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Prevalence and Prognostic Implications of Discordant Grading and Flow-Gradient Patterns in Moderate Aortic Stenosis

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ABSTRACT

BACKGROUND The prognostic implications of discordant grading in severe aortic stenosis (AS) are well known. However, the prevalence of different flow-gradient patterns and their prognostic implications in moderate AS are unknown.

OBJECTIVES The purpose of this study was to investigate the occurrence and prognostic implications of different flow-gradient patterns in patients with moderate AS.

METHODS Patients with moderate AS (aortic valve area >1.0 and ≤1.5 cm^2) were identified and divided in 4 groups based on transvalvular mean gradient (MG), stroke volume index (SVi), and left ventricular ejection fraction (LVEF): concordant moderate AS (MG ≥20 mm Hg) and discordant moderate AS including 3 subgroups: normal-flow, low-gradient moderate AS (MG <20 mm Hg, SVi ≥35 mL/m^2, and LVEF ≥50%); "paradoxical" low-flow, low-gradient moderate AS (MG <20 mm Hg, SVi <35 mL/m^2, and LVEF ≥50%) and "classical" low-flow, low-gradient moderate AS (MG <20 mm Hg and LVEF <50%). The primary endpoint was all-cause mortality.

RESULTS Of 1,974 patients (age 73 ± 10 years, 51% men) with moderate AS, 788 (40%) had discordant grading, and these patients showed significantly higher mortality rates than patients with concordant moderate AS ($P < 0.001$). On multivariable analysis, "paradoxical" low-flow, low-gradient (HR: 1.458; 95% CI: 1.072-1.983; $P = 0.014$) and "classical" low-flow, low-gradient (HR: 1.710; 95% CI: 1.270-2.303; $P < 0.001$) patterns but not the normal-flow, low-gradient moderate AS pattern were independently associated with all-cause mortality.

CONCLUSIONS Discordant grading is frequently (40%) observed in patients with moderate AS. Low-flow, low-gradient patterns account for an important proportion of the discordant cases and are associated with increased mortality. These findings underline the need for better phenotyping patients with discordant moderate AS.
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According to the American and European guidelines for the management of patients with valvular heart disease, moderate aortic stenosis (AS) is defined by several hemodynamic criteria, including aortic valve area (AVA) (1.0-1.5 cm^2), transvalvular mean gradient (MG) (20-40 mm Hg), and peak aortic jet velocity (3.0-4.0 m/s).[1,2] Although the combination of these criteria is easy to use when concordant, patients often present with discordant echocardiographic parameters, having moderate AS based on AVA but less-severe AS based on transvalvular MG/peak aortic jet velocity. This situation raises uncertainty to the actual severity of AS and may have important prognostic, and potentially even therapeutic, implications.[3-6]

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To better categorize patients with low-gradient AS, current guidelines acknowledge 4 categories based on flow-gradient measurements of AVA, transvalvular MG, stroke volume index (SVi), and left ventricular ejection fraction (LVEF). These 4 categories are known as concordant moderate AS (ie, both AVA and gradient are moderate) and discordant moderate AS (moderate AVA but with mild gradient), including 3 subcategories: low-flow, low-gradient AS with reduced LVEF ("classical" low-flow, low-gradient AS); low-flow, low-gradient AS with preserved LVEF ("paradoxical" low-flow, low-gradient AS); and normal-flow, low-gradient AS.[2] This classification has been previously proposed and applied for severe AS and has been shown to improve the diagnosis and risk stratification of low-gradient severe AS.[7]

A discordance in the AVA vs pressure-gradient findings is best known in patients with reduced LVEF ("classical" low-flow, low-gradient AS), and this phenotype is associated with poor outcomes in patients with severe AS.[8,9] Patients with severe AS also often present with "paradoxical" low-flow, low-gradient AS, defined as a reduced stroke volume in the presence of preserved LVEF.[10] Previous studies demonstrated that these patients are at a more advanced stage of their disease and also have worse prognosis if treated medically rather than surgically.[11-13]

Although the occurrence and clinical implications of these different flow-gradient patterns have been extensively investigated in severe AS, this classification system has not been evaluated in patients with moderate AS. Accordingly, the current study aimed to investigate the prevalence and prognostic implications of different flow-gradient patterns among patients with moderate AS.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

