to identify risk factors both unique to AS and AS+CAD patients and ones in common.

For fair comparison of outcomes in comparable patients, we used propensity score–based matching. Characteristics of AS or AS+CAD patients who could not be propensity matched provided insight into the profile of a subgroup of patients expected to have excellent long-term survival after operation, and another with substantially poorer survival. We believe these investigations provide both support for current guidelines as well as information useful for amplifying and refining them.

Methods

Patients. From October 1991 to July 2010, 4,372 patients at Cleveland Clinic underwent primary AVR with a single type of bovine pericardial prosthesis (Carpentier-Edwards PERIMOUNT, Edwards Lifesciences Corporation, Irvine, California) for severe AS (aortic valve area <1 cm^2 on transthoracic echocardiography [TTE]), with or without CABG. During this period, it was our policy to perform coronary angiography on all patients considered for AVR. Presence of CAD was defined as at least 1 epicardial artery (left main trunk, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery) with at least 50% stenosis or history of percutaneous coronary intervention. Groups were defined on the basis of the presence of CAD and CABG. Thus, we excluded 22 patients with <50% stenosis in all coronary vessels who underwent AVR and CABG, as well as 427 patients with 50% or greater coronary stenosis who underwent AVR alone. Remaining study groups consisted of 1,637 patients with severe AS without CAD who underwent AVR alone (isolated AS group) and 2,286 patients with severe AS and CAD who underwent AVR and CABG (AS+CAD group) (Online Fig. 1). Patients with missing coronary stenosis data, prior cardiac surgery, infective endocarditis, rheumatic valve disease, indications for AVR other than AS, and those who underwent thoracic aorta or valvar operations other than mitral or tricuspid procedures for functional or ischemic regurgitation were excluded. Patient characteristics are presented in Table 1.

Pre-operative, operative, and post-operative variables, including echocardiographic variables, were retrieved from prospective databases approved for use in research by the Institutional Review Board, with patient consent waived.

Pre-operative echocardiography. Pre-operative measurements were retrieved from the TTE performed nearest to, but preceding, the operation. Median interval between TTE and surgery was 7 days, and 3,020 patients (81%) underwent AVR within 30 days. Left ventricular (LV) mass was calculated using the formula validated by Devereux et al. (12), indexed to body surface area. Peak instantaneous aortic valve gradients were calculated from Doppler velocity. Pre-operative TTE measurements are summarized in Table 2.

Endpoints. Our primary endpoint was all-cause mortality from date of operation. Patients were systematically followed at 2 years, then every 5 years by telephone or mailed questionnaire. This active follow-up was supplemented with passive Social Security Death Master File data. Follow-up information was unavailable for 60 patients (1.5%). Median follow-up was 4.7 years; 25% of patients were followed more than 8 years and 10% more than 11 years; 21,005 patient-years of data were available for analysis.

Survival was estimated nonparametrically by the Kaplan-Meier method and parametrically by a multiphase hazard model (13). Parametric modeling was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate shaping parameters. These were modeled separately for each group. As is characteristic of cardiac surgery procedures, there was an initial phase of high risk immediately after surgery that merged with a phase of lower risk (14). The temporal decomposition of this phenomenon is illustrated in Online Figure 2, which shows what we term an *early*, rapidly declining hazard phase starting immediately after surgery, and a *late* rising hazard phase, which cross at about 7 to 12 months. Factors modulating each phase are expected to be quite different (nonproportional hazards), which is the motivation behind the approach. Because the temporal decomposition produces hazard phases with little overlap, modulating factors are processed simultaneously for all hazard phases (2 in this case).

Reference population survival estimates were generated from equations for the U.S. life tables for each patient according to age, race, and sex. These were averaged overall and within subgroups of patients.

Secondary endpoints were in-hospital morbidities defined by the Society of Thoracic Surgeons National Database.

Data analysis. PATIENT CHARACTERISTICS. Simple comparisons were made using Wilcoxon rank-sum nonparametric tests. When the frequency was <5, comparisons were made using chi-square and Fisher's exact tests.

Differences in pre-operative patient and echocardiographic measures between isolated AS versus AS+CAD patients were analyzed by multivariable logistic regression using variables listed in Online Appendix 1. CAD- and CABG-related variables defined the AS+CAD group, as did history of myocardial infarction and coronary artery stenosis variables; thus, we did not include them in the modeling. Variable selection, with a p value of 0.05 for

retention of variables, utilized bagging (15,16). Briefly, automated stepwise variable selection was performed on 250 bootstrap samples, and frequency of occurrence of variables related to procedure performed was ascertained by the median rule (15). In doing this, it became apparent that a number of continuous variables demonstrated a nonlinear relationship to group membership. Therefore, to demonstrate the shape of these relationships, we performed a Random Forests classification analysis, using all variables considered in the analysis, to produce nonparametric partial dependency risk-adjusted graphs of the probability of being in the AS+CAD group as a function of these variables (see Online Appendix 2 for details).

UNIQUE RISK FACTORS. To identify risk factors that may be unique to isolated AS and AS+CAD, separate parsimonious risk factor models were developed using variables listed in Online Appendix 1. Risk factors were then combined from the 2 parsimonious models (Online Tables 1a and 1b) to create semisaturated models (Online Table 1c) for each group, with all factors identified in both analyses included. On the basis of these, an overall model was constructed in which group-specific risk factors were incorporated as interaction effects.

SURVIVAL ANALYSIS. Due to differences in underlying patient characteristics, propensity matching of isolated AS with AS+CAD patients was employed (17). Multivariable logistic regression using pre-operative and procedure variables was used to identify factors associated with isolated AS versus AS+CAD, as described in the Patient Characteristics Subsection. After developing that parsimonious model, additional variables representing patient factors that might relate to unrecorded selection factors were added (semisaturated model; see Online Appendix 1). A propensity score was calculated for each patient by solving the saturated model for the probability of being in the AS+CAD group. Using only propensity scores, 1,082 isolated AS patients (66%) were matched to AS+CAD patients using a greedy matching strategy (Tables 1 and 2, Online Fig. 3) (18,19). Isolated AS patients whose propensity scores deviated more than 0.10 in probability scale from those of AS+CAD patients were considered unmatched.

