JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 71, NO. 5, 2018

PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Dobutamine Stress Echocardiography for Management of Low-Flow, Low-Gradient Aortic Stenosis

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ABSTRACT

BACKGROUND In the American College of Cardiology/American Heart Association guidelines, patients are considered to have true-severe stenosis when the mean gradient (MG) is ≥40 mm Hg with an aortic valve area (AVA) ≤1 cm^2 during dobutamine stress echocardiography (DSE). However, these criteria have not been previously validated.

OBJECTIVES The aim of this study was to assess the value of these criteria to predict the presence of true-severe AS and the occurrence of death in patients with low-flow, low-gradient aortic stenosis (LF-LG AS).

METHODS One hundred eighty-six patients with low left ventricular ejection fraction (LVEF) LF-LG AS were prospectively recruited and underwent DSE, with measurement of the MG, AVA, and the projected AVA (AVA_{Proj}), which is an estimate of the AVA at a standardized normal flow rate. Severity of AS was independently corroborated by macroscopic evaluation of the valve at the time of valve replacement in 54 patients, by measurement of the aortic valve calcium by computed tomography in 25 patients, and by both methods in 8 patients. According to these assessments, 50 of 87 (57%) patients in the study cohort had true-severe stenosis.

RESULTS Peak stress MG ≥40 mm Hg, peak stress AVA ≤1 cm^2, and the combination of peak stress MG ≥40 mm Hg and peak stress AVA ≤1 cm^2 correctly classified AS severity in 48%, 60%, and 47% of patients, respectively, whereas AVA_{Proj} ≤1 cm^2 was better than all the previous markers ($p < 0.007$), with 70% correct classification. Among the subset of 88 patients managed conservatively (47% of the cohort), 52 died during a follow-up of 2.8 ± 2.5 years. After adjustment for age, sex, functional capacity, chronic kidney failure, and peak stress LVEF, peak stress MG and AVA were not predictors of mortality in this subset. In contrast, AVA_{Proj} ≤1 cm^2 was a strong predictor of mortality under medical management (hazard ratio: 3.65; $p = 0.0003$).

CONCLUSIONS In patients with low LVEF LF-LG AS, the DSE criteria of a peak stress MG ≥40 mm Hg, or the composite of a peak stress MG ≥40 mm Hg and a peak stress AVA ≤1 cm^2 proposed in the guidelines to identify true-severe AS and recommend valve replacement, have limited value to predict actual stenosis severity and outcomes. In contrast, AVA_{Proj} better distinguishes true-severe AS from pseudo-severe AS and is strongly associated with mortality in patients under conservative management. (Multicenter Prospective Study of Low-Flow Low-Gradient Aortic Stenosis [TOPAS]; NCT01835028) (J Am Coll Cardiol 2018;71:475–85) © 2018 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.11.052

ACRONYMS AND ABBREVIATIONS

ACC/AHA = American College of Cardiology/American Heart Association

AS = aortic stenosis

AVA = aortic valve area

AVA_{Proj} = projected AVA

AVR = aortic valve replacement

DSE = dobutamine stress echocardiography

LF-LG = low-flow, low-gradient

LV = left ventricle/left ventricular

LVEF = LV ejection fraction

MDCT = multidetector computed tomography

MG = mean gradient

PSAS = pseudo-severe AS

Q = transvalvular flow rate

TSAS = true-severe AS

Although patients with depressed left ventricular ejection fraction (LVEF ≤50%) low-flow, low-gradient (LF-LG) aortic stenosis (AS) represent only 5% to 10% of the AS population, they constitute a highly challenging subset with regard to the assessment of AS severity and therapeutic decision making (1). In the presence of a LF state, the mean transvalvular pressure gradient (MG) can underestimate the stenosis severity due to its flow dependence, whereas the aortic valve area (AVA) may overestimate the stenosis severity due to incomplete opening of the valve orifice because of reduced opening forces (pseudo-severe AS [PSAS]). Hence, at rest, the patient often presents with discordant grading of AS severity, in which AVA is <1.0 cm^2, which suggests severe AS, but the MG is <40 mm Hg, which suggests nonsevere AS. In the current American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines (1), this entity is labeled "classical LF-LG AS" and is defined as an AVA ≤1.0 cm^2, a MG <40 mm Hg, and a LVEF <50%. Dobutamine stress echocardiography (DSE) has been shown to be useful in overcoming the discordant grading observed in these patients because it can identify the presence of true-severe AS (TSAS) (2). In the ACC/AHA valve guidelines (1), these patients are considered to have TSAS, and thus, they have an indication for aortic valve replacement (AVR) (Class IIa recommendation) if the MG is ≥40 mm Hg with an AVA ≤1.0 cm^2 during DSE (1). However, these DSE criteria to distinguish AS severity in low LVEF LF-LG AS have not been well validated.