LV = left ventricular/ventricle

LVEF = left ventricular ejection fraction

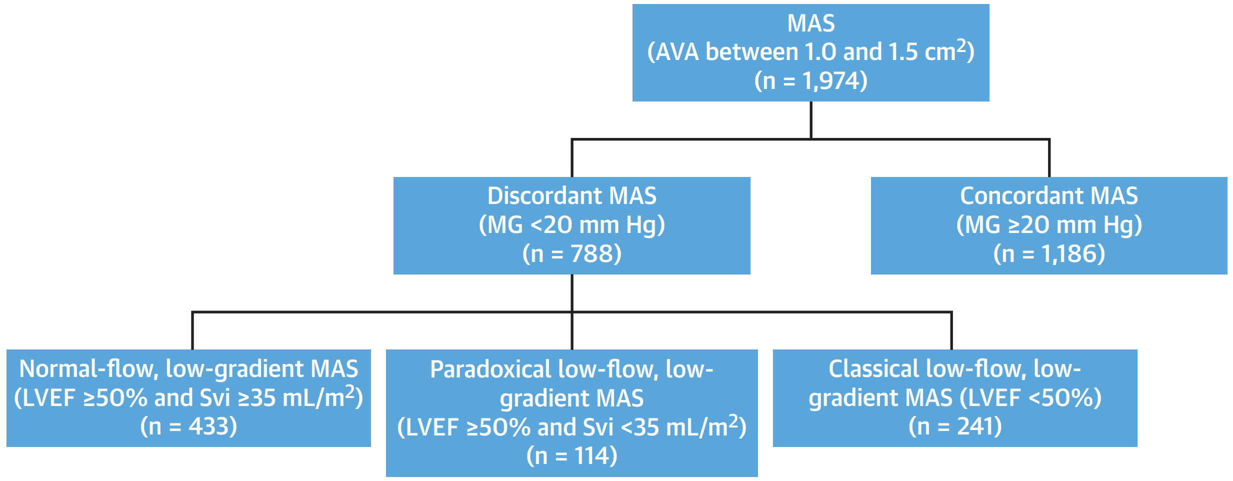
MG = mean gradient

SVi = stroke volume index

METHODS

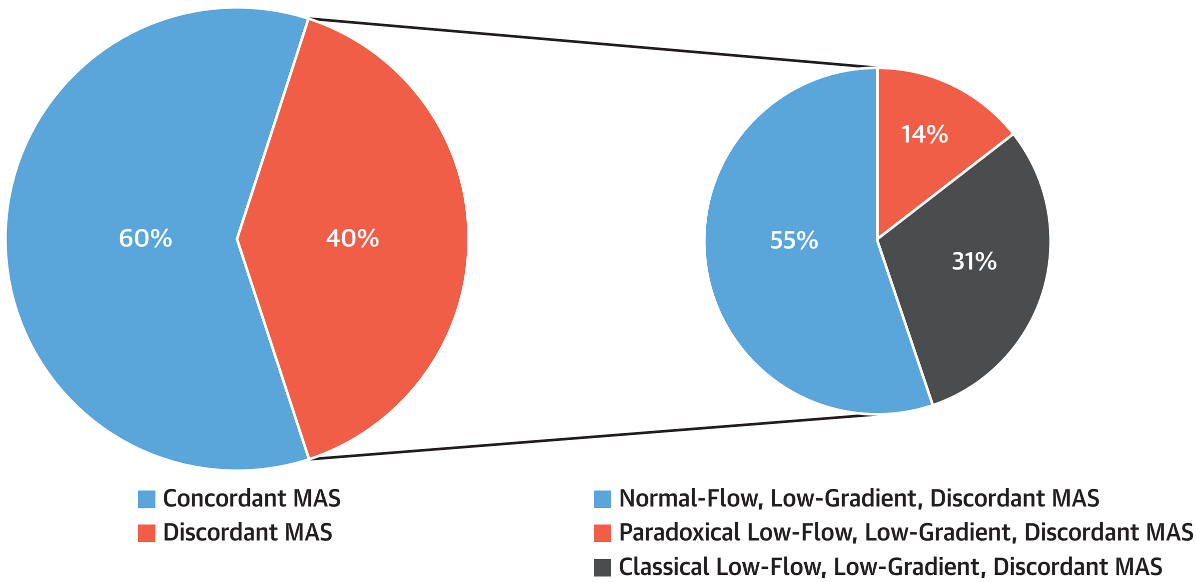
PATIENT POPULATION. From the ongoing registries of patients with moderate aortic valve stenosis from 3 academic institutions (Leiden University Medical Center, Leiden, the Netherlands; National University

FIGURE 1 Categorization of the Study Population Into Different Flow-Gradient Patterns



The figure shows the categorization of the study patients with moderate aortic stenosis in 4 groups according to the mean gradient, LVEF, and SVi. AVA = aortic valve area; LVEF = left ventricular ejection fraction; MAS = moderate aortic stenosis; MG = mean gradient; SVi = stroke volume index.

FIGURE 2 Distribution of Patients With Concordant vs Discordant Moderate AS

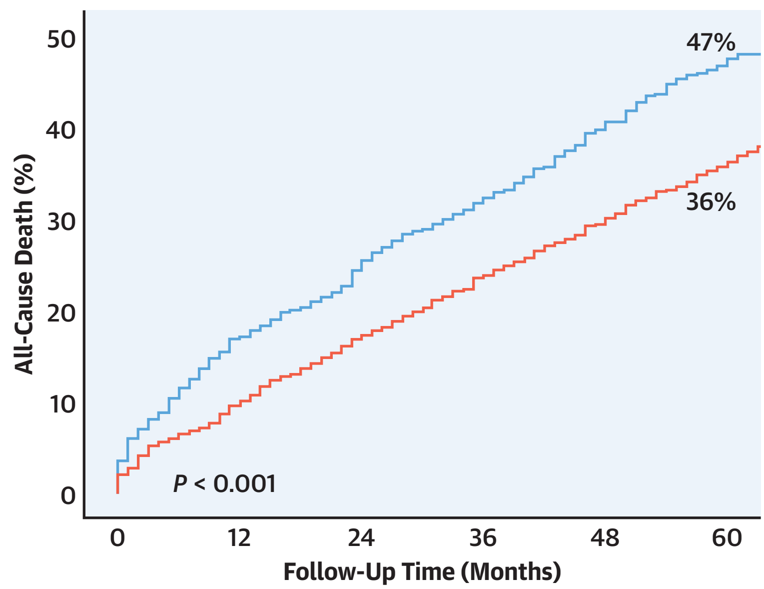


The pie chart shows the proportion of patients having concordant vs discordant moderate aortic stenosis and the different flow-gradient patterns in patients with discordant moderate aortic stenosis. MAS = moderate aortic stenosis.