Survival was compared for propensity-matched patients using the log-rank test and contrasted with that of unmatched isolated AS patients who did not fit the comorbidity profile of AS+CAD patients, and with unmatched AS+CAD patients whose comorbidity profile did not fit that of isolated AS patients (19).

Missing data. To account for missing values for some variables, 5-fold multiple imputation was performed (17) using a Markov Chain Monte Carlo technique (SAS PROC MI in version 9.1, SAS, Inc., Cary, North Carolina). Only covariables were imputed, not outcomes. Bootstrap bagging for variable selection, as described earlier, used 1 imputed dataset. Regression coefficients and their variance–covariance matrix for the final models were subsequently estimated for each imputed dataset and combined using the method of Rubin to produce the final estimates (17).

Presentation. Continuous variables are summarized as mean ± SD and as equivalent 15th, 50th (median), and 85th percentiles when values are skewed. Categorical data are summarized using frequencies and percentages. All analyses were performed using SAS statistical software (SAS version 9.1). Parametric survival estimates are accompanied by asymmetric 68% confidence limits, comparable to ±1 standard error.

Results

Unadjusted outcome comparisons. Compared with isolated AS patients, AS+CAD patients had worse early and late unadjusted survival (97.6% vs. 98.7%, 91% vs. 94%, 83% vs. 90%, and 43% vs. 59% at 30 days and 1, 5, and 10 years, respectively) (Fig. 1). They also experienced greater postoperative morbidity with significantly more septicemia (2.8% vs. 1.6%), renal failure (6.4% vs. 3.5%), prolonged ventilation (14% vs. 6.4%), and atrial fibrillation (36% vs. 32%) (Online Table 2).

Patient characteristics. Compared with isolated AS patients, AS+CAD patients tended to be older men with more severe symptoms; they were more likely to have LV dysfunction and comorbidities, including vasculopathies, systolic hypertension, diabetes, and anemia (Table 3). In contrast, isolated AS patients were more likely young and overweight with more severe AS, bicuspid valves, diastolic hypertension, less LV hypertrophy, and smaller left atria compared with AS+CAD patients.

Unique risk factors. In both groups, patients who were elderly and more symptomatic had increased risk of death early after surgery (Table 4). Late risk was associated with smoking and LV dysfunction. Some of these common factors had statistically significant different strengths between groups, including higher creatinine levels in the early hazard phase and older age and higher blood urea nitrogen in the late hazard phase.

Unique to isolated AS patients was early mortality associated with smaller LV diastolic volume and other systemic illnesses, including anemia and liver dysfunction (see Table 4). The status of the LV at time of surgery, notably presence of severe LV hypertrophy and left atrial (LA) dilation, was associated with increased late risk of death, with a more pronounced effect in younger patients (Online Fig. 5).

Unique to AS+CAD patients was early mortality associated with more severe LV systolic dysfunction and aortic or tricuspid valve regurgitation (see Table 4). In contrast to the isolated AS group, prior myocardial infarction, insulin-dependent diabetes, dialysis, and anemia were associated with increased risk of late death. Addition of an atrial fibrillation procedure or patent foramen ovale suture closure was associated with increased risk of death. Internal thoracic artery grafts used for CABG were associated with decreased mortality.

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Table 1 Patient Characteristics and Operative Details in Those With Severe AS Alone (Isolated AS) Versus AS+CAD

	Overall					Propensity Matched				
	Isolated AS (n = 1,637)		AS+CAD (n = 2,286)			Isolated AS (n = 1,082)		AS+CAD (n = 1,082)		
Characteristic	n*	No. (%) or Mean ± SD	n*	No. (%) or Mean ± SD	p Value	n*	No. (%) or Mean ± SD	n*	No. (%) or Mean ± SD	p Value
Demography										
Female	1,637	769 (47)	2,286	774 (34)	<0.0001	1,082	450 (42)	1,082	458 (42)	0.7
Age, yrs	1,637	70 ± 11	2,286	75 ± 8.1	<0.0001	1,082	73 ± 9.4	1,082	73 ± 8.6	0.5
BSA, m^2	1,607	2.0 ± 0.27	2,263	2.0 ± 0.25	0.03	1,059	2.0 ± 0.26	1,066	2.0 ± 0.26	0.04
Symptoms										
Pre-operative NYHA functional class	1,607		2,263		<0.0001	1,059		1,066		>0.9
I		395 (25)		346 (15)			222 (21)		227 (21)	
II		835 (52)		1,180 (52)			558 (53)		559 (52)	
III		325 (20)		573 (25)			233 (22)		239 (22)	
IV		52 (3.2)		164 (7.2)			46 (4.3)		41 (3.8)	
Canadian Angina class	1,231		1,946		<0.0001	833		882		<0.0001
0		537 (44)		624 (32)			366 (44)		307 (35)	
I		391 (32)		469 (24)			275 (33)		230 (26)	
II		260 (21)		656 (34)			163 (20)		286 (32)	
III		39 (3.2)		162 (8.3)			26 (3.1)		53 (6.01)	
IV		4 (0.32)		35 (1.8)			3 (0.36)		6 (0.68)	
Syncope	1,271	176 (14)	1,892	271 (14)	0.7	860	120 (14)	860	130 (15)	0.5
Dyspnea on exertion	1,170	613 (52)	1,771	897 (51)	0.4	789	418 (53)	800	410 (51)	0.5
Shortness of breath	1,169	687 (59)	1,772	976 (55)	0.05	788	451 (57)	801	463 (58)	0.8
Paroxysmal nocturnal dyspnea	1,168	84 (7.2)	1,771	171 (9.7)	0.02	787	61 (7.8)	800	69 (8.6)	0.5
Orthopnea	1,168	150 (13)	1,772	231 (13)	0.9	787	105 (13)	801	111 (14)	0.8
Valve pathology										
Pure aortic stenosis	1,603	1,203 (75)	2,219	1,682 (76)	0.6	1,054	778 (74)	1,056	794 (75)	0.5
Mixed aortic stenosis/ regurgitation	1,603	332 (21)	2,219	468 (21)	0.8	1,054	223 (21)	1,056	225 (21)	>0.9
Bicuspid aortic valve	1,637	659 (40)	2,286	411 (18)	<0.0001	1,082	298 (28)	1,082	296 (27)	>0.9
Mitral valve regurgitation severity	1,509		2,096		<0.0001	982		977		>0.9
None		811 (54)		923 (44)			478 (49)		490 (50)	>9
Mild		419 (28)		637 (30)			294 (30)		287 (29)	
Moderate		218 (14)		372 (18)			158 (16)		150 (15)	
Moderately severe		50 (3.3)		133 (6.3)			43 (4.4)		41 (4.2)	
Severe		11 (0.73)		31 (1.5)			9 (0.92)		9 (0.92)	
Tricuspid valve regurgitation severity	1,518		2,095		0.02	990		980		0.4
None		1,020 (67)		1,317 (63)			643 (65)		624 (64)	
Mild		318 (21)		462 (22)			211 (21)		219 (22)	
Moderate		120 (7.9)		220 (11)			91 (9.2)		87 (8.9)	
Moderately severe		42 (2.8)		74 (3.5)			31 (3.1)		42 (4.3)	
Severe		18 (1.2)		22 (1.1)			14 (1.4)		8 (0.82)	
Coronary artery disease										
Number of systems diseased ≥50%	1,629		2,284		<0.0001	1,076		1,080		<0.0001
0		1,629 (100)		105 (4.6)			1,076 (100)		73 (6.8)	
1		0 (0)		803 (35)			0 (0)		473 (44)	
2		0 (0)		745 (33)			0 (0)		322 (30)	
3		0 (0)		631 (28)			0 (0)		212 (20)	
LMT disease ≥50%	1,533	0 (0)	2,032	296 (15)	<0.0001	1,001	0 (0)	973	107 (11)	<0.0001
LAD system disease ≥50%	1,595	0 (0)	2,249	1,624 (72)	<0.0001	1,049	0 (0)	1,062	709 (68)	<0.0001
LCx system disease ≥50%	1,561	0 (0)	2,189	1,134 (52)	<0.0001	1,027	0 (0)	1,036	455 (44)	<0.0001
RCA system disease ≥50%	1,637	0 (0)	2,286	1,428 (62)	<0.0001	1,082	0 (0)	1,082	589 (54)	<0.0001

