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ORIGINAL RESEARCH

Prevalence and Outcomes of Patients With Discordant High-Gradient Aortic Stenosis

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ABSTRACT

BACKGROUND Conflicting prognostic results have been reported in patients with discordant high-gradient aortic stenosis ([DHG-AS] the combination of a mean pressure gradient ≥40 mm Hg and an aortic valve area [AVA] >1 cm^2). Moreover, existing studies only included selected patients without concomitant aortic regurgitation.

OBJECTIVES The authors assessed the prevalence and survival of patients presenting with DHG-AS in an unselected group of consecutive patients presenting to the echocardiography laboratory of a tertiary referral center.

METHODS A total of 3,547 adult patients with AVA ≤1.5 cm^2 and peak aortic jet velocity ≥2.5 m/s or mean gradient ≥25 mm Hg who presented between 2005 and 2015 were included. Baseline clinical and echocardiographic data, and, when available, aortic valve calcium (AVC) score were collected in an institutional database, with subsequent retrospective analysis. The primary endpoint was all-cause mortality during follow-up.

RESULTS DHG-AS was observed in 163 patients (11.6% of patients with a high gradient). After adjustment for potential confounders, overall mortality rate of patients with DHG-AS was similar to that of patients with concordant severe aortic stenosis (HR: 0.98 [95% CI: 0.66-1.44]; $P = 0.91$), and patients with discordant low-gradient aortic stenosis (HR: 0.85 [95% CI: 0.58-1.26]; $P = 0.42$), and higher than concordant moderate aortic stenosis (HR: 0.54 [95% CI: 0.36-0.81]; $P = 0.003$). After adjustment for aortic velocities, aortic regurgitation had no significant impact on survival. AVC was higher than in patients with concordant moderate aortic stenosis and discordant low-gradient aortic stenosis, and not significantly different from that of concordant severe aortic stenosis.

CONCLUSIONS DHG-AS is not uncommon. Whereas AVA >1.0 cm^2 is often seen as moderate aortic stenosis, a high-pressure gradient conveys a poor prognosis, whatever the AVA and the severity of concomitant aortic regurgitation. (J Am Coll Cardiol 2024;83:1109-1119) © 2024 by the American College of Cardiology Foundation.

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Severe aortic stenosis (AS) is defined as the combination of a peak aortic jet velocity of ≥4 m/s or a mean pressure gradient ≥40 mm Hg, and an aortic valve area (AVA) of ≤1.0 cm^2.[1,2] However, discordance among these parameters is common, even in patients with normal left ventricular ejection fraction (LVEF) and flow.[3,4] Discordance may present as low gradient when the mean gradient

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AU = arbitrary units

AVA = aortic valve area

AVC = aortic valve calcium

BSA = body surface area

CMod-AS = concordant moderate aortic stenosis

CSev-AS = concordant severe aortic stenosis

DHG-AS = discordant high-gradient aortic stenosis

DLG-AS = discordant low-gradient aortic stenosis

LV = left ventricular

LVEF = left ventricular ejection fraction

is <40 mm Hg and the AVA is <1.0 cm^2 or as high gradient when the mean gradient is ≥40 mm Hg and the AVA is ≥1.0 cm^2. Although discordant low-gradient aortic stenosis (DLG-AS) has been extensively studied, there is limited literature on the management and outcomes of patients with discordant high-gradient aortic stenosis (DHG-AS).[5-7] Divergent prognostic outcomes have been reported in patients with DHG-AS, with some showing better and others worse outcomes than for patients with concordant severe AS (CSev-AS).[5-7] In addition, existing studies have included a relatively small number of selected patients with DHG-AS and preserved LVEF and without concomitant aortic regurgitation or another valve disease.

In this study, we assessed the prevalence, clinical profile, management, and survival of patients with DHG-AS among unselected consecutive patients presenting to the echocardiography laboratory of a tertiary referral center.

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METHODS

PATIENT POPULATION. All consecutive adult patients with at least moderate AS (AVA ≤1.5 cm^2 and peak velocity ≥2.5 m/s or mean gradient ≥25 mm Hg) who underwent comprehensive transthoracic Doppler echocardiography imaging at rest at the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ) between 2005 and 2015 were included. Patients with reversible high flow status (severe anemia [hemoglobin <80 g/L], hyperthyroidism, arteriovenous shunts) and patients with discrete subaortic stenosis were excluded from the study. Patients receiving dobutamine, those with transesophageal echocardiography as the only available test, those with an incomplete echocardiographic study, and those who had previously had a valvular intervention were also excluded. All clinical and echocardiographic data were prospectively collected in an institutional database, with subsequent retrospective analysis. The study was approved by the ethics committee of the IUCPQ who waived the need for written consent because of the observational nature of the study.

CLINICAL DATA. Baseline clinical data included age, sex, body surface area (BSA), body mass index, diagnosis of hypertension (patients on antihypertensive medications or with known but untreated hypertension [blood pressure ≥140/90 mm Hg]), diabetes (patients on oral hypoglycemic or insulin medications or, in the absence of such medications, with a fasting glucose ≥7 mmol/L), hyperlipidemia (patients on lipid-lowering medication or, in the absence of such medication, with documented plasma low-density lipoprotein cholesterol ≥3.5 mmol/L), coronary artery disease (history of myocardial infarction, significant coronary artery stenosis [ie, >50%] on coronary angiography, and/or regional wall motion abnormality on echocardiogram), chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), and chronic obstructive pulmonary disease. Patients were considered symptomatic at baseline if they had dyspnea of NYHA functional class ≥II, angina, presyncope, or syncope deemed to be related to AS.

ECHOCARDIOGRAPHIC DATA. LVEF was calculated using the biplane Simpson method or by the visual method when Simpson was not possible. Left ventricular (LV) stroke volume was calculated using the LV outflow tract diameter (measured at the insertion of the aortic valve leaflets) and velocity time integral, and then indexed to BSA (stroke volume index). AS severity was assessed using evaluation of peak velocity, the mean gradient calculated using the simplified Bernoulli equation, and the AVA calculated using the continuity equation.