Hospital, Singapore; and National Heart Center Singapore, Singapore), patients age ≥18 years who presented between October 2001 and December 2019 with a first echocardiographic diagnosis of moderate AS were identified. Moderate AS was defined as an AVA between 1.0 and 1.5 cm^2 and an MG <40 mm Hg/ peak aortic jet velocity <4 m/s.[1,2] The definition of moderate AS based on AVA was used to avoid inclusion of patients with low-flow, low-gradient severe AS. Patients with previous aortic valve surgery, congenital heart disease, bicuspid aortic valve, active endocarditis, supravalvular or subvalvular AS, or dynamic left ventricular (LV) outflow tract obstruction were excluded. Patients included in the analysis were further dichotomized into 2 main groups: discordant moderate AS with low (mild) gradient (MG <20 mm Hg) and concordant moderate AS with moderate gradient (MG ≥20 mm Hg but <40 mm Hg). In a second stage, the patients with discordant grading were divided into 3 subgroups: normal-flow, low-gradient moderate AS (MG <20 mm Hg, Svi ≥35 mL/m^2, and LVEF ≥50%); "paradoxical" low-flow, low-gradient moderate AS (MG <20 mm Hg, SVi <35 mL/m^2, and LVEF ≥50%); and "classical" low-flow, low-gradient moderate AS (MG <20 mm Hg and LVEF <50%) (**Figure 1**). All patients underwent complete clinical and echocardiographic evaluation at the time of first diagnosis of moderate AS. Patient information was prospectively collected from the departmental cardiology information system and was retrospectively analyzed. Clinical data included demographic characteristics, cardiovascular risk factors, New York Heart Association functional class, and comorbidities. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Boards of each center. Due to the retrospective design of the study, the medical ethical committee of each participating center waived the need for written informed consent.

TRANSTHORACIC ECHOCARDIOGRAPHY. All echocardiographic studies were performed using commercially available ultrasound systems and images were retrospectively analyzed in each center according to current guidelines.[14] From the parasternal long-axis view, LV dimensions were assessed and LV mass was calculated using Devereux's formula and indexed for body surface area.[14] LV volumes were assessed and LVEF was calculated according to Simpson's biplane method.[14] Left atrial volumes were measured by the biplane Simpson method and indexed for body surface area.[14] From the apical 3- or 5-chamber views and the parasternal right view, continuous wave Doppler recordings were obtained to estimate peak aortic jet velocity.[15] Mean and peak transvalvular pressure gradients were calculated using the Bernoulli equation.[15] AVA was calculated

FIGURE 3 Kaplan-Meier Curve According to Concordant vs Discordant MAS



Number at risk

Discordant MAS (MG <20 mm Hg)	788	637	522	439	341	244
Concordant MAS (MG ≥20 mm Hg)	1,186	1,058	939	825	685	556

The Kaplan-Meier curve demonstrates the cumulative event rates of all-cause mortality according to concordant vs discordant moderate aortic stenosis. Differences between groups were analyzed using the log-rank test. MAS = moderate aortic stenosis; MG = mean gradient.

using the LV outflow tract diameter and velocity time integrals of the aortic valve and LV outflow tract.[15] Severity of mitral and tricuspid regurgitation was graded using a multiparametric approach.[16] The right ventricular systolic pressure was calculated from the peak velocity of the tricuspid regurgitant jet, adding the right atrial pressure determined by the inspiratory collapse and diameter of the inferior vena cava.[14,17] For the evaluation of right ventricular systolic function, anatomical M-mode was applied on the focused apical 4-chamber view of the right ventricle to measure tricuspid annular plane systolic excursion.[17]

CLINICAL ENDPOINTS. All patients were followed up for all-cause mortality until March 1, 2021. Survival data were obtained by review of hospital records linked to the governmental death registry database.

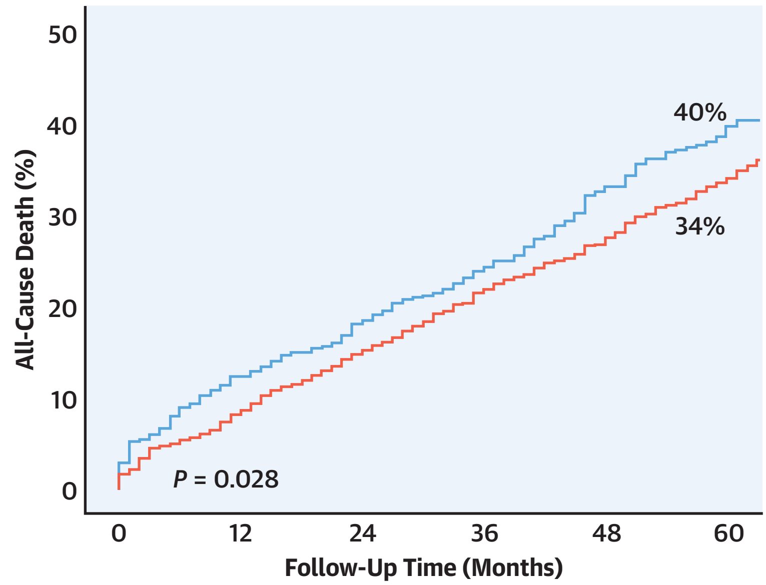
STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD when normally distributed and as median (IQR) when not normally distributed. Categorical data are presented as frequencies and percentages. For comparison of continuous variables between groups, the 1-way analysis of variance with Bonferroni's post hoc analysis or the Kruskal-Wallis test were used for normally and non-normally distributed variables, respectively. Categorical variables were compared using the Pearson chi-square test. Event-free survival curves were generated using the Kaplan-Meier method, and differences between groups were analyzed using the log-rank test. For the Kaplan-Meier curves, patients were censored at the time of last follow-up (March 1, 2021) or 5-year follow-up. Univariable and multivariable Cox proportional hazard analyses were performed to assess the association of the different flow-gradient patterns and the endpoint of all-cause mortality. The occurrence of aortic valve replacement (AVR) was entered as a time-dependent covariate. For the Cox regression analysis, time to death or last follow-up was used. For both univariable and multivariable analysis, HRs with 95% CIs were presented. A 2-sided *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows, version 25.0 (IBM).

