JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2024

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Cardiac Damage in Early Aortic Stenosis

Is the Valve to Blame?

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ABSTRACT

BACKGROUND Despite the close association between aortic stenosis (AS) and cardiac damage (CD), it is unclear if CD is limited to patients with moderate and severe AS and which factors affect its progression. Although altered valvular hemodynamic status may drive the development of CD in AS, commonly occurring comorbidities may contribute.

OBJECTIVES The aim of this study was to determine the prevalence of and factors associated with CD in mild AS.

METHODS This retrospective study included 9,611 patients with mild AS (peak aortic valve velocity [V_{max}] 2-3 m/s and description of abnormal aortic valve) from 2010 through 2021. CD was staged using the Genereux classification.

RESULTS All but 20% (n = 1,901; stage 0) of patients with mild AS demonstrated CD: 1,613 (17%) stage 1, 4,843 (50%) stage 2, 891 (9%) stage 3, and 363 (4%) stage 4. Patients with higher stages had more comorbidities (hypertension, heart failure, ischemic heart disease, stroke, peripheral arterial disease, chronic kidney disease, chronic pulmonary disease, and diabetes mellitus) but had valvular hemodynamic status similar to those without CD. CD stage did not worsen with higher V_{max} range (stage >1 in 64% with V_{max} <2.5 m/s vs 61% with V_{max} ≥2.5 m/s) but increased with the number of comorbidities, with stage >1 occurring in 50%, 53%, 60%, 66%, 72%, and 73% in the presence of 0, 1, 2, 3, 4, and 5 or more comorbidities, respectively.

CONCLUSIONS CD was highly prevalent in patients with mild AS. Among patients with mild AS, there was no relationship between the degree of CD and AS severity; instead, CD was highly associated with comorbidities.
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Aortic stenosis (AS) is characterized by left ventricular (LV) pressure overload, which eventually leads to increased wall stress, LV remodeling, and ultimately heart failure. For decades, LV remodeling was considered an adaptive response that might preserve wall stress in the normal range, thereby preventing heart failure. However, it has become evident that the remodeling process alters LV diastolic properties,[1] triggering a detrimental cascade that leads to increased LV filling pressures,[2] left atrial (LA) dilatation,[3] right ventricular dysfunction,[4] impairment in exercise hemodynamic status,[5] development of heart failure symptoms,[2] and a poor prognosis.[3,6]

Recently, a new staging classification characterizing the extent of extra-aortic valve (AV) cardiac damage (CD) including the LV, LA, mitral valve, pulmonary vasculature, tricuspid valve, and right ventricle has emerged.[7] Using this classification, it was demonstrated that >95% of patients with severe AS referred for AV replacement (AVR) have some degree of CD and that the extent of CD greatly affects

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 25, 2024; revised manuscript received April 30, 2024, accepted May 2, 2024.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2024.05.003

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AUC = area under the receiver-operating characteristic curve

AV = aortic valve

AVR = aortic valve replacement

CD = cardiac damage

LA = left atrial/atrium

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

SVi = stroke volume index

V_{max} = peak aortic valve velocity

outcome, as it may not improve even after AVR.[8] Moreover, a recent study suggested that CD may also be common in asymptomatic moderate and severe AS, with an impact on prognosis.[9] Despite the use of an alternative CD staging, this study substantiated the recent view that moderate AS may not be as benign as once believed, which has been suggested by recent prognostic data.[10]

Despite the close association between AS and CD, it is unclear if this process is limited to patients with moderate and severe AS and which extravalvular factors affect its development. Although altered valvular hemodynamic status may drive this response, we hypothesized that commonly occurring comorbidities such as hypertension, ischemic heart disease, and atrial fibrillation may contribute to the CD process seen in patients with AS.

Thus, the focus of this study was to determine the prevalence of CD in patients with mild AS, to identify factors associated with its presence, and to study the impact of CD on outcome.

METHODS

STUDY PATIENTS. The study was approved by the Mayo Clinic Institutional Review Board, and only patients allowing access to their records were included. This retrospective study included all patients >18 years of age diagnosed with mild AS (defined as peak AV velocity [V_{max}] from 2-3 m/s and a description of an abnormal AV on clinically indicated transthoracic echocardiography) from January 1, 2010, through December 31, 2021, who underwent 1 or more additional transthoracic echocardiographic examinations at least 6 months later (Supplemental Figure 1). All echocardiographic studies were performed at Mayo Clinic locations, including Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida. Patients with moderate or more AV regurgitation were excluded. To understand the impact of CD on outcome among patients with mild AS, only those with more than 6 months of follow-up were included. Electrocardiographic parameters and patient history on the basis of International Classification of Diseases-9th Revision (ICD-9) and International Classification of Diseases-10th Revision (ICD-10) codes were obtained from the electronic medical records. Follow-up from the day of the baseline echocardiographic examination was obtained from the electronic medical records. Death information was obtained via Minnesota State Death Records and the Mayo Clinic registration system. Subjects were censored at last known follow-up within the Mayo Clinic system. The endpoint for this study was all-cause mortality.