Continued on the next page

Table 1 Continued

Characteristic	Overall: Isolated AS (n = 1,637) n*	Overall: Isolated AS (n = 1,637) No. (%) or Mean ± SD	Overall: AS+CAD (n = 2,286) n*	Overall: AS+CAD (n = 2,286) No. (%) or Mean ± SD	Overall p Value	Propensity Matched: Isolated AS (n = 1,082) n*	Propensity Matched: Isolated AS (n = 1,082) No. (%) or Mean ± SD	Propensity Matched: AS+CAD (n = 1,082) n*	Propensity Matched: AS+CAD (n = 1,082) No. (%) or Mean ± SD	Propensity Matched p Value
Cardiac comorbidity										
Previous myocardial infarction	1,637	126 (7.7)	2,286	652 (29)	<0.0001	1,082	117 (11)	1,082	112 (10)	0.7
Atrial fibrillation/flutter	1,458	114 (7.8)	2,009	204 (10)	0.02	957	90 (9.4)	927	79 (8.5)	0.5
Complete heart block/pacer	1,452	62 (4.3)	2,002	115 (5.7)	0.05	951	55 (5.8)	926	51 (5.5)	0.8
Ventricular arrhythmia	1,492	167 (11)	2,074	274 (13)	0.07	982	121 (12)	967	130 (13)	0.5
Heart failure	1,637	330 (20)	2,286	691 (30)	<0.0001	1,082	257 (24)	1,082	248 (23)	0.6
Noncardiac comorbidity										
Peripheral arterial disease	1,637	65 (4.0)	2,286	278 (12)	<0.0001	1,082	57 (5.3)	1,082	65 (6.0)	0.5
Carotid disease	1,637	500 (31)	2,286	1,215 (53)	<0.0001	1,082	424 (39)	1,082	430 (40)	0.8
Stroke	1,637	102 (6.2)	2,286	221 (9.7)	0.0001	1,082	85 (7.9)	1,082	78 (7.2)	0.6
Hypertension	1,637	1,063 (65)	2,286	1,811 (79)	<0.0001	1,082	782 (72)	1,082	798 (74)	0.4
Insulin-treated diabetes	1,600	61 (3.8)	2,213	212 (9.6)	<0.0001	1,055	55 (5.2)	1,056	53 (5.0)	0.8
Pharmacologically treated diabetes	1,602	243 (15)	2,219	582 (26)	<0.0001	1,055	199 (19)	1,059	201 (19)	>0.9
BUN, mg·dl^{-1}	1,606	20 ± 8.3	2,249	23 ± 11	<0.0001	1,057	21 ± 8.7	1,062	21 ± 9.6	0.6
Creatinine, mg·dl^{-1}	1,606	1.03 ± 0.45	2,235	1.2 ± 0.59	<0.0001	1,058	1.08 ± 0.47	1,053	1.08 ± 0.51	0.6
Pre-operative renal dialysis	1,377	12 (0.87)	1,929	34 (1.8)	0.03	898	9 (1.0)	908	14 (1.5)	0.3
COPD	1,637	201 (12)	2,286	327 (14)	0.07	1,082	132 (12)	1,082	149 (14)	0.3
Smoking	1,630	803 (49)	2,266	1,247 (55)	0.0004	1,077	536 (50)	1,077	529 (49)	0.8
Cholesterol, mg·dl^{-1}	1,266	187 ± 45	1,683	181 ± 46	0.0002	813	183 ± 44	834	186 ± 45	0.2
Triglycerides, mg·dl^{-1}	1,262	132 ± 75	1,668	135 ± 80	0.2	810	132 ± 74	829	134 ± 77	0.4
HDL cholesterol, mg·dl^{-1}	1,261	54 ± 18	1,672	48 ± 15	<0.0001	808	51 ± 16	830	51 ± 15	0.6
LDL cholesterol, mg·dl^{-1}	1,260	108 ± 39	1,666	106 ± 41	0.2	807	106 ± 38	830	109 ± 40	0.15
Bilirubin, mg·dl^{-1}	1,529	0.67 ± 0.46	2,102	0.68 ± 0.54	>0.9	1,000	0.69 ± 0.52	1,000	0.69 ± 0.67	0.6
Hematocrit, %	1,551	39 ± 5.4	2,124	38 ± 5.6	<0.0001	1,017	38 ± 5.5	1,010	38 ± 5.5	0.6
Concomitant procedures										
Mitral valve repair	1,637	22 (1.3)	2,286	77 (3.4)	<0.0001	1,082	17 (1.6)	1,082	13 (1.2)	0.5
Tricuspid valve repair	1,637	33 (2.0)	2,286	53 (2.3)	0.5	1,082	26 (2.4)	1,082	27 (2.5)	0.9
Aortic endarterectomy	1,637	49 (3.0)	2,286	125 (5.5)	0.0002	1,082	37 (3.4)	1,082	40 (3.7)	0.7
Any atrial fibrillation procedure	1,637	97 (5.9)	2,286	143 (6.3)	0.7	1,082	74 (6.8)	1,082	71 (6.6)	0.8
Septal myectomy	1,637	30 (1.8)	2,286	34 (1.5)	0.4	1,082	21 (1.9)	1,082	26 (2.4)	0.5
ASD/PFO suture closure	1,637	27 (1.6)	2,286	37 (1.6)	0.9	1,082	16 (1.5)	1,082	18 (1.7)	0.7
Aortic valve prosthesis										
Valve size, mm	1,637		2,286		0.5	1,082		1,082		0.4
19		240 (15)		350 (15)			163 (15)		190 (18)	
21		483 (30)		666 (29)			312 (29)		319 (29)	
23		532 (32)		786 (34)			353 (33)		316 (29)	
25		303 (18)		394 (17)			200 (18)		207 (19)	
27		68 (4.2)		79 (35)			50 (4.6)		44 (4.1)	
29		11 (0.67)		11 (0.48)			4 (0.37)		6 (0.55)	
Standardized size (z value)	1,605	−0.42 ± 0.99	2,262	−0.41 ± 0.95	0.8	1,059	−0.42 ± 0.99	1,066	−1.42 ± 1.01	0.9