RESULTS

PATIENT POPULATION. A total of 1,974 patients (age 73 ± 10 years; 51% men) were included in the study. There were 1,186 (60%) patients with concordant

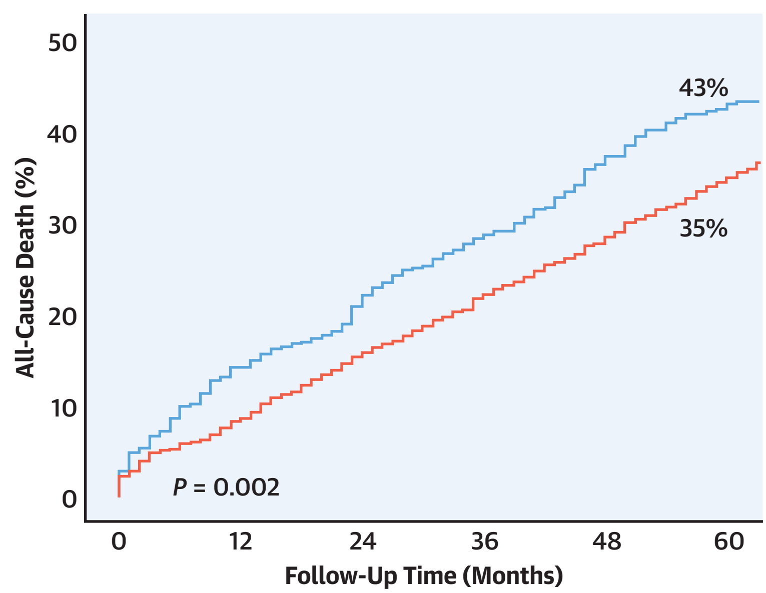
FIGURE 4 Kaplan-Meier Curves According to LVEF and SVi in MAS

A



Number at risk						
Discordant MAS (MG <20 mm Hg)	547	463	393	338	269	195
Concordant MAS (MG ≥20 mm Hg)	1,040	941	844	747	629	507

B



Number at risk						
Discordant MAS (MG <20 mm Hg)	562	470	392	341	267	196
Concordant MAS (MG ≥20 mm Hg)	1,085	984	877	776	647	520

The Kaplan-Meier curves demonstrate the cumulative event rates of all-cause mortality according to concordant vs discordant moderate aortic stenosis in patients with preserved LVEF **(A)** and preserved SVi **(B)**. Differences between groups were analyzed using the log-rank test. LVEF = left ventricular ejection fraction; MAS = moderate aortic stenosis; MG = mean gradient; SVi = stroke volume index.

moderate AS and 788 (40%) patients with discordant moderate AS (**Figure 2**). Baseline characteristics are shown in Supplemental Table 1, whereas Supplemental Table 2 summarizes the echocardiographic data for these patients.

Patients with discordant moderate AS were significantly older; had a higher prevalence of arterial hypertension, diabetes mellitus, and previous myocardial infarction; had more impaired renal function; and were more symptomatic than patients with concordant moderate AS. In terms of echocardiographic data, patients with low-gradient moderate AS had larger LV end-systolic volumes, lower LVEF and SVi, more impaired right ventricular systolic function, and more concomitant moderate to severe mitral and tricuspid regurgitation.

OUTCOMES OF LOW-GRADIENT VS NORMAL-GRADIENT MODERATE AS. During a median follow-up of 50 months (IQR: 24-82 months), 874 (44%) patients died. Patients with discordant moderate AS showed significantly higher mortality rates at 1-, 3-, and 5-year follow-up (17%, 32%, and 47%, respectively) when compared with patients with concordant moderate AS (10%, 24%, and 36%, respectively) ($P < 0.001$) (**Figure 3**). Patients in the discordant group were less likely to undergo AVR at follow-up (17%) compared with patients in the concordant group (40%) ($P < 0.001$).

Interestingly, when only considering patients with preserved LVEF (≥50%) or preserved SVi (≥35 mL/m^2), patients with discordant moderate AS still showed worse outcomes compared with patients with concordant moderate AS (**Figure 4**). On multivariable analysis, adjusting for other relevant prognostic variables (including AVR as a time-dependent covariable), discordant moderate AS also remained independently associated with all-cause mortality (HR: 1.187; 95% CI: 1.006-1.401; $P = 0.043$) (**Table 1**), addressing the need to better characterize patients with low-gradient moderate AS.

PATIENT CHARACTERIZATION ACCORDING TO DIFFERENT FLOW-GRADIENT PATTERNS. To better characterize patients with low-gradient moderate AS, the study population was divided into 4 groups according to 3 hemodynamic parameters (MG, LVEF, and SVi). These groups were concordant moderate AS and discordant moderate AS including 3 subgroups: normal-flow, low-gradient moderate AS; "classical" low-flow, low-gradient moderate AS; and "paradoxical" low-flow, low-gradient moderate AS (**Figure 1**). Baseline characteristics are shown in **Tables 2 and 3** summarizes the echocardiographic data for these patients.