DEFINITION OF COMORBIDITIES. Comorbidities prior to the date of baseline echocardiography were identified using ICD-9 and ICD-10 codes (see Supplemental Table 1 for a list of diagnosis codes). Specifically, comorbidities pertinent to this study were hypertension, heart failure, ischemic heart disease, stroke, peripheral arterial disease, chronic kidney disease, chronic pulmonary disease, and diabetes mellitus. Patients were stratified into 6 groups according to the number of comorbidities present (0, 1, 2, 3, 4, and 5 or more).

ECHOCARDIOGRAPHY. Echocardiography was performed using commercially available ultrasound equipment (Acuson Sequoia [Siemens Medical], Vivid 9 [GE Healthcare], and iE33 or EPIQ [Philips]) in accordance with guidelines,[11,12] with interpretation performed by an experienced cardiologist with level III training in echocardiography.

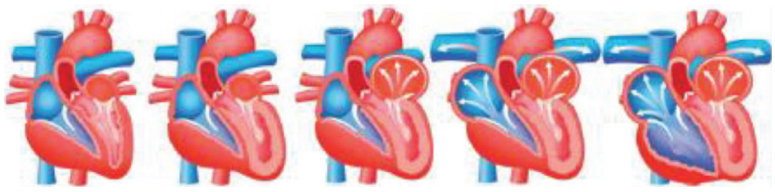
Doppler values were calculated as the average of 3 cardiac cycles for patients in sinus rhythm and at least 5 cycles for those with atrial fibrillation. LV outflow tract diameter was measured in the parasternal long-axis view in early systole at the points of aortic cusp insertion into the interventricular septum and intervalvular fibrosa. AV area was estimated using quantitative Doppler ultrasound with the continuity equation. Continuous-wave Doppler flow across the AV was interrogated from at least 3 windows including with the Pedoff probe to ensure optimal alignment with flow across the valve. Peak and mean flow velocities across the valve were determined using the window in which the highest velocity could be recorded. Mean transvalvular gradients were estimated using the modified Bernoulli equation.[12]

Left ventricular ejection fraction (LVEF) was determined using Simpson's biplane method, 3-dimensional imaging, and/or the modified method of Quinones; the final reported LVEF method was at the discretion of the expert echocardiographer.[13,14] LV stroke volume was calculated using pulsed-wave Doppler as the product of LV outflow area and LV outflow tract time-velocity integral and indexed to body surface area (stroke volume index [SVi]). LV mass index was estimated using Devereux's formula. LV mass index >115 g/m^2 (in men) or >95 g/m^2 (in women) was considered indicative of LV hypertrophy. Relative wall thickness was calculated for assessment of LV geometry using standard methods and considered increased when >0.42.[11] Pulse pressure was calculated as: systolic blood pressure –

CENTRAL ILLUSTRATION CD in Patients With Mild AS

CD in Early AS: Relation to Comorbidities

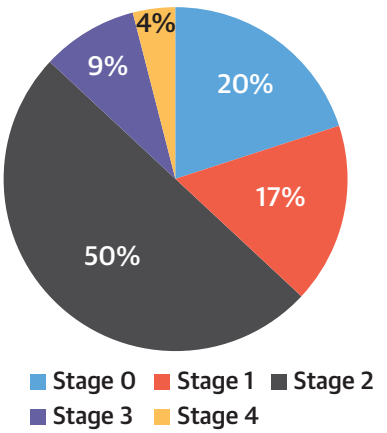
V_{max} = 2 to 3 m/s



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	n = 1,901	n = 1,613	n = 4,843	n = 891	n = 363
LV damage					
LVEF <50%		11%	12%	15%	26%
LV hypertrophy		56%	47%	48%	43%
E/e' >14		67%	52%	69%	62%
LA or MV damage					
LAVi >34 mL/m^2			89%	84%	67%
≥Moderate MR			13%	45%	26%
Atrial fibrillation			39%	53%	58%
Pulmonary vasculature or tricuspid damage					
SPAP ≥60 mm Hg				46%	20%
≥Moderate TR				84%	41%
RV damage					
TAPSE <16 mm					100%