Patients were divided into 4 hemodynamic groups according to different AVA- and mean gradient-based patterns as follows:

- Concordant moderate aortic stenosis (CMod-AS): mean gradient <40 mm Hg and AVA >1.0 cm^2.
- Concordant severe aortic stenosis (CSev-AS): mean gradient ≥40 mm Hg and AVA ≤1.0 cm^2.
- Discordant high-gradient aortic stenosis (DHG-AS): mean gradient ≥40 mm Hg and AVA >1.0 cm^2.
- Discordant low-gradient aortic stenosis (DLG-AS): mean gradient <40 mm Hg and AVA ≤1.0 cm^2.

AORTIC VALVE CALCIUM SCORE. A subset of 716 patients had noncontrast electrocardiogram-gated cardiac computed tomography examinations as part of their clinical evaluation. The aortic valve calcium (AVC) score was calculated in this subset of patients. Calcification was defined as at least 4 contiguous pixels with a density of 130 Hounsfield units or greater using the method described by Agatston et al[8] and is reported in arbitrary units (AU). The AVC was calculated using commercially available software (Aquarius, TeraRecon) and then divided by sex-specific thresholds (1,200 AU in women and 2,000 AU in men) to calculate the AVC ratio. An AVC ratio ≥1 indicates severe AS in men and women.[9]

STUDY ENDPOINTS. The primary endpoint was all-cause mortality during follow-up. The end of study was December 31, 2019. Mortality data were confirmed for all patients from a provincial government statistical institution (Institut de la Statistique du Québec); thus, follow-up was 100%. To optimize the interrogation of this database, a list with multiple demographic data (including first and last names, dates of birth, and social security numbers) and a delay of 1 year between interrogation and closing follow-up dates were used. The secondary endpoint was the composite of all-cause mortality or aortic valve replacement, either surgical or transcatheter, with or without concomitant interventions. Information regarding aortic valve replacement was retrieved retrospectively from the patients' charts.

STATISTICAL ANALYSIS. Continuous data were tested for normality of distribution and homogeneity of variance with the Shapiro-Wilk and Levene tests, respectively. Continuous variables with normal distribution are presented as mean ± SD and were compared between groups using a 1-way analysis of variance with Sidak post hoc analyses. Continuous variables with non-normal distribution are presented as median (Q1-Q3) and were compared between groups using a Kruskal-Wallis test with Dunn post hoc analyses. Categorical variables are expressed as number (%) and were compared using chi-square or Fisher exact tests, as appropriate.

Survival analyses were performed using Cox regression analyses adjusted for clinically relevant variables and variables associated ($P < 0.05$) with mortality in univariate analysis. The complete follow-up time was calculated between the echocardiographic examination date until the date of death or until the end-of-the-study date (ie, December 31, 2019). Patients alive at that date were censored. The variables used for Cox regression adjustment were age, sex, BSA, NYHA functional class, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, coronary artery disease, kidney disease, hemoglobin, mitral regurgitation, aortic regurgitation, stroke volume index, and LVEF. Aortic valve replacement was used as a time-dependent variable in the overall survival analysis.

A P value <0.05 was considered statistically significant. All analyses were performed using STATA 14.2 (StataCorp).

RESULTS

BASELINE CHARACTERISTICS AND CLINICAL PROFILE. A total of 3,547 patients were included. DHG-AS was observed in 163 patients (4.6% of the whole study population and 11.6% of the patients with high-gradient AS): 1,131 patients (31.9%) had DLG-AS, 1,010 (28.5%) had CMod-AS, and 1,243 (35.0%), had CSev-AS.

The baseline characteristics of the different groups are shown in **Table 1**. Compared with patients with CMod-AS, patients with DHG-AS had similar age and sex distribution, and had a similar comorbidity profile, except that diabetes was less frequent. Patients with DHG-AS were more often symptomatic than CMod-AS patients. On echocardiography, DHG-AS patients had a lower AVA than CMod-AS patients, but also had a lower Doppler velocity index, a larger stroke volume index, and a greater LVEF. Aortic regurgitation was more prevalent in the DHG-AS group, as was bicuspid aortic valve, but there was no significant difference in the prevalence of mitral regurgitation.

Compared with patients with CSev-AS, patients with DHG-AS were younger, were more often men, and had a lower prevalence of kidney failure; the prevalence of symptoms in the 2 groups was similar. On echocardiography, patients with DHG-AS had, as expected, a larger AVA. In addition, LV outflow tract diameter, stroke volume index, and LVEF were larger; aortic valve velocities and mean gradients were slightly lower. The prevalence of mitral regurgitation was similar in the 2 groups; grade 2 aortic regurgitation was less frequent but grade 3 to 4 was more prevalent, as was bicuspid aortic valve.

Compared with patients with DLG-AS, patients with DHG-AS were younger, were more often men, and had fewer comorbidities; the prevalence of symptoms was similar. On echocardiography, the AVA, aortic velocities, and gradients were, by definition, larger. The LV outflow tract diameter, stroke volume index, Doppler velocity index, and LVEF were larger in the patients with DHG-AS. Mitral regurgitation was less prevalent, whereas aortic regurgitation ≥grade 2 and bicuspid aortic valve were more prevalent.

CLINICAL OUTCOMES. During a median follow-up of 7.64 years (IQR: 7.31-8.01 years), there were 946 deaths and 2,399 aortic valve replacements.

The impact of hemodynamic pattern on overall mortality and on the combined endpoint of mortality and aortic valve replacement is shown in the **Central Illustration**, **Figure 1**, and Supplemental Figure 1. After adjustment for potential confounders, survival of patients with DHG-AS was insignificantly worse than that of patients with CMod-AS and with DLG-AS, and was similar to that of patients with CSev-AS