TABLE 1 Cox Regression Analysis for Concordant vs Discordant Moderate AS

	All-Cause Mortality	
	HR (95% CI)	*P* Value
Univariable analysis		
Mean gradient, mm Hg (continuous)	0.977 (0.969-0.986)	<0.001
Mean gradient ≥20 mm Hg (concordant moderate AS)	Reference group	
Mean gradient <20 mm Hg (discordant moderate AS)	1.396 (1.219-1.599)	<0.001
Multivariable analysis[a]		
Mean gradient, mm Hg (continuous)	0.986 (0.976-0.997)	0.009
Mean gradient ≥20 mm Hg (concordant moderate AS)	Reference group	
Mean gradient <20 mm Hg (discordant moderate AS)	1.187 (1.006-1.401)	0.043

[a]Adjusted for surgical aortic valve replacement/transcatheter aortic valve replacement as a time-dependent covariate, age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, New York Heart Association functional class II-IV, stroke volume index, and left atrial volume index.

AS = aortic stenosis.

OUTCOMES ACCORDING TO DIFFERENT FLOW-GRADIENT PATTERNS. Mortality rates at 1-, 3-, and 5-year follow-up were significantly higher in patients with "paradoxical" low-flow, low-gradient moderate AS (14%, 33%, and 51%, respectively) ($P = 0.002$) and "classical" low-flow, low-gradient moderate AS (27%, 50%, and 64%, respectively) ($P < 0.001$), but not in normal-flow, low-gradient moderate AS (12%, 22%, and 37%, respectively) ($P = 0.774$), when compared with patients with concordant moderate AS (10%, 24%, and 36%, respectively) (**Central Illustration**). The Kaplan-Meier curve showing the relationship between "classical" low-flow, low-gradient moderate AS and all-cause mortality according to SVi is shown in Supplemental Figure 1.

On multivariable Cox regression analysis, "paradoxical" low-flow, low-gradient moderate AS (HR: 1.458; 95% CI: 1.072-1.983; $P = 0.014$) and "classical" low-flow, low-gradient moderate AS (HR: 1.710; 95% CI: 1.270-2.303; $P < 0.001$), but not normal-flow, low-gradient moderate AS (HR: 1.122; 95% CI: 0.946-1.332; $P = 0.186$) were independently associated with all-cause mortality (**Table 4**).

DISCUSSION

The main findings of the current study can be summarized as follows: 1) discordant grading is frequently observed in patients with moderate AS and is associated with increased risk of mortality compared with concordant moderate AS; 2) the normal-flow, low-gradient pattern accounted for the vast majority (55%) of discordant cases, whereas the classical low-flow, low-gradient pattern accounted for 31% and the paradoxical low-flow, low-gradient pattern for 14% of these cases; and 3) among patients with discordant grading, the paradoxical and

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TABLE 2 Clinical Characteristics of the Study Population According to Different Flow-Gradient Patterns

	Concordant MAS (n = 1,186)	Normal-Flow, Low-Gradient, Discordant MAS (n = 433)	Paradoxical Low-Flow, Low-Gradient, Discordant MAS (n = 114)	Classical Low-Flow, Low-Gradient, Discordant MAS (n = 241)	*P* Value
Age, y	72.3 ± 10.4	75.4 ± 10.0[a]	74.9 ± 10.1	73.7 ± 10.4	<0.001
Male	606 (51.1)	183 (42.3)[a]	59 (51.8)	159 (66.0)[a,b]	<0.001
BSA, m^2	1.74 ± 0.26	1.66 ± 0.22[a]	1.83 ± 0.26[a,b]	1.73 ± 0.26[b,c]	<0.001
Arterial hypertension	934 (79.0)	351 (81.3)	96 (84.2)	206 (86.2)	0.122
Dyslipidemia	878 (74.3)	310 (71.9)	86 (75.4)	192 (80.3)	0.119
Diabetes mellitus	389 (32.9)	160 (37.0)	38 (33.3)	100 (41.8)[a]	0.042
Current smoker	91 (8.0)	38 (9.2)	11 (10.7)	32 (13.7)	0.062
Obesity	237 (20.5)	57 (13.2)[a]	31 (28.7)[b]	41 (17.5)	<0.001
CAD	509 (43.0)	172 (39.8)	53 (46.5)	145 (60.4)[a,b]	<0.001
Previous MI	166 (14.0)	83 (19.3)	25 (21.9)	99 (41.3)[a,b,c]	<0.001
Atrial fibrillation	322 (27.2)	104 (24.1)	49 (43.0)	90 (37.5)	<0.001
Previous stroke	176 (14.9)	58 (13.4)	28 (24.6)[a,b]	37 (15.4)	0.030
COPD	86 (7.3)	21 (4.9)	13 (11.4)	22 (9.2)	0.106
NYHA functional class II-IV	451 (38.5)	184 (42.9)	56 (50.5)	156 (65.0)[a,b]	<0.001
Angina	115 (9.8)	19 (4.4)[a]	8 (7.1)	28 (11.7)[b]	0.002
Syncope	31 (2.1)	24 (0.5)	2 (1.8)	3 (1.3)	0.155
Beta-blocker	556 (47.1)	210 (49.0)	55 (48.7)	147 (61.3)[a,b]	0.002
ACE inhibitor or ARB	600 (50.8)	186 (43.4)[a]	50 (44.2)	143 (59.6)[b,c]	<0.001
MRA	53 (4.5)	10 (2.3)	12 (10.6)[a,b]	31 (12.9)[a,b]	<0.001
Diuretic agent	404 (34.2)	105 (24.5)[a]	41 (36.3)	128 (53.3)[a,b,c]	0.005
CCB	490 (41.5)	169 (39.4)	47 (41.6)	66 (27.5)[a,b,c]	0.001
Statin	824 (69.8)	280 (65.3)	76 (67.3)	183 (76.3)[b]	0.028
Aspirin	550 (46.6)	185 (43.1)	44 (38.9)	145 (60.4)[a,b,c]	0.013
OAC	209 (17.7)	88 (20.5)	35 (31.0)[a]	60 (25.0)	0.001
eGFR, mL/min/1.73 m^2	68.3 (45.6-88.6)	71.8 (47.7-89.4)	63.0 (44.4-88.5)	54.1 (28.0-75.5)[a,b]	<0.001
Hemoglobin, g/dL	12.5 (10.9-13.7)	12.5 (10.9-13.5)	13.0 (11.3-14.2)	12.2 (10.7-13.7)	0.075