*Patients with data available.

AS = aortic stenosis; ASD/PFO = atrial septal defect/patent foramen ovale; BSA = body surface area; BUN = blood urea nitrogen; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LDL = low-density lipoprotein; LMT = left main trunk; NYHA = New York Heart Association; RCA = right coronary artery.

Matched outcome comparisons. Survival was similar among propensity-matched isolated AS and AS+CAD patients (93% vs. 93%, 80% vs. 80%, and 55% vs. 50% at 1, 5, and 10 years, respectively) (Fig. 2). Within the isolated AS group, matched patients had a significantly lower survival than unmatched patients with few comorbidities (93% vs. 97%, 80% vs. 90%, and 55% vs. 70% at 1, 5, and 10 years, respectively) (Online Tables 3a and 3b, Fig. 2). Conversely, AS+CAD matched patients had significantly higher survival than unmatched patients with myocardial

Table 2 Pre-Operative Echocardiographic Measurements

	Overall					Propensity Matched				
	Isolated AS (n = 1,637)		AS+CAD (n = 2,286)			Isolated AS (n = 1,082)		AS+CAD (n = 1,082)		
Measurement	n*	Mean ± SD	n*	Mean ± SD	p Value	n*	Mean ± SD	n*	Mean ± SD	p Value
Aortic valve hemodynamics										
Area, cm^2	1,426	0.65 ± 0.14	1,992	0.67 ± 0.14	<0.0001	942	0.65 ± 0.14	932	0.66 ± 0.14	0.5
Mean gradient, mm Hg	1,468	52 ± 16	2,042	45 ± 16	<0.0001	969	50 ± 16	957	49 ± 16	0.4
Peak gradient, mm Hg	1,474	87 ± 26	2,042	76 ± 25	<0.0001	975	84 ± 25	956	84 ± 24	>0.9
Left ventricle										
Morphology										
Posterior wall thickness, cm	1,430	1.3 ± 0.24	1,894	1.3 ± 0.23	0.5	932	1.3 ± 0.24	905	1.3 ± 0.22	0.8
Septal thickness, cm	1,440	1.5 ± 0.29	1,915	1.5 ± 0.31	0.6	939	1.5 ± 0.28	915	1.5 ± 0.29	0.9
Mass index, $g \cdot m^{-2}$	1,398	128 ± 42	1,863	134 ± 41	<0.0001	908	132 ± 43	886	131 ± 42	0.6
End-diastolic diameter, cm	1,446	4.6 ± 0.79	1,934	4.7 ± 0.81	<0.0001	945	4.6 ± 0.82	927	4.6 ± 0.82	0.2
End-systolic diameter, cm	1,432	3.0 ± 0.84	1,911	3.1 ± 0.90	<0.0001	940	3.0 ± 0.86	920	3.0 ± 0.85	0.2
Function										
Ejection fraction, %	1,509	55 ± 11	2,134	51 ± 13	<0.0001	987	54 ± 11	1,006	54 ± 11	0.4
Left atrium										
Diameter, cm	1,352	4.1 ± 0.76	1,836	4.3 ± 0.75	<0.0001	887	4.2 ± 0.75	857	4.2 ± 0.75	0.4

*Patients with data available.
Abbreviations as in Table 1.

damage and many comorbidities (93% vs. 89%, 78% vs. 67%, and 50% vs. 36% at 1, 5, and 10 years, respectively) (Online Tables 4a and 4b, Fig. 2). Differences in survival relate to the disparate patient profiles that resulted in propensity matching intermediate profile groups (Fig. 3, Table 1).

Post-operative in-hospital morbidity was similar among matched patients, except for more prolonged ventilation in AS+CAD patients (Online Table 2).