TABLE 1 Characteristics of the Study Cohort

	DHG-AS (n = 163; 4.6%)	CMod-AS (n = 1,010; 28.5%)	CSev-AS (n = 1,243; 35.0%)	DLG-AS (n = 1,131; 31.9%)	*P* Value
Age, y	69.5 ± 12.6	69.5 ± 14.0	72.8 ± 11.0[a]	76.2 ± 10.8[a]	<0.001
Men	117 (72)	710 (70)	776 (62)[a]	644 (57)[a]	<0.001
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2[a]	1.8 ± 0.2[a]	<0.001
Body mass index, kg/m^2	29.3 ± 5.9	29.0 ± 6.0	28.1 ± 5.9	27.4 ± 5.6[a]	<0.001
Hemoglobin, g/dL	135 (122-146)	132 (120-144)[a]	133 (120-143)	129 (119-140)[a]	<0.001
Hypertension	122 (75)	795 (79)	962 (78)	947 (84)[a]	<0.001
Diabetes	37 (23)	317 (31)[a]	353 (29)	384 (34)[a]	0.003
Coronary artery disease	76 (47)	527 (52)	591 (48)	694 (62)[a]	<0.001
Chronic pulmonary disease	29 (18)	166 (17)	206 (17)	198 (18)	0.88
Kidney failure	28 (17)	213 (21)	304 (25)[a]	361 (32)[a]	<0.001
Atrial fibrillation/flutter	53 (33)	320 (32)	321 (26)	432 (38)	<0.001
NYHA functional class					<0.001
1	27 (17)	412 (41)[a]	198 (16)	260 (23)	
2	93 (58)	492 (49)[a]	741 (60)	626 (56)	
3	39 (24)	99 (10)[a]	289 (23)	221 (20)	
4	2 (1)	4 (0)	11 (1)	16 (1)	
LVIDD, cm	4.7 ± 0.7	4.8 ± 0.7	4.6 ± 0.6	4.6 ± 0.7	<0.001
Left ventricular outflow tract diameter, cm	2.4 ± 0.3	2.3 ± 0.2[a]	2.2 ± 0.2[a]	2.1 ± 0.2[a]	<0.001
Aortic maximal velocity, cm/s	462.7 ± 52.9	299.9 ± 42.2[a]	477.0 ± 57.2[a]	345.6 ± 47.7[a]	<0.001
Mean aortic gradient, mm Hg	50.8 ± 10.5	20.0 ± 6.6[a]	56.2 ± 14.2[a]	27.7 ± 7.7[a]	<0.001
AVA, cm^2	1.26 ± 0.28	1.40 ± 0.43[a]	0.65 ± 0.16[a]	0.77 ± 0.15[a]	<0.001
AVA index, cm^2/m^2	0.67 ± 0.18	0.74 ± 0.24[a]	0.35 ± 0.09[a]	0.43 ± 0.09[a]	<0.001
Aortic valve area/height, cm^2/m	0.75 ± 0.18	0.83 ± 0.26[a]	0.39 ± 0.10[a]	0.47 ± 0.09[a]	<0.001
Stroke volume index, mL/m^2	69.74 ± 23.64[a]	46.76 ± 15.67[a]	39.51 ± 10.00[a]	33.48 ± 7.92[a]	<0.001
Doppler velocity index	0.28 ± 0.10	0.35 ± 0.10[a]	0.17 ± 0.04[a]	0.22 ± 0.05[a]	<0.001
Mitral regurgitation grade					<0.001
0	26 (16)	163 (16)	155 (12)	118 (10)[a]	
1	61 (37)	389 (39)	448 (36)	344 (30)[a]	
2	58 (36)	356 (35)	510 (41)	460 (41)[a]	
3	17 (10)	84 (8)	112 (9)	169 (15)[a]	
4	1 (1)	18 (2)	18 (1)	40 (4)[a]	
Mitral regurgitation ≥2	76 (47)	458 (45)	640 (51)	669 (59)[a]	<0.001
Aortic regurgitation grade					<0.001
0	30 (18)	333 (33)[a]	252 (20)	317 (28)[a]	
1	39 (24)	189 (19)[a]	285 (23)	278 (25)[a]	
2	61 (37)	349 (35)[a]	561 (45)[a]	434 (38)[a]	
3	27 (17)	116 (11)[a]	135 (11)[a]	96 (9)[a]	
4	6 (4)	23 (2)[a]	10 (1)[a]	6 (1)[a]	
Aortic regurgitation ≥2	94 (58)	488 (48)[a]	706 (57)	536 (47)[a]	<0.001
Bicuspid aortic valve, %	43 (26)	179 (18)[a]	201 (16)[a]	121 (11)[a]	<0001
LVEF, %	62.0 ± 8.1	59.5 ± 9.7[a]	59.0 ± 10.3[a]	55.1 ± 13.3[a]	<0.001
Patients with LVEF <50%	11 (7)	120 (12)[a]	160 (13)[a]	268 (24)[a]	<0.001

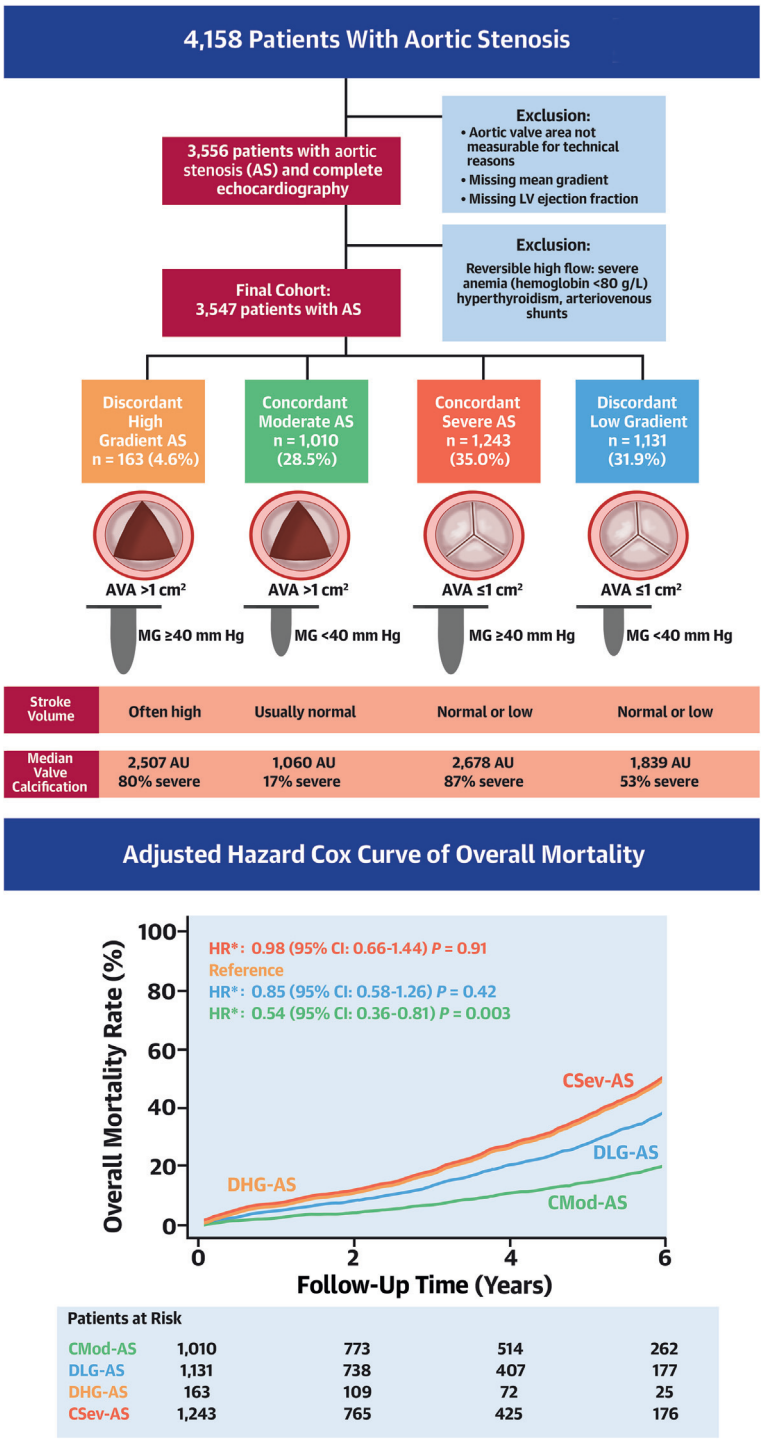
Values are mean ± SD, n (%), or median (Q1-Q3). [a]$P < 0.05$ vs DHG-AS.