Values are mean ± SD, n (%), or median (IQR). [a]$P < 0.05$ vs Group I. [b]$P < 0.05$ vs Group II. [c]$P < 0.05$ vs Group III.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; MAS = moderate aortic stenosis; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

classical low-flow, low-gradient patterns but not the normal-flow, low-gradient pattern were independently associated with worse outcomes (**Central Illustration**).

PREVALENCE OF DISCORDANT GRADING IN MODERATE AS. Accurate evaluation of AS severity using echocardiographic measurements is essential for risk stratification and management. However, discordant grading raises uncertainty with regard to the actual severity of AS and can lead to suboptimal treatment. Discordant grading has been reported in up to 30%-40% of patients having severe AS.[8,13,18,19] The present study suggests that the prevalence of discordant grading (ie, 40%) is similar or even higher in moderate AS.

Discordant grading may be caused by different flow-gradient patterns. Hachicha et al[12] reported a normal-flow, low-gradient pattern in 38% of patients having severe AS.[11,12] Similar to these results, the current study shows that the presence of discordant grading caused by a normal-flow state was also more frequent than discordant grading caused by a low-flow state. This means that low flow is not a necessary prerequisite for inconsistent low gradients. Discordant grading of AS severity in normal-flow patients may be related to multiple factors including measurement errors, small body size, or reduced arterial compliance.[18,20] In addition, based on the Gorlin formula (and assuming normal cardiac output), an AVA of 1.0 cm^2 actually corresponds to an MG of 26 mm Hg, whereas an MG of 40 mm Hg is related to an AVA of 0.8 cm^2, suggesting that the guidelines may per se be inherently inconsistent.[11,21]

Patients with moderate AS can also have discordant grading caused by low-flow (ie, SVi <35 mL/m^2).[1,2] As heart failure affects up to 15% of the elderly population,[22] reduced LVEF often coexists with moderate AS, and the AS itself may contribute to LV systolic dysfunction through afterload mismatch.[23] "Classical" low-flow, low-gradient moderate AS is characterized

TABLE 3 Echocardiographic Characteristics of the Study Population According to Different Flow-Gradient Patterns

	Concordant MAS (n = 1,186)	Normal-Flow, Low-Gradient, Discordant MAS (n = 433)	Paradoxical Low-Flow, Low-Gradient, Discordant MAS (n = 114)	Classical Low-Flow, Low-Gradient, Discordant MAS (n = 241)	*P* Value
LV EDD, mm	48 ± 7	46 ± 6	46 ± 6	54 ± 9[a,b,c]	<0.001
LV ESV, mL	37 (28-50)	33 (26-42)[a]	38 (25-45)	80 (58-108)[a,b,c]	<0.001
LV EDV, mL	97 (79-123)	92 (78-113)[a]	92 (70-112)[a]	124 (95-166)[a,b,c]	<0.001
LVEF, %	60.4 ± 10.1	63.7 ± 7.4[a]	61.0 ± 7.1[b]	35.1 ± 8.6[a,b,c]	<0.001
LVMI, g/m^2	117 ± 35	101 ± 29[a]	114 ± 29[b]	133 ± 39[a,b,c]	<0.001
LAVi, mL/m^2	36 (29-47)	35 (28-45)	33 (26-44)	44 (35-53)[a,b,c]	<0.001
E/e'	14.6 (11.0-19.7)	11.9 (8.9-16.1)[a]	14.7 (11.3-20.6)[b]	18.3 (12.5-25.0)[a,b,c]	<0.001
Moderate or severe MR	82 (6.9)	38 (8.8)	13 (11.4)	55 (22.8)[a,b]	<0.001
Stroke volume index, mL/m^2	52 ± 12	48 ± 9[a]	30 ± 4[a,b]	37 ± 10[a,b,c]	<0.001
Peak aortic velocity, m/s	3.4 ± 0.4	2.7 ± 0.4[a]	2.4 ± 0.3[a,b]	2.4 ± 0.4[a,b]	<0.001
Mean pressure gradient, mm Hg	28 ± 6	15 ± 4[a]	14 ± 4 [a,b]	14 ± 4[a,b]	<0.001
Aortic valve area, cm	1.20 ± 0.15	1.28 ± 0.14[a]	1.20 ± 0.13[b]	1.22 ± 0.14[a,b]	<0.001
TAPSE, mm	22 (19-25)	22 (18-24)	20 (16-24)[a]	18 (15-21)[a,b,c]	<0.001
PASP, mm Hg	33 (26-41)	33 (28-40)	31 (24-43)	39 (30-49)[a,b,c]	<0.001
Moderate or severe TR, %	146 (12.4)	76 (17.7)[a]	31 (27.4)[a]	63 (26.3)[a]	<0.001

Values are mean ± SD, median (IQR), or n (%). [a]$P < 0.05$ vs Group I. [b]$P < 0.05$ vs Group II. [c]$P < 0.05$ vs Group III.