Coexisting Comorbidities	Prevalence (%)
Hypertension	6,843 (71)
Diabetes mellitus	2,953 (31)
Ischemic heart disease	4,144 (43)
Heart failure	2,536 (26)
Chronic kidney disease	2,601 (27)
Stroke	1,018 (11)
Peripheral arterial disease	3,229 (34)
Chronic pulmonary disease	1,386 (14)

Prevalence and Extent of CD



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(Left) Prevalence of various stages of cardiac damage (CD) in patients with mild aortic stenosis (AS). (Top right) Comorbidities common in mild AS. (Bottom right) Prevalence and extent of CD. Heart illustrations reproduced from Figure 1 in Genereux et al[7]; used under Creative Commons Attribution Non-Commercial License. LA = left atrial; LAVi = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MV = mitral valve; RV = right ventricular; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; Vmax = peak aortic valve velocity.

TABLE 1 Clinical Characteristics According to Genereux Stages of CD

	Stage 0 (n = 1,901)	Stage 1 (n = 1,613)	Stage 2 (n = 4,843)	Stage 3 (n = 891)	Stage 4 (n = 363)	*P* Value
Age, y	67 ± 12	70 ± 12	73 ± 11	75 ± 13	75 ± 11	<0.001
Female	634 (33)	820 (51)	1,752 (36)	466 (52)	114 (31)	<0.001
Body mass index, kg/m^2	30.1 ± 6.3	31.1 ± 7.1	30.6 ± 6.9	30.1 ± 7.6	30.2 ± 6.5	<0.001
Hypertension	1,157 (61)	1,163 (72)	3,590 (74)	664 (75)	269 (74)	<0.001
Diabetes mellitus	442 (23)	561 (35)	1,523 (31)	289 (32)	138 (38)	<0.001
Atrial fibrillation	0 (0)	0 (0)	1,880 (39)	469 (53)	212 (58)	<0.001
Ischemic heart disease	610 (32)	605 (38)	2,241 (46)	440 (49)	248 (68)	<0.001
Heart failure	151 (8)	337 (21)	1,370 (28)	485 (54)	193 (53)	<0.001
Chronic kidney disease	256 (14)	393 (24)	1,499 (31)	321 (36)	132 (36)	<0.001
Stroke	150 (8)	173 (11)	567 (12)	93 (10)	35 (10)	<0.001
Peripheral arterial disease	553 (29)	519 (32)	1,701 (35)	322 (36)	134 (37)	<0.001
Chronic pulmonary disease	223 (12)	238 (15)	699 (14)	162 (18)	64 (18)	<0.001

Values are mean ± SD or n (%).
CD = cardiac damage.

diastolic blood pressure, and systemic arterial compliance was assessed as SVi/pulse pressure.[15]

CD STAGING CLASSIFICATION. Patients were stratified according to the CD staging scheme proposed by Genereux et al[7] as stage 0 (no extra-AV CD), stage 1 (LV damage as defined by the presence of LV hypertrophy, severe LV diastolic dysfunction [E/e′ ratio >14], and/or LV systolic dysfunction [LVEF <50%]), stage 2 (LA and/or mitral valve damage defined by the presence of LA enlargement [LA volume index >34 mL/m^2] and/or atrial fibrillation and/or moderate or greater mitral regurgitation), stage 3 (pulmonary artery vasculature and/or tricuspid valve damage defined by the presence of systolic pulmonary hypertension [systolic pulmonary arterial pressure ≥60 mm Hg] and/or the presence of moderate or greater tricuspid regurgitation), or stage 4 (right ventricular damage defined by the presence of moderate or greater right ventricular systolic dysfunction, determined as a tricuspid annular plane systolic excursion <16 mm). In addition, we tested an additional CD stage model recently reported by Tastet et al[9] in patients with moderate AS using different thresholds for LVEF (<60%) and tricuspid annular plane systolic excursion (<17 mm) and labeling SVi <30 mL/m^2 as stage 4 CD. In both staging schemes, patients were hierarchically classified in a given stage (worst stage) if at least 1 of the proposed criteria was met within that stage.

STATISTICAL ANALYSIS. Data are presented as mean ± SD or as number (percentage). Differences in values between groups were tested using 1-way ANOVA; categorical variables were tested using the chi-square exact test. For overall tests, a value of $P < 0.05$ was considered to indicate statistical significance, and 2-sided tests were used. Associations between baseline clinical and echocardiographic variables and CD were studied using linear regression analysis. Multivariable analysis included only variables with values of $P < 0.05$ but did not include atrial fibrillation, as this comorbidity is part of the CD classification. Furthermore, we performed logistic regression analysis to test the variables' impact to identify CD stage >1 and stage >2. Comparison of each method's predictive capability was performed by comparing the C-statistics derived from the area under the receiver-operating characteristic curve (AUC) using the generalized U-statistic as proposed by DeLong et al.[16] The association of AS severity on CD was tested by stratifying patients according to a V_{max} threshold of 2.5 m/s, as some guidelines suggest that mild AS is present only when V_{max} is >2.5 m/s,[17] and also in 5 groups, ranging from 2.0 to 2.2 m/s to 2.8 to 3.0 m/s depending on V_{max}. The impact of comorbidities on CD was tested by stratifying patients according to the number of a priori defined comorbidities other than atrial fibrillation and also according to a diagnosis of heart failure. For patients with CD stages 0 and 1, logistic regression analysis was performed to identify factors associated with CD stage >1 on the subsequent echocardiographic study.