AVA = aortic valve area; CMod-AS = concordant moderate aortic stenosis; CSev-AS = concordant severe aortic stenosis; DHG-AS = discordant high gradient aortic stenosis; DLG-AS = discordant low gradient aortic stenosis; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal end-diastolic diameter.

(Central Illustration). As compared with patients with DHG-AS, using the composite endpoint of mortality or aortic valve replacement, event-free survival was better in patients with DLG-AS and patients with CMod-AS, and worse in patients with CSev-AS (Figure 1).

AORTIC VALVE CALCIUM SCORING. Calcium scoring was performed in 716 patients, including 40 patients with DHG-AS. The hemodynamic data for this subset of patients are shown in Table 2 (clinical data in Supplemental Table 1). The AVA of patients with DHG-AS was 1.20 cm^2, a value close to that of patients with CMod-AS (1.27 cm^2), and, as expected, higher than that of patients with Csev-AS and DLG-AS (0.62 and 0.74 cm^2, respectively). The AVC ratio (Figure 2A) and the percentage of patients with an

CENTRAL ILLUSTRATION Study Design, Major Findings, and Adjusted Cox Curves of Mortality



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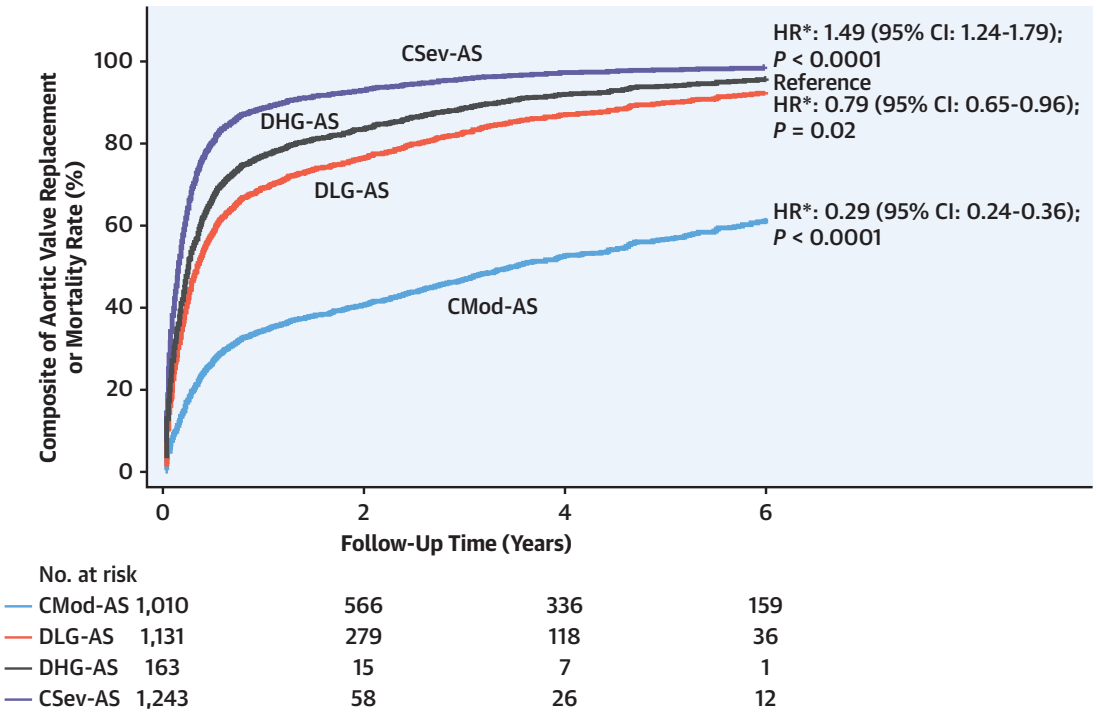
By design, patients with DHG-AS had an AVA >1.0 cm^2 and a mean pressure gradient (MG) ≥40 mm Hg. The stroke volume was higher than in all other AS groups, and aortic valve calcium score was similar to that of concordant severe AS. Mortality rate of patients with discordant high-gradient AS was similar to that of patients with CSev-AS, was nonsignificantly higher than that of DLG-AS, and was higher than that of CMod-AS. *Adjusted for age, sex, body surface area, NYHA functional class, atrial fibrillation, diabetes, chronic pulmonary disease, hypertension, hyperlipidemia, coronary artery disease, kidney disease, hemoglobin, mitral regurgitation, aortic regurgitation, stroke volume index, left ventricular ejection fraction, and aortic valve replacement as a time-dependent variable. AS = aortic stenosis; AVA = aortic valve area; CMod-AS = concordant moderate aortic stenosis; CSev-AS = concordant severe aortic stenosis; DHG-AS = discordant high-gradient aortic stenosis; DLG-AS = discordant low-gradient aortic stenosis.