Matched and unmatched patient characteristics. Unmatched patients within the isolated AS group, on average, represent younger persons with mild symptoms and few to no comorbidities (Fig. 4, Online Tables 3a and 3b). However, they had the most hemodynamically severe form of AS among the groups, with high aortic valve gradients and a predominance of bicuspid valves (65% matched vs. 28% unmatched). They tended to have isolated AS, with few having concomitant mitral or tricuspid valve disease. This

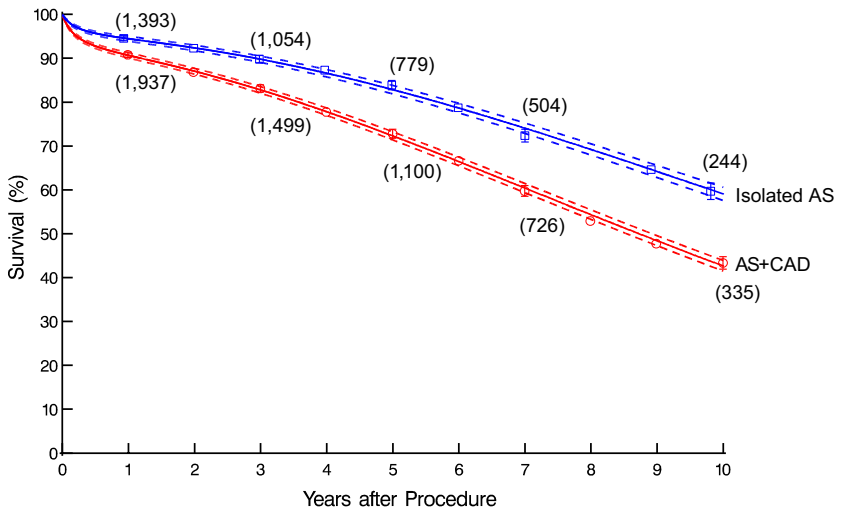

Figure 1 Unadjusted Survival Among Patients After Surgery

Unadjusted survival among patients after surgery for isolated aortic stenosis (**blue**; isolated AS) versus AS with coronary artery disease (**red**; AS+CAD). Symbols represent Kaplan-Meier nonparametric estimates at yearly intervals, accompanied by **vertical bars** representing confidence limits equivalent to ±1 standard error. **Solid lines** enclosed within **dashed confidence bands** equivalent to ±1 standard error represent parametric estimates.

Table 3 Patient Variables Associated With Severe AS Alone (Isolated AS) Versus AS+CAD

Variable*	Coefficient ± SE	Odds Ratio (68% CI)	p Value	Reliability (%)†
Higher likelihood of isolated AS				
Larger BMI‡	0.34 ± 0.094	—*	0.0003	82
Shortness of breath	0.29 ± 0.10	1.3 (1.2–1.5)	0.006	97
COPD	0.22 ± 0.11	1.2 (1.1–1.4)	0.05	41
Higher aortic valve peak gradient§	−0.85 ± 0.098	—*	<0.0001	100
Bicuspid aortic valve	0.56 ± 0.092	1.8 (1.6–1.9)	<0.0001	100
Tricuspid valve regurgitation 3+/4+	0.45 ± 0.20	1.6 (1.3–1.9)	0.02	64
Higher diastolic blood pressure‖	−0.20 ± 0.085	—*	0.02	74
Higher likelihood of AS+CAD				
Older age¶	2.2 ± 0.32	—*	<0.0001	89
Male	0.78 ± 0.087	2.2 (2.0–2.4)	<0.0001	98
Higher NYHA functional class	0.25 ± 0.053	1.3 (1.2–1.4)	<0.0001	99
Lower ejection fraction#	−0.42 ± 0.12	—*	0.0005	98
Peripheral arterial disease	0.58 ± 0.16	1.8 (1.5–2.1)	0.0002	82
Carotid disease	0.63 ± 0.078	1.9 (1.7–2.03)	<0.0001	100
Hypertension	0.54 ± 0.088	1.7 (1.6–1.9)	<0.0001	100
Higher systolic blood pressure**	0.33 ± 0.15	—*	0.03	74
Diabetes	0.47 ± 0.099	1.6 (1.4–1.8)	<0.0001	100
Lower hematocrit††	−0.90 ± 0.28	—*	.001	81
Lower HDL‡‡	−0.60 ± 0.14	—*	<0.0001	100
Aorta procedure	0.43 ± 0.19	1.5 (1.3–1.9)	0.02	81

*See Online Figure 4 for an illustration of the nature of the relationship of continuous variables to likelihood of having coronary artery disease. †Percent of times variables appeared in 250 bootstrap models. ‡$(BMI/30)^2$, squared transformation. §(80/AV peak gradient), inverse transformation. ‖$(75/\text{diastolic blood pressure})^2$, inverse squared transformation. ¶Log(age), logarithmic transformation. #$(\text{Ejection fraction}/55)^2$, squared transformation. **$(\text{Systolic blood pressure}/135)^2$, squared transformation. ††Log(hematocrit), logarithmic transformation. ‡‡Log(HDL), logarithmic transformation.
AV = aortic valve; BMI = body mass index; CI = confidence interval; other abbreviations as in Table 1.

stands in contrast to matched isolated AS patients who had hemodynamically less severe AS, but significantly higher prevalence of comorbid conditions, including vasculopathies, stroke, hypertension, diabetes, and renal disease. These matched patients also had worse LV systolic function, more heart failure, complete heart block, atrial fibrillation, and greater LV hypertrophy and LA dilation compared with unmatched isolated AS patients.

In contrast, unmatched AS+CAD patients represent the opposite spectrum of disease severity. They tended to be older males with the most severe symptoms and extensive comorbidities (Fig. 4, and Online Tables 4a and 4b). Unmatched AS+CAD patients had the least severe AS; however, they had the highest prevalence of CAD risk factors among the groups, including vasculopathies, smoking, hypertension, diabetes, and renal disease. They also had more heart failure and LV dysfunction, the most severe LV hypertrophy and dilation, and more ischemic mitral disease and atrial fibrillation.