Mortality rates were calculated using the product limit method and plotted according to the Kaplan-Meier method; mortality was compared using the log-rank test. Further estimation of risk was performed using Cox proportional hazards models. The assumptions (proportional hazards assumption, linearity of continuous variables, and lack of interaction) were tested using Schoenfeld residual tests and plotting Martingale residuals and found to be valid.

TABLE 2 Echocardiographic Data According to Genereux Stages of CD

	Stage 0 (n = 1,901)	Stage 1 (n = 1,613)	Stage 2 (n = 4,843)	Stage 3 (n = 891)	Stage 4 (n = 363)	*P* Value
V_{max}, m/s	2.32 ± 0.27	2.31 ± 0.27	2.32 ± 0.27	2.30 ± 0.27	2.29 ± 0.26	<0.001
Mean gradient, mm Hg	12.1 ± 3.5	11.9 ± 3.4	11.8 ± 3.6	11.6 ± 3.4	11.7 ± 3.2	<0.001
AV area, cm^2	2.00 ± 0.49	1.97 ± 0.51	2.04 ± 0.55	1.90 ± 0.48	1.85 ± 0.46	<0.001
Bicuspid AV	451 (24)	181 (11)	346 (7)	31 (4)	20 (6)	<0.001
LVEF, %	64 ± 5	62 ± 10	61 ± 10	60 ± 12	55 ± 13	<0.001
Stroke volume index, mL/m^2	48 ± 9	49 ± 10	51 ± 12	47 ± 12	43 ± 10	<0.001
LV mass index, g/m^2	85 ± 14	106 ± 26	110 ± 30	109 ± 35	108 ± 32	<0.001
Medial E/e′ ratio	10 ± 2	16 ± 26	16 ± 8	19 ± 9	18 ± 10	<0.001
LA volume index, mL/m^2	27 ± 5	29 ± 4	44 ± 12	50 ± 20	48 ± 21	<0.001
TAPSE, mm	23 ± 4	23 ± 4	23 ± 5	21 ± 4	13 ± 3	<0.001
Systemic arterial compliance, mL/mm Hg·m^2	0.92 ± 0.33	0.86 ± 0.32	0.87 ± 0.34	0.83 ± 0.31	0.81 ± 0.29	<0.001

Values are mean ± SD or n (%). Available values in the dataset included AV area in 9,337 patients, bicuspid AV in 9,611, mean gradient in 9,226, medial E/e′ ratio in 8,825, LA volume index in 8,765, LVEF in 9,590, LV mass index in 9,125, systemic arterial compliance in 7,933, TAPSE in 2,947, and V_{max} in 9,609. Values were available for all patients for the other variables.

AV = aortic valve; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular positive systolic excursion; V_{max} = peak aortic valve velocity; other abbreviation as in Table 1.

Statistical analysis was performed using Stata/BE version 18.0 (StataCorp).

RESULTS

Of the 9,611 patients (mean age 71 ± 12 years, 3,786 [39%] women), all but 20% (n = 1,901) demonstrated some degree of CD at baseline, with 1,613 (17%) in stage 1, 4,843 (50%) in stage 2, 891 (9%) in stage 3, and 363 (4%) in stage 4 (Central Illustration). ICD-9 and ICD-10 diagnostic codes were available for all. Comorbidities were highly prevalent, and only 979 (10%) of the cohort had none. There was a significant relationship between CD with comorbidities and age so that increasing stage of CD was associated with increasing age and greater accumulation of comorbidities such as hypertension, diabetes, ischemic heart disease, heart failure, chronic kidney disease, chronic pulmonary disease, and peripheral arterial disease (Table 1).