FIGURE 1 Adjusted Cox Curves for the Composite Endpoint



No. at risk				
CMod-AS	1,010	566	336	159
DLG-AS	1,131	279	118	36
DHG-AS	163	15	7	1
CSev-AS	1,243	58	26	12

Adjusted Cox curves showing that the occurrence of the composite of aortic valve replacement or mortality of patients with DHG-AS was lower than that of patients with CSev-AS, and higher than both DLG-AS and CMod-AS. *Adjusted for age, sex, body surface area, NYHA functional class, atrial fibrillation, diabetes, chronic pulmonary disease, hypertension, hyperlipidemia, coronary artery disease, kidney disease, hemoglobin, mitral regurgitation, aortic regurgitation, stroke volume index, and left ventricular ejection fraction. CMod-AS = concordant moderate aortic stenosis; CSev-AS = concordant severe aortic stenosis; DHG-AS = discordant high-gradient aortic stenosis; DLG-AS = discordant low-gradient aortic stenosis.

AVC ratio ≥1 (ie, severe AS) (Figure 2B) were higher in patients with DHG-AS compared with those with CMod-AS and DLG-AS and similar to those with CSev-AS.

After adjustment, the presence of severe AVC (AVC ratio ≥1) was significantly associated with increased mortality (HR: 1.49 [95% CI: 1.11-2.01]; $P = 0.008$) (Figure 2C, univariate in Supplemental Figure 2), increased composite outcome of aortic valve replacement, or mortality (HR: 1.53 [95% CI: 1.25-1.87]; $P < 0.0001$) (Supplemental Figure 3).

After adjustment for age, the AVC ratio (as a continuous variable: HR: 2.58 [95% CI: 1.01-6.59]; $P = 0.048$) was independently associated with mortality in patients with DHG-AS.

IMPACT OF AORTIC REGURGITATION. The presence of aortic regurgitation grade ≥2 had no significant impact on survival in univariate or multivariate (Figure 3A) analysis in the whole cohort (both $P \geq 0.32$), or in the subgroup of patients with DHG-AS ($P \geq 0.61$). However, aortic regurgitation ≥2 was significantly associated with a higher incidence of aortic valve replacement, as survival free of aortic valve replacement was lower in patients with aortic regurgitation ≥2 in univariate (HR: 1.27 [95% CI: 1.17-1.38]; $P < 0.0001$) and multivariate (Figure 3B) analysis.

Using a group definition based on Doppler velocity index (DVI) ≤0.25 instead of AVA ≤1 cm^2, both the prevalence of DHG-AS (10%) and the prognosis were similar.

DISCUSSION

Our results show that DHG-AS: 1) is not an unusual hemodynamic presentation, being observed in >10% of patients with a high transaortic gradient (≥40 mm Hg); 2) is associated with a poor prognosis, similar to that of patients with CSev-AS; 3) is associated with high AVC values, close to those observed in

TABLE 2 Characteristics of the Subgroup of Patients in Whom a Calcium Score Was Available

	DHG-AS (n = 40)	CMod-AS (n = 74)	CSev-AS (n = 321)	DLG-AS (n = 281)	*P* Value
LVIDD, cm	4.8 ± 0.7	4.7 ± 0.9	4.5 ± 0.6	4.7 ± 0.7	0.002
Left ventricular outflow tract diameter, cm	2.5 ± 0.3	2.3 ± 0.2[a]	2.2 ± 0.2[a]	2.2 ± 0.2[a]	<0.001
Aortic maximal velocity, cm/s	453.9 ± 42.2	310.5 ± 43.3[a]	476.3 ± 56.8[a]	359.9 ± 45.8[a]	<0.001
Mean aortic gradient, mm Hg	50.3 ± 9.1	22.0 ± 6.8[a]	56.2 ± 14.5[a]	29.3 ± 7.3[a]	<0.001
AVA, cm^2	1.20 ± 0.18	1.27 ± 0.30	0.62 ± 0.16[a]	0.74 ± 0.16[a]	<0.001
AVA index, cm^2/m^2	0.65 ± 0.12	0.67 ± 0.17	0.34 ± 0.09[a]	0.41 ± 0.09[a]	<0.001
Aortic valve area/height, cm^2/m	0.72 ± 0.11	0.75 ± 0.17	0.37 ± 0.10[a]	0.44 ± 0.10[a]	<0.001
Stroke volume index, mL/m^2	69.06 ± 19.58	45.27 ± 12.24[a]	38.20 ± 9.99[a]	32.94 ± 8.59[a]	<0.001
Doppler velocity index	0.24 ± 0.07	0.30 ± 0.08[a]	0.17 ± 0.04[a]	0.20 ± 0.05[a]	<0.001
LVEF, %	60.9 ± 11.6	56.5 ± 13.6	57.4 ± 12.4	50.7 ± 16.0	<0.001
AVC score, AU	2,507 (1,885-3,650)	1,060 (670-2,155)[a]	2,678 (1,803-3,772)	1,839 (1,149-2,536)[a]	<0.001
AVC ratio >1	32 (80.0)	17 (23.0)[a]	278 (86.6)	149 (53.0)[a]	<0.001

Values are mean ± SD, median (Q1-Q3), or n (%). [a]$P < 0.05$ vs DHG-AS.
AVC = aortic valve calcium; other abbreviations as in Table 1.

patients with CSev-AS; and 4) often presents as mixed aortic valve disease, but concomitant aortic regurgitation has no further impact on mortality beyond increasing the pressure gradient.