Discussion

Principal findings. Overall, AS+CAD patients had poorer short- and long-term prognosis than those with isolated AS and more post-operative morbidity. Increased mortality of AS+CAD patients was associated with effects of pre-existing ischemic myocardial damage and comorbidities. In contrast, prognosis for isolated AS patients was adversely influenced by the negative influence of LV hypertrophy and diastolic dysfunction at operation. But further analyses using propensity matching clearly identified distinct patient subgroups with differing prognosis. The first comprised patients with isolated AS who had the best outcome and whose survival was adversely affected by LV hypertrophy and diastolic dysfunction. The second comprised patients with CAD without evidence of ischemic myocardial damage. These patients had outcome similar to those with isolated AS and similar non-CAD comorbidities. The third group comprised patients with severe AS+CAD and ischemic damage and multiple comorbidities, unlike patients with isolated severe AS. They had the poorest survival, despite the least degree of AS.

Patient profiles. That patients with AS+CAD were older and more symptomatic with less severe AS, but more risk factors for CAD than patients with isolated AS, has been documented by others (3). Onset of symptoms likely results from the combined effects of CAD and AS, resulting in catheterization and earlier intervention for their valvar and coronary diseases. This stands in contrast to milder, but slowly developing symptoms more characteristic of patients with isolated AS.

Unique risk factors. Patients with AS+CAD display risk profiles reflecting CAD (20–22). Survival is dominated by comorbidities, particularly vasculopathy. Many of their risk factors have been described by others (5,23,24), including older age, more severe symptoms, vasculopathy, previous stroke, diabetes, previous myocardial infarction, and renal disease.

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Table 4 Overall Model for Incremental Risk Factors for Death After Procedure

	Common		Isolated AS		AS+CAD	
Risk Factor	Coefficient ± SE	p Value	Coefficient ± SE	p Value	Coefficient ± SE	p Value
Early hazard phase						
Isolated AS	3.7 ± 0.89	<0.0001				
AS+CAD						
LMT stenosis ≥70%					0.76 ± 0.25	0.002
LAD stenosis ≥70%					0.34 ± 0.16	0.03
RCA stenosis ≥50%					0.404 ± 0.18	0.02
LCx stenosis >0%					0.62 ± 0.27	0.02
Older age*	1.9 ± 0.34	<0.0001				
Larger height/weight ratio					0.55 ± 0.19	0.004
NYHA functional class III/IV	0.66 ± 0.13	<0.0001				
Heart failure					0.34 ± 0.16	0.04
Aortic valve regurgitation 3+/4+					0.64 ± 0.27	0.02
Tricuspid valve regurgitation 4+					1.02 ± 0.38	0.007
Lower LV diastolic volume†			0.097 ± 0.028	0.0004		
Lower ejection fraction					0.061 ± 0.022	0.006
Lower HDL‡			0.11 ± 0.034	0.002		
Carotid disease (less risk)					−0.35 ± 0.15	0.02
COPD					0.51 ± 0.18	0.005
Treated diabetes					0.52 ± 0.17	0.002
Higher creatinine§			−1.3 ± 0.43	0.003	−0.64 ± 0.25	0.01
Higher bilirubin			0.24 ± 0.12	0.05		
Lower hematocrit‖			−1.6 ± 0.51	0.002	−0.60 ± 0.34	0.08
Smaller AV prosthesis (value)					−0.25 ± 0.086	0.004
Earlier date of operation¶					1.2 ± 0.38	0.001
Late hazard phase						
AS alone	−3.2 ± 0.76	<0.0001				
AS+CAD						
ITA graft used (less risk)					−0.24 ± 0.079	0.002
Older age*			3.7 ± 0.43	<0.0001	2.3 ± 0.24	<0.0001
Myocardial infarction					0.24 ± 0.082	0.004
Larger BMI#			0.41 ± 0.11	0.0002		
Syncope			0.34 ± 0.14	0.02		
Lower ejection fraction**	−0.52 ± 0.15	0.001				
Larger LA diameter††			0.86 ± 0.35	0.01	0.34 ± 0.44	0.4
LV mass index‡‡			0.73 ± 0.18	<0.0001	−0.35 ± 0.202	0.09
Interaction: LA diameter · LV mass index index§§					0.42 ± 0.19	0.03
Interaction: age · LV mass index‖‖			−0.65 ± 0.21	0.002		
Insulin-treated diabetes					0.72 ± 0.13	<0.0001
Smoking	0.25 ± 0.065	<0.0001				
COPD			0.59 ± 0.16	0.0002		
Dialysis					1.4 ± 0.303	<0.0001
Higher BUN¶¶			0.14 ± 0.036	0.0002	0.062 ± 0.015	<0.0001
Lower hematocrit‖					−0.60 ± 0.18	0.001
Any atrial fibrillation procedure					0.64 ± 0.20	0.001
ASD/PFO suture closure					0.83 ± 0.26	0.002

*$(Age/75)^2$, squared transformation. †$(100/LV\ diastolic\ volume)^2$, inverse squared transformation. ‡$(50/HDL)^2$, inverse squared transformation. §(1/creatinine), inverse transformation. ‖$(Hematocrit/40)^2$, squared transformation. ¶(1/[interval to date of operation from January 1, 1991]), inverse transformation. #$(BMI/30)^2$, squared transformation. **(Ejection fraction/55), scaled variable. ††(LA diameter/4.5), scaled variable. ‡‡$(LV\ mass\ index/125)^2$, squared transformation. §§Interaction: (LA diameter/4.5) · $(LV\ mass\ index/125)^2$. ‖‖Interaction: $(age/75)^2$ · $(LV\ mass\ index/125)^2$. ¶¶$(BUN/20)^2$, squared transformation.

LA = left atrial; LV = left ventricular; ITA = internal thoracic artery; other abbreviations as in Tables 1 and 3.