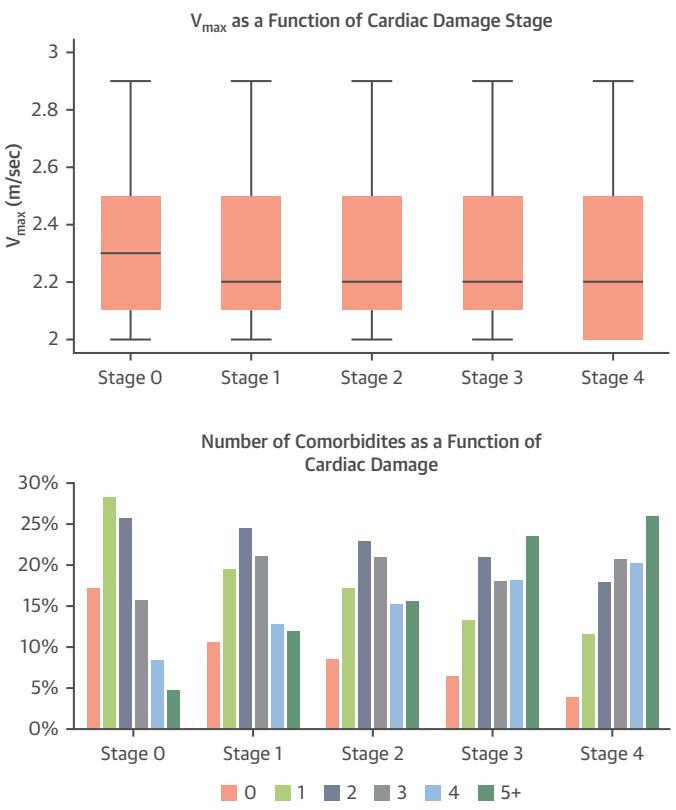
Patients with the higher stages of CD were less likely to have bicuspid AVs than those with no CD. Valvular hemodynamic status was similar among stages (Table 2).

TABLE 3 Factors Associated With CD Stage >1 (Logistic Regression)

	Univariable			Multivariable	
	OR (95% CI)	*P* Value	AUC (SE)	OR (95% CI)	*P* Value
Age, per year	1.03 (1.03-1.04)	<0.001	0.61 (0.006)	1.03 (1.02-1.03)	<0.001
Female	0.88 (0.81-0.96)	0.003	0.52 (0.005)	0.89 (0.81-0.98)	0.02
Body mass index, per kg/m^2	1.00 (1.00-1.01)	0.94			
Systolic blood pressure, per mm Hg	1.00 (1.00-1.01)	0.005		1.00 (1.00-1.01)	0.003
Hypertension	1.48 (1.35-1.62)	<0.001	0.54 (0.005)	0.96 (0.86-1.07)	0.44
Diabetes mellitus	1.18 (1.07-1.29)	<0.001	0.52 (0.005)	0.88 (0.79-0.97)	0.01
Ischemic heart disease	1.75 (1.61-1.91)	<0.001	0.57 (0.005)	1.24 (1.12-1.37)	<0.001
Heart failure	3.14 (2.81-3.50)	<0.001	0.60 (0.004)	2.67 (2.36-3.01)	<0.001
Peripheral arterial disease	1.25 (1.14-1.36)	<0.001	0.53 (0.005)	1.09 (0.99-1.21)	0.08
Stroke	1.27 (1.11-1.46)	0.001	0.51 (0.003)	0.98 (0.84-1.14)	0.76
Chronic kidney disease	2.08 (1.88-2.30)	<0.001	0.57 (0.004)	1.81 (1.62-2.04)	<0.001
Chronic pulmonary disease	1.18 (1.05-1.34)	0.006	0.51 (0.004)	0.89 (0.78-1.02)	0.09
Bicuspid aortic valve	0.32 (0.28-0.36)	<0.001	0.56 (0.004)	0.50 (0.43-0.58)	<0.001
V_{max}, per m/s	0.81 (0.70-0.95)	0.008	0.52 (0.006)	0.90 (0.76-1.06)	0.19
Aortic valve area, per cm^2	1.07 (0.99-1.16)	0.09	0.51 (0.006)		
Systemic arterial compliance, per mL/mm Hg·m^2	0.72 (0.64-0.82)	<0.001	0.54 (0.006)	1.35 (1.13-1.62)	0.001

AUC = area under the receiver-operating characteristic curve; V_{max} = peak aortic valve velocity; other abbreviation as in Table 1.

FIGURE 1 CD as a Function of V_{max} and Number of Comorbidities



Cardiac damage (CD) stage was similar irrespective of peak aortic jet velocity (V_{max}) (top), but the prevalence of CD increased with increasing number of comorbidities (bottom).