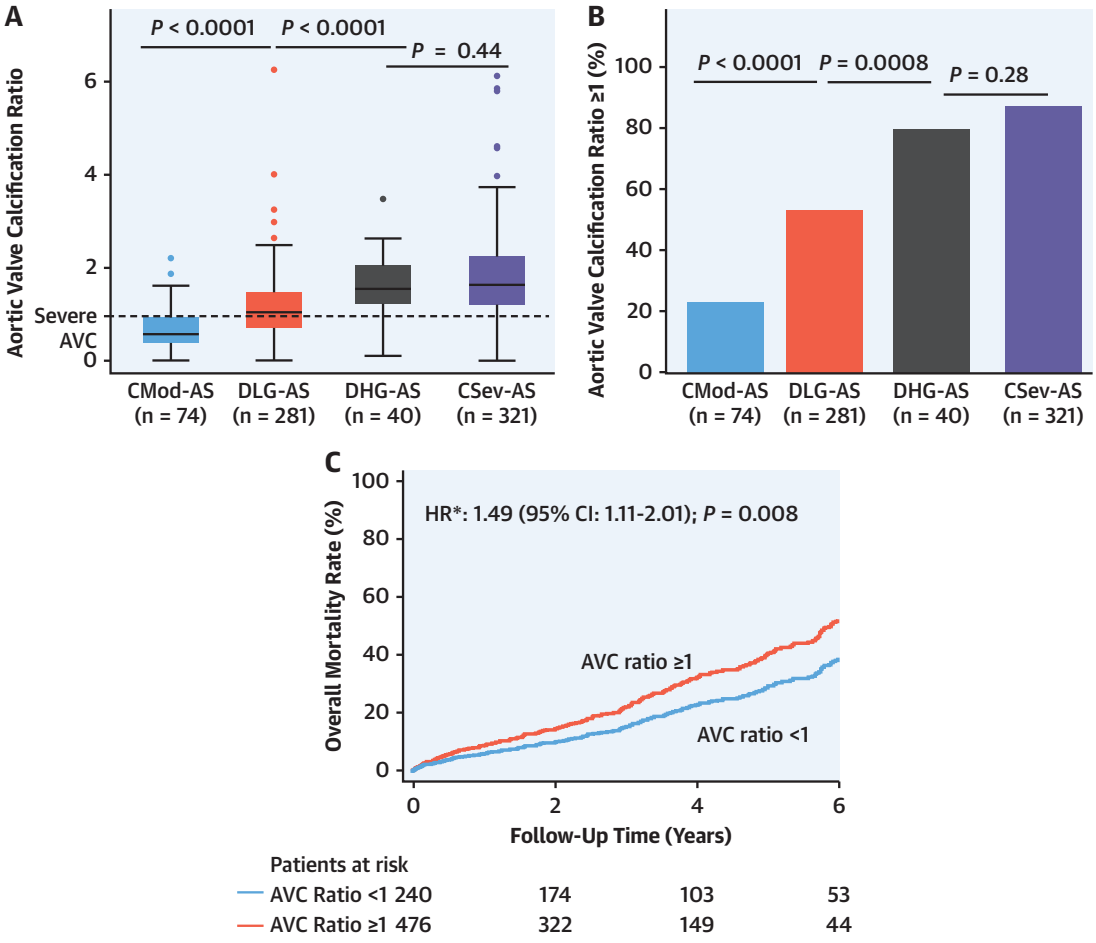
PREVALENCE. Our series, the largest to date of patients with DHG-AS, showed a prevalence of DHG-AS of 11.6% among patients with AS and a mean aortic pressure gradient ≥40 mm Hg in our tertiary care center. Of note, this prevalence exceeds that observed by Minners et al[4] and Bohbot et al[5] who, respectively, reported DHG-AS in only 2.1% and 3.5% of patients with a pressure gradient ≥40 mm Hg. The apparent discrepancy may result from different referral practices, but also most likely from inclusion of patients with aortic regurgitation, mitral regurgitation, and with reduced LVEF in the current study.

CLINICAL PROFILE. Symptom prevalence was similar in patients with DHG-AS, DLG-AS, and CSev-AS, and was significantly higher than in those with CMod-AS. Although the clinical profile of patients with DHG-AS was similar to that of patients with CMod-AS or CSev-AS, it differed from that of patients with DLG-AS in terms of younger age and fewer comorbidities. DHG-AS was associated with a large stroke volume index and, not unexpectedly, with a higher prevalence of grade ≥2 aortic regurgitation and a lower prevalence of grade ≥2 mitral regurgitation compared with patients with DLG-AS. Bicuspid aortic valve was more frequent in patients with DHG-AS than in all other hemodynamic groups.

OUTCOMES. Patients with DHG-AS had a poorer prognosis than did patients with CMod-AS and an overall survival similar to that of CSev-AS patients. Survival without aortic valve replacement was slightly better in patients with DHG-AS than in patients with CSev-AS. Discrepant results regarding the prognosis of patients with DHG-AS have been reported. In a study by Chew et al,[7] presence of DHG-AS did not independently predict mortality or hospitalization, whereas Vulesevic et al[6] observed an event-free survival in these patients that was similar to that of patients with CSev-AS. In a study by Bohbot et al,[5] survival of patients with DHG-AS was worse than that of those with CSev-AS, presumably because of a more conservative therapeutic approach including fewer or later aortic valve replacement surgeries. The current policy of our institution, which favors early aortic valve replacement in high-gradient AS, irrespective of AVA value, may have contributed to reduce such referral bias.

The observed poor outcome in the patients with DHG-AS is likely explained by the high-pressure gradient, which results in increased afterload,[10] the latter being directly related to the extent of cardiac damage,[11] regardless of the AVA. The high AVC score observed in these patients, which was not significantly different from that of CSev-AS patients, may also explain the poor prognosis. Indeed, the AVC is a powerful independent predictor of mortality in patients with AS,[12] and predicts faster AS progression.[13] A high calcium score has been reported previously, in a small series of patients with DHG-AS.[6] The extent of aortic valve calcification correlates with the AVA,[14] so it is surprising that although the AVA was consistent with moderate AS, the calcium score of patients with DHG-AS was close to that of CSev-AS patients, thus those with severe AS. These findings raise the hypothesis that high flow conditions (indeed, the stroke