In contrast, survival of patients with isolated AS is dominated by secondary effects of AS on myocardium, notably LV hypertrophy and diastolic dysfunction (25). Severe LV hypertrophy only partly regresses after AVR (26,27), is associated with decreased long-term survival (28), and results in decreased ventricular compliance and ischemia-induced myocardial fibrosis, contributing to LV diastolic dysfunction (29,30). Although LV mass index and LA diameter were smaller in the isolated AS group, these factors, particularly LA diameter (31), are strongly associ-

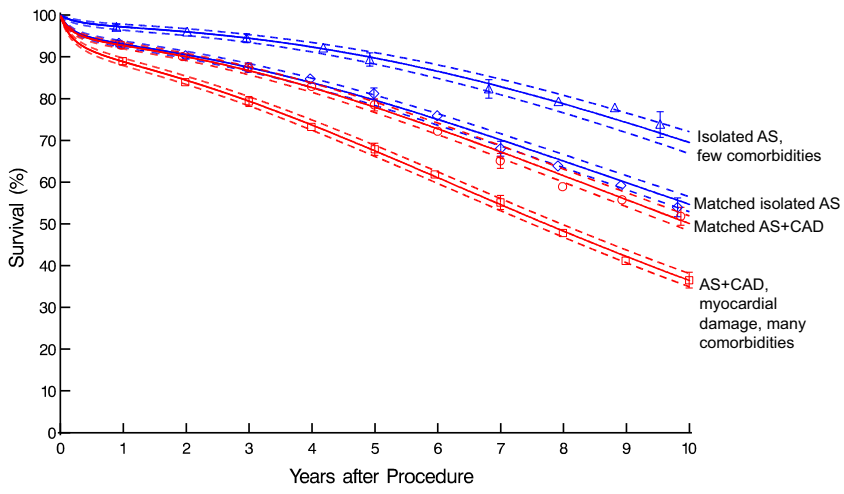

Figure 2 **Survival of Propensity-Matched and Unmatched Patients**

Survival of patients with isolated AS with few comorbidities **(blue triangles)** compared with isolated AS and non–CAD comorbidities matching those of patients with both AS **(blue diamonds)** and AS+CAD (**red circles**). These are all contrasted with patients having AS and CAD with myocardial damage and a comorbidity profile that is completely unlike that of patients with isolated AS **(red squares)**. Format as in Figure 1. Abbreviations as in Figure 1.

ated with increased late mortality not seen in AS+CAD patients despite their having larger left heart measures. This suggests that structural heart changes in the 2 groups are different. Given the extensive comorbidity profile of the AS+CAD group, secondary effects of more prominent disease processes, such as hypertension (32), may be responsible. Nonetheless, long-term survival of patients with isolated AS appears to be more sensitive to the presence of LV hypertrophy and diastolic dysfunction.

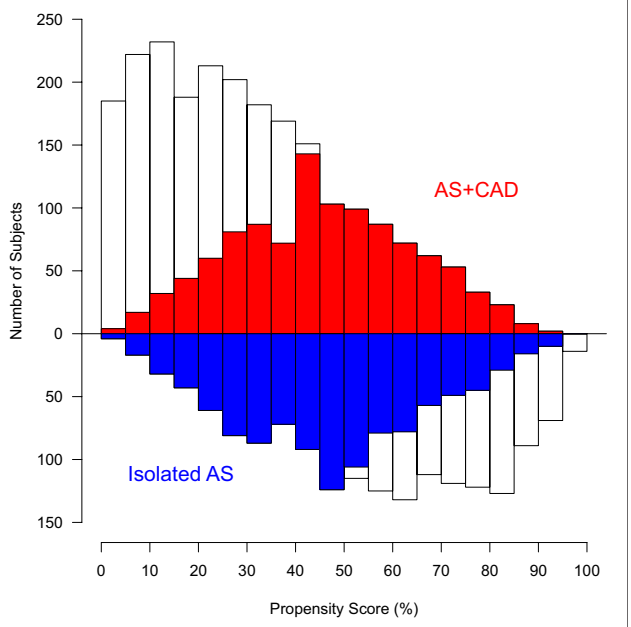

Figure 3 **Distribution of Propensity Scores**

Mirrored histogram of distribution of propensity scores for patients with isolated AS **(blue)** versus AS+CAD **(red)**. **Red** and **blue** areas represent 1,082 matched patient pairs. Abbreviations as in Figure 1.

Survival comparison. In general, patients with severe AS and coexisting CAD have worse survival than those with isolated AS. However, the heterogeneity of patient characteristics makes simple survival comparisons between the 2 groups inaccurate (19). Propensity matching provides an opportunity to compare outcomes of patients with isolated AS with those of patients with AS+CAD and otherwise similar non-CAD comorbidity profiles. Matched survival was similar, consistent with the propensity-matched comparison by Roberts et al. (3), suggesting that surgical revascularization at the time of AVR neutralizes the adverse effects of CAD, provided that ischemic myocardial damage has not occurred. However, the distribution of propensity scores (see Fig. 3) demonstrates that this matched population is an intermediate risk group, different from both average isolated AS and AS+CAD patients. This is reflected in survival of the unmatched groups. Unmatched isolated AS patients had better, and AS+CAD patients worse, survival than their respective matched group. Given the age discrepancies of patients, it is helpful to reference survival curves to expected U.S. age-sex-race–matched survival. Isolated AS patients, both matched and unmatched, had better than expected survival, as did the matched AS+CAD patients (Online Fig. 6). However, unmatched AS+CAD patients have poor survival, falling below that of the U.S. life table by 8 to 10 years post-operatively.