Multiple variables were univariately associated with CD. Discrimination rates were modest, and age (AUC = 0.61), chronic kidney disease, and ischemic heart disease (AUC = 0.57 for both) were the best to identify patients with CD stage >1 (Table 3). Although V_{max} was univariately associated with CD stage >1, this association was abolished in the multivariable analysis adjusted for comorbidities. However, forcing V_{max} and AV area into the final multivariate model including age, sex, ischemic heart disease, heart failure, chronic kidney disease, and bicuspid AV provided statistically significant but little information (AUC from 0.686 to 0.688; $P = 0.017$).

In line with this, CD was not worse with increasing ranges of V_{max} (Figure 1). In contrast, the number of comorbidities resulted in a clinically significant increment in the proportion of patients with higher CD stages. Depending on the presence of 0, 1, 2, 3, 4, or 5 or more comorbidities, the proportion of those with no CD (stage 0) were progressively lower, at 33%, 29%, 22%, 16%, 12%, and 7%, respectively (Table 4, Figure 1). The associations of clinical and echocardiographic variables with CD were further explored using linear regression analysis and logistic regression analysis for CD stage >2, with consistent findings (Supplemental Tables 2 and 3). Sensitivity analysis of our models after excluding patients with diagnoses of heart failure showed a similar association between comorbidities and CD stage.

Using the modified CD model (Tastet et al[9]), rates of CD were even higher; only 16% of subjects were in stage 0. Rates of CD for those with V_{max} ≥2.5 m/s were similar irrespective of the model chosen (Supplemental Table 4). We repeated all analyses including regression models defining CD according to Tastet et al,[9] with consistent findings.

All patients underwent subsequent echocardiography a median of 1.3 years (Q1-Q3: 0.8-2.4 years) after baseline evaluation. Of 3,514 patients with baseline CD stages 0 and 1, 1,115 (32%) subsequently developed stage 2 CD, 118 (3%) stage 3 CD, and 64 (2%) stage 4 CD. Factors associated with progression to CD stage >1 are shown in Table 5.

OUTCOMES. During a median follow-up period of 4.7 years (Q1-Q3: 2.7-7.5 years), 3,332 patients died, and 1,203 underwent AVR. Five-year mortality increased depending on CD stage (Figure 2). The association between CD stage and mortality persisted after adjusting for comorbidities (Supplemental Table 5).

DISCUSSION

In this large cohort study of patients with mild AS: 1) CD was a common manifestation even in the earliest stages of AS; 2) CD was highly associated with comorbidities, and the association between CD and valvular hemodynamic status was abolished when adjusted for comorbidities; and 3) the degree of CD in patients with mild AS was associated with all-cause mortality.

AS is a progressive disease that shares many risk factors with atherosclerosis. With currently no preventive therapies, patients are followed until they progress to develop severe AS and symptoms become manifest, warranting AVR. This approach was implemented because AS was previously considered a benign entity prior to its progression to a symptomatic stage.[18] A growing body of evidence, however, has challenged this view, as it has become evident that the development of symptoms is frequently associated with LV hypertrophy,[19] myocardial fibrosis,[20] and alterations in LV function[2] that may be irreversible and associated with worse outcomes.[8] Thus, attention has been directed toward identifying markers in AS that could identify patients who likely

TABLE 4 Characteristics and CD Stage According to the Number of Comorbidities

		Number of Comorbidities						
	All	0 (n = 979)	1 (n = 1,839)	2 (n = 2,240)	3 (n = 1,882)	4 (n = 1,334)	≥5 (n = 1,337)	*P* Value
Female	3,786 (39)	483 (49)	807 (44)	882 (39)	671 (36)	478 (36)	465 (35)	<0.001
Age, y	71 ± 12	65 ± 14	69 ± 12	72 ± 11	73 ± 11	73 ± 11	74 ± 10	<0.001
V_{max}, m/s	2.31 ± 0.27	2.32 ± 0.27	2.31 ± 0.27	2.32 ± 0.27	2.30 ± 0.27	2.31 ± 0.28	2.29 ± 0.26	0.04
Mean gradient, mm Hg	11.9 ± 3.5	11.9 ± 3.3	11.8 ± 3.4	11.9 ± 3.7	11.8 ± 3.5	12.0 ± 3.8	11.7 ± 3.5	0.45
Aortic valve area, cm^2	2.00 ± 0.52	2.01 ± 0.54	2.02 ± 0.53	2.02 ± 0.53	2.02 ± 0.53	2.02 ± 0.52	1.95 ± 0.49	0.01
LVEF, %	61 ± 10	64 ± 6	63 ± 8	62 ± 9	61 ± 9	59 ± 12	57 ± 13	<0.001
Stroke volume index, mL/m^2	49 ± 11	51 ± 11	50 ± 11	50 ± 12	49 ± 11	48 ± 11	47 ± 11	<0.001
LV mass index, g/m^2	104 ± 29	92 ± 22	98 ± 25	103 ± 28	106 ± 29	111 ± 33	117 ± 32	<0.001
Medial E/e′ ratio	15 ± 7	13 ± 6	14 ± 6	14 ± 7	16 ± 7	17 ± 8	19 ± 9	<0.001
LAVi, mL/m^2	39 ± 15	36 ± 16	37 ± 13	38 ± 14	40 ± 13	42 ± 16	44 ± 16	<0.001
TAPSE, mm	22 ± 5	23 ± 5	23 ± 5	22 ± 5	21 ± 5	21 ± 6	20 ± 6	<0.001
CD								<0.001
Normal (stage 0)	1,901 (20)	326 (33)	539 (29)	488 (22)	298 (16)	158 (12)	92 (7)	
Stage 1	1,613 (17)	170 (17)	313 (17)	394 (18)	338 (18)	206 (16)	192 (14)	
Stage 2	4,843 (50)	412 (42)	827 (45)	1,107 (49)	1,011 (54)	736 (55)	750 (56)	
Stage 3	891 (9)	57 (6)	118 (6)	186 (8)	160 (9)	161 (12)	209 (16)	
Stage 4	363 (4)	14 (1)	42 (2)	65 (3)	75 (4)	73 (6)	94 (7)	