FIGURE 2 Distribution of AVC Ratio and Impact on Overall Mortality

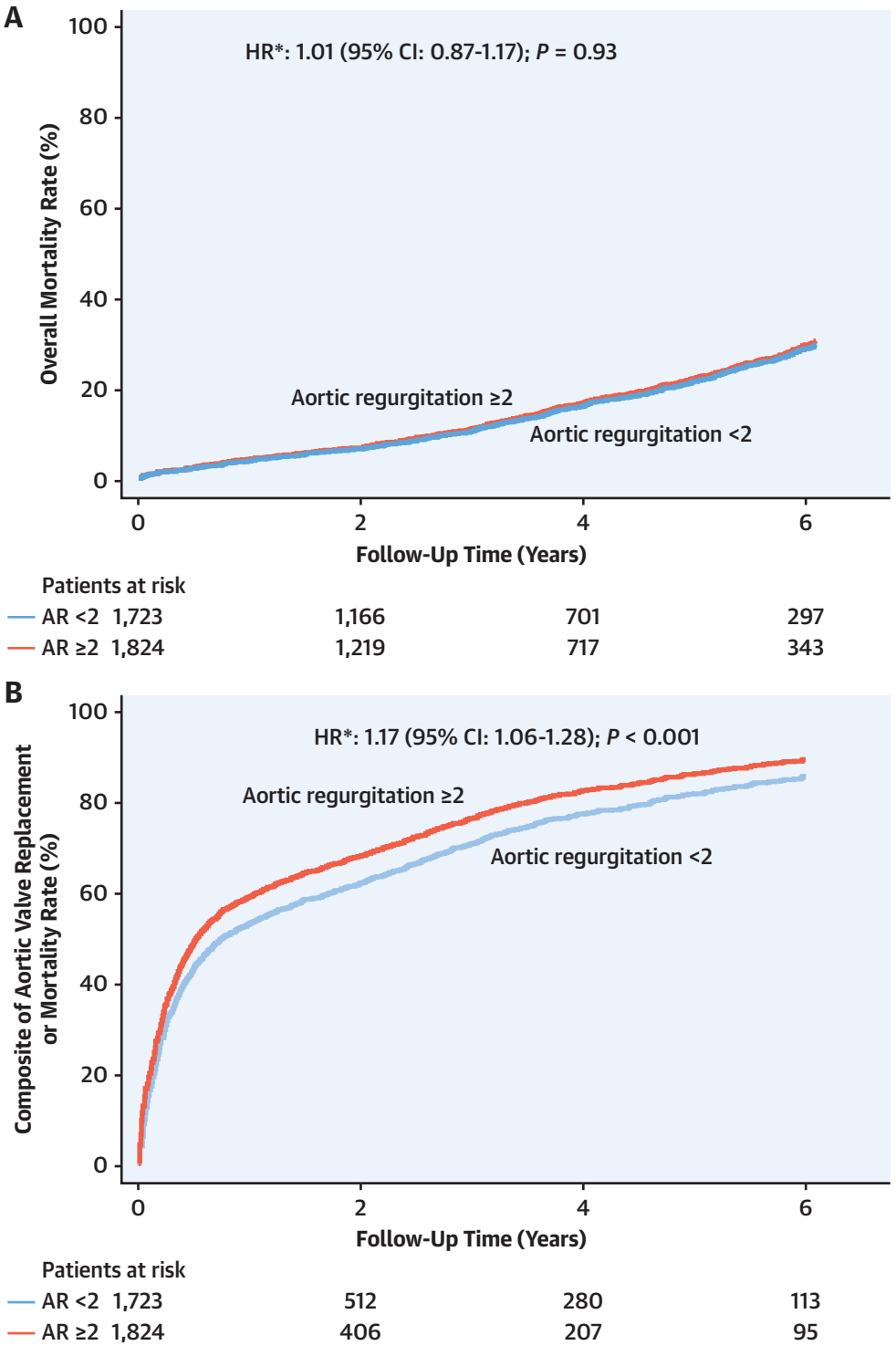


(A) Box plot distribution of AVC. (B) Percentage of severe AVC (ie, AVC ratio>1). (C) Adjusted Cox curves of mortality rate according to AVC severity. The AVC ratio (A) and the percentage of patients with an AVC ratio ≥1 (ie, severe AS [B]) were higher in patients with DHG-AS compared with those with CMod-AS and DLG-AS and were similar to those with CSev-AS. After adjustment, the presence of severe aortic valve calcification (AVC ratio ≥1) was significantly associated with increased mortality (C). *Adjusted for age, sex, NYHA functional class, atrial fibrillation, diabetes, chronic pulmonary disease, hypertension, coronary artery disease, kidney disease, hemoglobin, mitral regurgitation, aortic stenosis groups, left ventricular ejection fraction, and aortic valve replacement as a time-dependent variable. AVC = aortic valve calcification; other abbreviations as in Figure 1.

volume index was on average 1.8 times larger than that of patients with CSev-AS) may result in increased opening of the aortic valve, enabling speculation that some of these patients might have "pseudo-moderate AS," a condition in which AVA would be <1.0 cm^2 under normal flow conditions. Consistent with this hypothesis is the observation that some patients included in the TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study who had an AVA <1.0 cm^2 at a 250 mL/s flow rate experienced an increase in AVA (>1.0 cm^2) at higher flow rates induced by dobutamine infusion.[15] In addition, even a high calcium score does not preclude residual pliability,[16] especially in patients with a large LV outflow tract. However, for definitive proof of this concept, the effects of an acute reduction in transvalvular flow on AVA would need to be assessed, which is difficult to achieve safely in clinical practice.

Transaortic flow can be markedly elevated in patients with mixed aortic valve disease and may therefore result in DHG-AS.[17] Although our results confirm the previously reported poor prognosis of mixed aortic valve disease when transaortic velocities are elevated,[18-20] they do not suggest that aortic

FIGURE 3 Effect of Aortic Regurgitation on Mortality and/or Aortic Valve Replacement Rates



Adjusted Cox curves of mortality (A) and the composite of aortic valve replacement or mortality (B) in patients with aortic regurgitation grade <2 and ≥2 in the whole cohort. The presence of aortic regurgitation grade ≥2 had no significant impact on mortality (A), but was significantly associated with a higher rate of aortic valve replacement (B). *Adjusted for age, sex, body surface area, NYHA functional class, atrial fibrillation, diabetes, chronic pulmonary disease, hypertension, hyperlipidemia, coronary artery disease, kidney disease, hemoglobin, mitral regurgitation, aortic stenosis groups, stroke volume index, left ventricular ejection fraction, and aortic valve replacement as a time-dependent variable. Abbreviations as in Figure 1.

regurgitation has any additional negative effect on prognosis beyond that of increasing the transaortic pressure gradient.