AR = aortic regurgitation; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; ESV = end-systolic volume; LAVI = left atrial volume index; LV = left ventricular; LVMI = left ventricular mass index; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

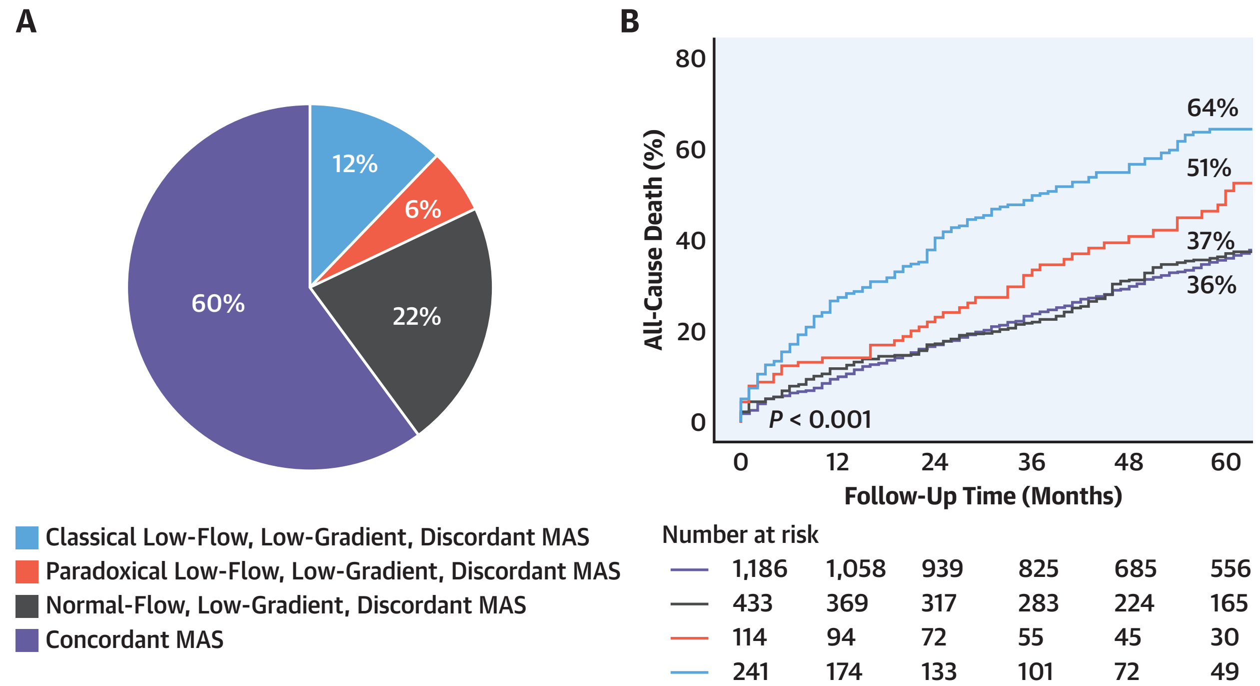
by LV eccentric remodeling, and reduced LVEF.[5] These patients often have a high prevalence of concomitant cardiovascular comorbidities, and these comorbidities may lead to symptoms that confound the symptoms of moderate AS.[5] AS severity in these patients may therefore often be misclassified by the transvalvular MG as mild AS, influencing decision-making on the timing of follow-up and aortic valve intervention. Paradoxical low-flow, low-gradient moderate AS is characterized by LV concentric remodeling, LV diastolic dysfunction, and elevated arterial impedance.[11] A low-flow state in these patients is frequently associated with significant diastolic dysfunction, significant mitral and tricuspid regurgitation, mitral stenosis, atrial fibrillation, and right ventricular systolic dysfunction.[24] The prevalence of "paradoxical" low-flow, low-gradient moderate AS found in this study (6%) is similar to the study of Lancellotti et al[25] (7%), who described clinical outcomes of asymptomatic patients with severe AS and LVEF ≥55%. Adda et al[26] observed a low-flow, low-gradient pattern in 9% of 340 patients having severe AS with normal LVEF.

PROGNOSTIC IMPLICATIONS. Recent studies have shown poor outcomes in patients with moderate AS.[3,4] Hence, identifying patients with moderate AS at higher mortality risk and who may benefit from close surveillance is crucial. The current study shows that low-gradient AS is significantly associated with worse outcomes, although marked differences were noted between different flow-gradient patterns, underscoring the need to better phenotype patients with discordant moderate AS.

Van Gils et al[5] showed that patients with moderate AS and reduced LVEF (of whom 81% had an MG <20 mm Hg) had a cumulative incidence of 61% for the composite endpoint of death, heart failure hospitalization, or AVR at 4 years of follow-up.[5] Current guidelines do not recommend AVR in patients with moderate AS and reduced LVEF unless they require cardiac surgery for another indication.[1,2] Nonetheless, because each incremental increase in AS severity imposes an additional pressure load on the LV, it has been hypothesized that AVR at an earlier stage might be beneficial in patients with HF and reduced LVEF. The TAVR UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure; NCT02661451) trial is currently recruiting patients to explore the hypothesis that transcatheter AVR may improve outcomes in patients with moderate AS and reduced LVEF.

In the current study, patients with "paradoxical" low-flow, low-gradient moderate AS also had a significant higher mortality risk compared with patients with normal-gradient AS. This association remained significant after adjusting for important demographic and clinical baseline characteristics. Reduced flow

CENTRAL ILLUSTRATION Prevalence and Prognostic Implications of Flow-gradient Patterns in Moderate Aortic Stenosis



Stassen J, et al. J Am Coll Cardiol. 2022;80(7):666-676.