Values are n (%) or mean ± SD.

LAVi = left atrial volume index; other abbreviations as in Tables 1 and 2.

would benefit from early AVR, moving the scope from focusing primarily on valvular hemodynamic status toward also incorporating a comprehensive evaluation of the myocardium.[21]

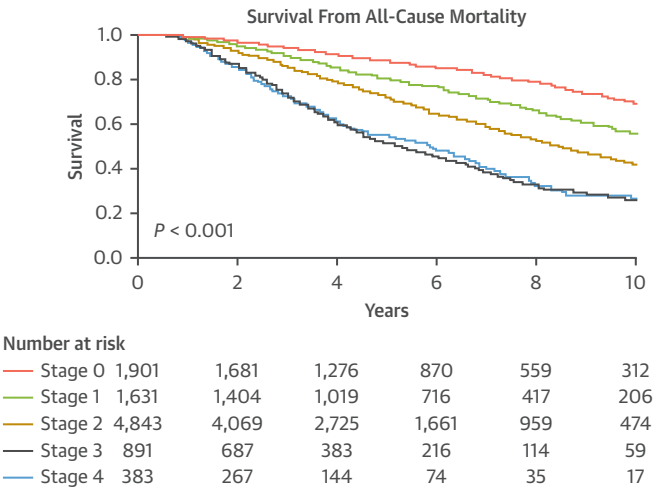
The CD classification, recently proposed by Genereux et al,[7] has been suggested as such a tool. It allows the grading of severity of cardiac dysfunction on the basis of the extent of CD, including no damage, LV

TABLE 5 Factors Associated With Development of CD Stage >1 (Logistic Regression) in 3,514 Patients With Baseline CD Stage 0 or 1

	Univariable		Multivariable	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.03 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Time between echocardiographic examinations	1.11 (1.07-1.15)	<0.001	1.14 (1.10-1.18)	<0.001
Female	0.97 (0.85-1.12)	0.69		
Body mass index	1.01 (1.00-1.02)	0.31		
Systolic blood pressure	1.01 (1.00-1.01)	<0.001		
Hypertension	1.63 (1.40-1.89)	<0.001	1.32 (1.13-1.56)	0.001
Diabetes mellitus	1.22 (1.05-1.42)	0.009		
Ischemic heart disease	1.27 (1.10-1.46)	0.001		
Heart failure	1.65 (1.36-2.00)	<0.001	1.55 (1.26-1.91)	<0.001
Peripheral arterial disease	1.18 (1.02-1.37)	0.026		
Stroke	1.18 (0.94-1.50)	0.15		
Chronic kidney disease	1.47 (1.23-1.74)	<0.001	1.30 (1.08-1.57)	0.006
Chronic pulmonary disease	1.23 (1.01-1.50)	0.04		
Bicuspid aortic valve	0.44 (0.36-0.54)	<0.001	0.68 (0.54-0.85)	0.001
V_{max}	0.87 (0.68-1.12)	0.29		
Aortic valve area	1.21 (1.05-1.39)	0.007	1.37 (1.18-1.59)	<0.001
Systemic arterial compliance	0.73 (0.59-0.91)	0.005		

V_{max} = peak aortic valve velocity; other abbreviation as in Table 1.