STUDY LIMITATIONS. The first limitations are that this study is single-center and lacks a core lab. In addition, because of the retrospective data analysis, therapeutic management of patients may have been influenced by unmeasured factors. Thus, our observation of a poor prognosis of patients with DHG-AS does not necessarily mirror only valve-related prognosis; it may also have been influenced by the quality of follow-up visits, the referral policy, and the comorbidities even if survival curves were adjusted for the latter. Calcium scoring was only available in a limited subset of patients, so we cannot exclude a selection bias. However, the hemodynamic characteristics of the subgroup of patients who underwent calcium scoring was similar to those of the whole study population (Table 2). The LV outflow tract diameter was larger in patients with DHG-AS. Because of the lack of 3-dimensional measurements, one cannot rule out the possibility that the major axis of the elliptically shaped LV outflow tract was close to the actual transthoracic LV outflow tract measurement in these patients ("vertical-oval" shape), resulting in an AVA overestimation using the continuity equation. However, this is unlikely because one would then expect a lower Doppler velocity index, but this was larger than in patients with CSev-AS. In addition, a bicuspid aortic valve, which was more prevalent in the DHG-AS group, predicts a "horizontal-oval" rather than "vertical-oval" shape of the LV outflow tract.[21] AVA is dependent on body size, and the higher values observed in DHG-AS patients might reflect different body size. However, indexation to BSA has intrinsic limitations, including overestimation of AS severity in obese patients. Height indexation has been proposed to overcome this limitation.[22] As shown in Table 1, all these parameters were consistent with moderate AS in DHG-AS patients.

CONCLUSIONS

DHG-AS is not uncommon. After excluding reversible causes of a high gradient, DHG-AS was present in >10% of patients with an aortic pressure gradient >40 mm Hg in this series. Although an AVA ≥1.0 cm^2 is often seen as reassuring and mistaken as moderate AS, a high-pressure gradient conveys a poor prognosis, whatever the AVA and independent of the presence of concomitant aortic regurgitation. Whether the diagnosis of severe AS is achieved by area alone, by gradients alone, or both, pertains a poor prognosis compared with moderate AS. The observations of high stroke volume index, elevated calcium score, and poor prognosis in patients with DHG-AS support the hypothesis of "pseudo-moderate" AS, namely that an AVA ≥1.0 cm^2 under high flow conditions could actually be <1.0 cm^2 at standard flows, and thus consistent with severe concordant AS.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: AVA has prognostic value in patients with low-gradient aortic stenosis, but a high systolic pressure gradient (>40 mm Hg) is associated with reduced survival, irrespective of AVA or the severity of concomitant aortic regurgitation.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to determine the optimal timing and outcomes of intervention in patients with high-gradient aortic stenosis but valve area >1.0 cm^2.

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. ESC/EACTS Scientific Document Group. *Eur Heart J*. 2022;43:561–632.

2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:450–500.

3. Berthelot-Richer M, Pibarot P, Capoulade R, et al. Discordant grading of aortic stenosis severity: echocardiographic predictors of survival benefit associated with aortic valve replacement. *J Am Coll Cardiol Img*. 2016;9:797–805.

4. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J*. 2008;29:1043–1048.

5. Bohbot Y, Kubala M, Rusinaru D, Maréchaux S, Vanoverschelde JL, Tribouilloy C. Survival and management of patients with discordant high-gradient aortic stenosis: a propensity-matched study. *J Am Coll Cardiol Img*. 2021;14:1672–1674.

6. Vulesevic B, Burwash IG, Beauchesne LM, et al. Outcomes of patients with discordant high-gradient aortic valve stenosis. *J Am Coll Cardiol Img*. 2020;13:1636–1638.

7. Chew WS, Ho YJ, Ngiam JHN, et al. Clinical, echocardiographic and prognostic outcomes of patients with concordant and discordant high-gradient aortic stenosis in an Asian cohort. *Int J Cardiovasc Imaging*. 2002;38:1351–1360.

8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827–832.

9. Clavel MA, Messika-Zeitoun D, Pibarot P, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. *J Am Coll Cardiol*. 2013;62:2329–2338.

10. Zilberszac R, Gabriel H, Schemper M, et al. Outcome of combined stenotic and regurgitant aortic valve disease. *J Am Coll Cardiol*. 2013;61:1489–1495.

11. Généreux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38:3351–3358.

12. Pawade T, Sheth T, Guzzetti E, Dweck MR, Clavel MA. Why and how to measure aortic valve calcification in patients with aortic stenosis. *J Am Coll Cardiol Img*. 2019;12:1835–1848.

13. Tastet L, Shen M, Capoulade R, et al. Sex differences in the progression of aortic valve calcification and clinical outcomes - the PROGRESSA study. *J Am Coll Cardiol Img*. 2022;15:1349–1351.

14. Cueff C, Serfaty JM, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart*. 2011;97:721–726.

15. Blais C, Burwash IG, Mundigler G, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. *Circulation*. 2006;113:711–721.

16. Sato K, Wang TKM, Desai MY, et al. Physical and physiological effects of dobutamine stress echocardiography in low-gradient aortic stenosis. *Am J Physiol Heart Circ Physiol*. 2022;322(1):H94–H104.

17. Unger P, Clavel MA. Mixed aortic valve disease: a diagnostic challenge, a prognostic threat. *Structural Heart*. 2020;4:468–474.

18. Isaza N, Desai MY, Kapadia SR, et al. Long-term outcomes in patients with mixed aortic valve disease and preserved left ventricular ejection fraction. *J Am Heart Assoc*. 2020;9:e014591.

19. Egbe AC, Poterucha JT, Warnes CA. Mixed aortic valve disease: midterm outcome and predictors of adverse events. *Eur Heart J*. 2016;37:2671–2678.

20. Rashedi N, Popović ZB, Stewart WJ, Marwick T. Outcomes of asymptomatic adults with combined aortic stenosis and regurgitation. *J Am Soc Echocardiogr*. 2014;27:829–837.

21. Bhatia N, Dawn B, Siddiqui TS, Stoddard MF. Impact and predictors of noncircular left ventricular outflow tract shapes on estimating aortic stenosis severity by means of continuity equations. *Tex Heart Inst J*. 2015;42:16–24.

22. Tribouilloy C, Bohbot Y, Maréchaux S, et al. Outcome implication of aortic valve area normalized to body size in asymptomatic aortic stenosis. *Circ Cardiovasc Imaging*. 2016;9:e005121.

KEY WORDS aortic stenosis, discordant high gradient, echocardiography, outcomes

APPENDIX For supplemental figures and a table, please see the online version of this paper.