(A) The pie chart shows that discordant grading is frequently observed in patients with moderate aortic stenosis and is caused by different flow-gradient patterns. **(B)** The Kaplan-Meier curve demonstrates the cumulative event rates of all-cause mortality according to different flow-gradient patterns in patients with moderate aortic stenosis. Differences between groups were analyzed using the log-rank test. MAS = moderate aortic stenosis.

despite preserved LVEF has been associated with increased mortality in patients with severe AS.[10,27] Some studies have suggested that this group may represent a more advanced stage of AS, with more adverse events such as atrial fibrillation and heart failure.[10,27] Yet, the majority of these patients do not undergo surgery, probably due to the fact that a reduced gradient often leads to an underestimation of the severity of the disease. Although we observed a similar association among "paradoxical" low-flow, low-gradient moderate AS; inappropriate remodeling; and adverse outcomes, the causal relationship remains unclear. Indeed, other comorbidities may have caused inappropriate remodeling, which

TABLE 4 Cox Regression Analysis for Different Flow-Gradient Patterns

	All-Cause Mortality			
	Univariable Analysis		Multivariable Analysis[a]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Concordant MAS	Reference group		Reference group	
Normal-flow, low-gradient, discordant MAS	1.023 (0.857-1.222)	0.797	1.122 (0.946-1.332)	0.186
"Paradoxical" low-flow, low-gradient, discordant MAS	1.528 (1.157-2.020)	0.003	1.458 (1.072-1.983)	0.014
"Classical" low-flow, low-gradient, discordant MAS	2.224 (1.849-2.675)	<0.001	1.710 (1.270-2.303)	<0.001

[a]Adjusted for age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, obesity (body mass index ≥30 kg/m^2) coronary artery disease, previous myocardial infarction, atrial fibrillation, chronic obstructive pulmonary artery disease, estimated glomerular filtration rate, left atrial volume index, moderate-severe mitral regurgitation, moderate-severe tricuspid regurgitation and surgical aortic valve replacement/transcatheter aortic valve replacement as a time dependent covariate. The HRs relate to end of follow-up data.

AS = aortic stenosis; MAS = moderate aortic stenosis.

resulted in a low-flow state. On the other hand, it is not unlikely that the underlying moderate AS contributes significantly to inappropriate remodeling. This emphasizes that the clinical focus should not only be on the AS severity, but rather on the complex interaction between the LV myocardium and the ventricular-valvular afterload. It is recommended to screen patients with "paradoxical" low-flow, low-gradient moderate AS for concomitant cardiovascular comorbidities, which should be treated to improve symptoms and/or prognosis. Whether earlier AVR may improve outcomes in these patients requires prospective evaluation.

Current guidelines mention that patients with moderate AS should be followed up every 1-2 years.[1,2] The current study shows that patients with moderate AS have a different risk profile according to their flow-gradient pattern and patients with low-flow, low-gradient patterns should perhaps be followed up more closely (even when LVEF is still preserved). Therefore, MG, SVi, and LVEF should be taken into account when risk-stratifying patients with moderate AS. The Progress (A Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve replacement; NCT04889872) trial is recruiting patients to explore the hypothesis that early transcatheter AVR could improve outcomes in patients with moderate AS.

STUDY LIMITATIONS. This study is subject to the limitations of its retrospective, observational design. Referral and selection bias for AVR may be present, although all patients were screened by the multidisciplinary heart team in the respective centers, as per guideline recommendations. Because the study was performed in tertiary referral centers, patients presented with significant comorbidities, partially explaining the high mortality rate of this study population. To avoid inclusion of patients with severe AS in this moderate AS population, we elected to use an AVA of 1.0-1.5 cm^2 as the inclusion criteria in the present study. However, by doing so, we excluded the other category of discordant grading that may be observed in the moderate AS population: ie, discordant grading with severe AVA (<1.0 cm^2) and moderate gradient (20-40 mm Hg). Hence, in the general moderate AS population, the prevalence of overall discordant grading may be higher than what is reported in the present study. We chose to not use the AVA indexed for body surface area to define AS severity because the indexed AVA may result in overestimation of AS severity in obese people, and about 25% of the patients included in this study were obese. Dobutamine stress echocardiography was not systematically performed to confirm severity of AS in classical low-flow, low-gradient AS because current guidelines do not recommend this imaging technique in patients with moderate AS. Also, CT aortic valve calcium scoring was not performed to confirm AS severity in paradoxical low-flow, low-gradient or normal-flow, low-gradient AS because it is not recommended in the guidelines for moderate AS and because there is no validated cutoff values of aortic valve calcium score to differentiate moderate vs mild AS. Mortality was ascertained by review of hospital records and linked to the governmental death registry database, and it was not possible to determine cardiac vs noncardiac death.

CONCLUSIONS

Discordant grading is frequently observed in patients with moderate AS. Among patients with discordant moderate AS, low-flow, low-gradient patterns but not the normal-flow, low-gradient pattern were independently associated with worse outcomes. These findings underscore the need to better phenotype patients with discordant moderate AS. Prospective trials are needed to determine whether AVR at an earlier stage would be beneficial in patients with "classical" and "paradoxical" low-flow, low-gradient moderate AS.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients with moderate AS, the normal-flow, low-gradient pattern accounts for more discordant cases than classical and paradoxical low-flow, which are associated with worse outcomes.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to determine whether earlier aortic valve replacement would benefit patients with classical and paradoxical low-flow, low-gradient moderate AS.

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KEY WORDS discordant grading, low-flow, low-gradient aortic stenosis, moderate aortic stenosis, mortality

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