FIGURE 2 Kaplan-Meier Survival Curves Show the Impact of CD Stage on All-Cause Mortality



With increasing CD stage, survival decreased. Abbreviation as in Figure 1.

dysfunction, LA or mitral valve dysfunction, damage to pulmonary vasculature or the tricuspid valve, and finally right ventricular dysfunction in a 5-stage score. In the original paper, which was based on PARTNER (Placement of Aortic Transcatheter Valve) 2 trial data that included intermediate-risk patients with severe symptomatic AS undergoing AVR, only 3% of the total cohort had no signs of CD (stage 0) prior to their AVR, and this risk score provided prognostic information after AVR.[7] The high rate of CD has since been corroborated by Vollema et al[22] in 1,189 patients with severe AS. However, these studies solely included symptomatic patients, and no causes of CD other than AS were sought.

The latter is important, as it is well established that the development and progression of AS are associated with atherosclerotic risk factors.[23-26] Consequently, comorbidities that may contribute to CD are commonly prevalent among patients with AS, irrespective of AS severity. Indeed, in the PARTNER 2 trial and the study of Vollema et al,[22] patients presented with multiple comorbidities. In line with this, we demonstrated similarly high rates of diabetes, hypertension, and ischemic heart disease in our cohort with mild AS; only 10% presented without comorbidities. Recently, Tastet et al[9] demonstrated that CD also was common in patients with at least moderate AS and suggested that this risk score might help identify patients who could benefit from early surgery. In this study of 735 patients with asymptomatic AS and AV area <1.5 cm^2 and excluding those with LVEFs <50%, only 12 % showed no signs of CD, while nearly two-thirds had CD stage 2 or higher. However, this study used different thresholds to grade CD, hence making comparison with the previous studies[7,22] difficult.

It is thus reassuring that we found similar CD rates for the models of both Genereux et al[7] and Tastet et al,[9] but it is surprising that the rates of CD in patients with mild AS were similar to those in patients with moderate to severe AS, with more than 60% being in stage 2 or higher. This finding has important implications, as it is unlikely that mild alteration in valvular hemodynamic status contributed significantly to the CD process. Indeed, we found no association between CD and AS severity within the range of mild AS but observed that the degree of CD was instead associated with the number of coexisting comorbidities. This implies that comorbidities such as hypertension, diabetes, and ischemic heart disease, rather than mild alteration in valvular hemodynamic status, are major contributors to CD in the early stages of AS. It is noteworthy that among patients with mild AS, only 13% had advanced stages of CD (stages 3 and 4), whereas in the original study by Genereux et al, these higher stages were present in 33% of those with severe AS. This may suggest that although comorbidities contribute to the earlier stages of CD, AS severity plays an important role later. In multivariable analysis of factors related to new development of CD, comorbidities but not V_{max} were contributors (Table 5). It may be that V_{max} was not correlated because the range of V_{max} in this study was limited by the study design.

In line with previous publications,[7,9,22] we demonstrated that CD stage was highly associated with mortality even in those with early AS and when adjusted for comorbidities. We thus believe that although the CD staging system provides great prognostic information, it should not be used in isolation to determine the ideal timing for AVR but rather in conjunction with other clinical and echocardiographic data on AS severity.

STUDY LIMITATIONS. This was a retrospective review of prospectively gathered data from a single institution, and its accuracy depended on the availability of information within the medical records. As our institution is a tertiary referral center, patients' comorbidities may have been more prevalent, and it is possible that we have overestimated the risk for CD. The requirement for follow-up echocardiography may have also favored a cohort with more comorbidities and CD. The numerous statistical tests may have resulted in type I error. We included only patients with mild AS, limiting the ability to study the

association between all ranges of AS severity and CD. Information on the cause of death was not available, although it has been suggested that all-cause mortality is a more robust parameter than cause-specific death.[27]

CONCLUSIONS

CD was commonly present in patients with mild AS and was associated with worse outcomes. Among patients with mild AS, we found no relationship between the degree of CD and AS severity but demonstrated that CD was highly associated with AS-related comorbidities.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Dahl was supported by a grant from Odense University Hospital. The study was supported by a grant from the Mayo Clinic Department of Cardiovascular Medicine. Dr Pellikka is supported as the Betty Knight Scripps-George M. Gura, Jr., MD, Professor of Cardiovascular Diseases Clinical Research and receives research support from Edwards Lifesciences, with money paid to her institution. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with mild AS, CD as assessed by echocardiography was highly prevalent and was associated with AS-related comorbidities rather than AS severity. The risk for mortality increased in proportion to the extent of CD.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine if treatment of underlying AS-related comorbidities may reduce the degree of CD in the early stages of AS and improve outcome.

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KEY WORDS aortic stenosis, cardiac damage, echocardiography, left ventricular remodeling, valve disease

APPENDIX For supplemental tables and a figure, please see the online version of this paper.