Patient profile: a determinant of outcomes in severe AS. Patients' comorbidity profiles affected survival more than the procedure they underwent. Even in the absence of CAD,

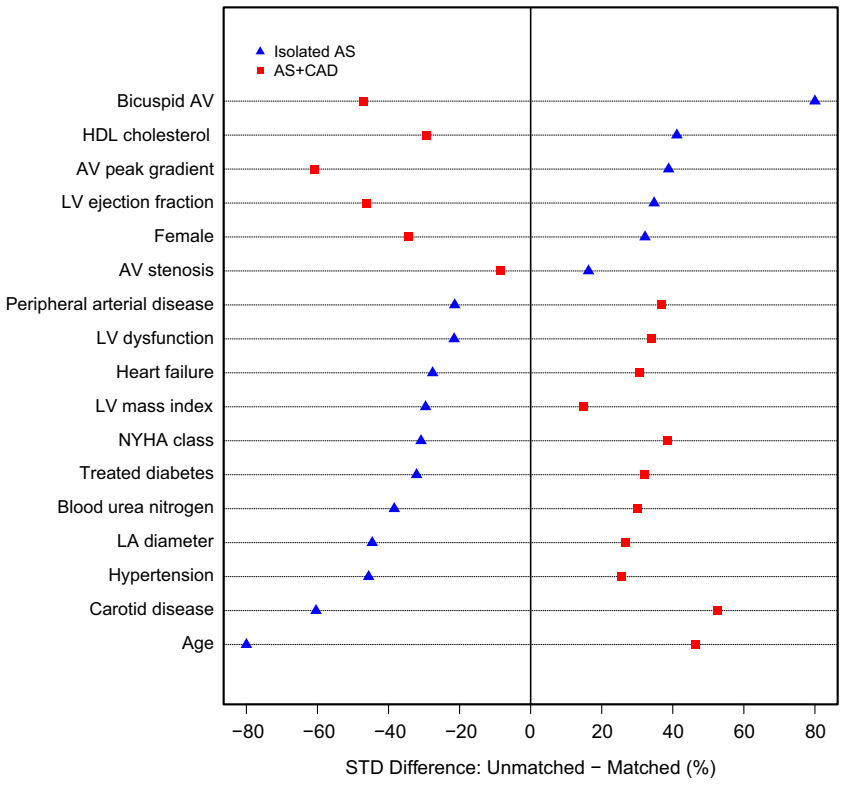

Figure 4 **Differences Between Unmatched Patients**

Standardized differences between unmatched patients with isolated aortic stenosis **(blue triangles)** group and AS+CAD **(red squares)** group (44).
AV = aortic valve; HDL = high-density lipoprotein; LA = left atrial; LV = left ventricular; NYHA = New York Heart Association; other abbreviations as in Figure 1.

patients who underwent AVR, but had comorbidities including smoking, vasculopathies, hypertension, diabetes, and renal disease, had survival equal to matched patients with CAD who underwent AVR+CABG. Unmatched AS+CAD patients had poor survival with a high-risk comorbidity profile and signs of irreversible ischemic heart damage. Even if these patients survive surgery, they have poor survival relative to other patients undergoing the same procedures. They require chronic disease management for their comorbidities, as these will ultimately determine their outcomes. It may be argued whether surgery should be performed on these patients. The answer may have implications for future therapies. For example, late results of transcatheter AVR+percutaneous coronary intervention may also be determined by patients' systemic diseases. Therefore, because of their patient profile, results may not be as good as those for patients receiving transcatheter AVR alone (33).

Strengths and limitations. This is a large, contemporary, single-institution observational study comparing patients who received either AVR alone for isolated severe AS, or AVR+CABG for severe AS and CAD. All patients were evaluated by heart catheterization to define coronary artery stenosis and underwent primary heart surgery with a single prosthesis type for isolated degenerative AS. Prior analyses of these groups evaluated patient risk factors for survival, which, as both this and other studies noted, are limited on the basis of the distinct profiles of the patients undergoing these procedures (6). The application of propensity analysis enabled direct comparison of a subset of these patients. Given their similar profiles after matching, patients undergoing surgery for isolated AS and AS+CAD had equal survival and thus no effect of CAD after intervention.

Diagnosis of CAD was on the basis of catheterization with at least 1 vessel with stenosis ≥50%. This definition was based on clinical practice within our institution for treatment of CAD, guided by current American Heart Association and American College of Cardiology recommendations (4). This is reflected in the relatively small number of patients (n = 427) who underwent AVR alone, but had CAD meeting these criteria; these patients were excluded from this analysis. Others have applied stricter criteria, such as 70% to 75% stenosis (34). Only 22 patients underwent AVR+CABG without meeting our criteria for CAD, but 20 of these procedures were for ostial occlusion by the prosthesis. Thus, our definition reflects current clinical practice.

Implications. Patients with severe AS range from young patients with isolated bicuspid valve disease and excellent expected survival to elderly patients with extensive comorbidities resulting in poor functional status and survival. Therefore, for many patients, AS is not a simple mechanical disease process, but represents 1 of many concurrent comorbidities. Our analysis distinguishes between groups on the basis of comorbidities and risk factors. These factors should be used for accurate interpretation of results for current and future therapies for AS, including percutaneous procedures. Although patients with isolated AS have excellent survival, their outcomes are more sensitive to the consequences of long-standing pressure overload leading to LV hypertrophy and diastolic dysfunction, as reflected by left atrial size (31,35–37). These results add to evidence that these patients may need AVR before symptom development and irreversible left heart remodeling. In contrast, those with the highest risk profile have poor survival because of advanced comorbidities that are not reversed by AVR.

Complete assessment of patient characteristics should be incorporated into the decision-making process. In patients with severe AS and LV hypertrophy, early surgery may be indicated before symptoms develop. Although current guidelines for treating valvar heart disease recognize that risk factors for CAD and AS frequently coexist, there are no recommendations for early evaluation or diagnosis of CAD in these patients. Our study demonstrates the devastating effects on survival of ischemic damage in patients with AS; this indicates the need for early diagnosis of CAD in these patients.

The common practice of advocating delay of surgery for patients with AS in order to avoid anticoagulation associated with mechanical prostheses can adversely affect long-term survival because of the potential for myocardial ischemic damage. The results of our study strongly suggest changing practice and modifying guidelines to include early evaluation of CAD in asymptomatic patients with severe AS and risk factors for CAD so that timely AVR+CABG is performed before ischemic myocardial damage occurs. Generally these patients will have reached an age for which contemporary bioprostheses have lifetime durability in the great majority (38) and transcatheter valve-in-valve procedures may obviate the need for reoperation in the future (39–41). Elderly patients with AS and risk factors for CAD should be considered for active investigation of CAD before evaluation for AVR. In contrast, patients with poor functional status and advanced comorbidities may be best served with medical management alone.

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Key Words: aortic stenosis ■ aortic valve replacement ■ coronary artery disease ■ outcomes.

APPENDIX

For additional tables, figures, and appendices, please see the online version of this article.