SEE PAGE 486

Our objective was to evaluate the usefulness of the MG and AVA of the DSE criteria proposed in the guidelines to predict stenosis severity and the outcome of patients with low LVEF LF-LG AS.

METHODS

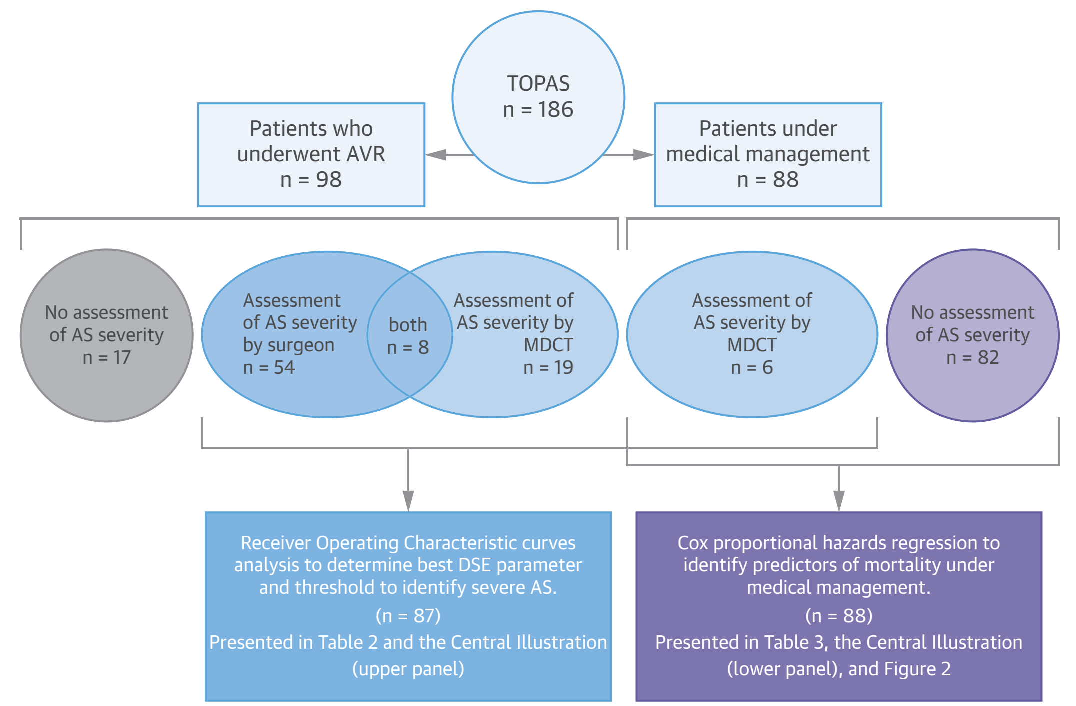
POPULATION. A total of 186 patients were prospectively recruited in the TOPAS (Multicenter Prospective Study of Low-Flow Low-Gradient Aortic Stenosis) study. The design and methods of this prospective multicenter observational study have been previously described (3-5). Patients were included in the TOPAS study if they had a MG <40 mm Hg, an indexed AVA ≤0.6 cm^2/m^2, and a LVEF ≤40% on a resting echocardiogram. Patients were excluded if they had more than mild aortic regurgitation, moderate mitral regurgitation, or mild mitral stenosis, as assessed by the multiparametric integrative approach recommended in the current guidelines for native valve regurgitation and stenosis (6-8). The study was approved by the institutional review board committee of the participating centers, and the patients provided informed consent. At study entry, all patients underwent echocardiography at rest and with dobutamine stress. A subset of patients (those recruited after 2009) underwent multidetector computed tomography (MDCT) for the quantitation of aortic valve calcification. Clinical data were collected and included age, sex, body surface area, Duke activity status index, hypertension (patients receiving antihypertensive medications or having known, but untreated, hypertension [blood pressure ≥140/90 mm Hg]), diabetes, renal failure, hyperlipidemia, coronary artery disease (history of myocardial infarction or ≥50% coronary artery stenosis on coronary angiography), congestive heart failure, acute pulmonary edema, and chronic obstructive pulmonary disease. The treatment (AVR or medical management) was left to the discretion of the treating physician who was blinded to the projected AVA and aortic valve calcium scoring data but not to the standard resting and DSE parameters of AS severity (resting and stress AVA and MG). Patients were followed, in accordance with protocol, annually for 5 years.

DOPPLER ECHOCARDIOGRAPHY. Resting Doppler echocardiograms and DSE were performed using a commercially available ultrasound system. The

a fellowship grant from "L'Agence de la santé et des services sociaux de la Capitale nationale-ADLSSS", Québec, Québec, Canada. Dr. Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research; and has received institutional research support from Edwards Lifesciences and Medtronic. Dr. Clavel holds a junior scholarship from Fonds de Recherche du Québec-Santé (FRQS). Dr. Dahou has received a research grant from Grant Edwards LLC. Dr. Baumgartner has received travel support from Edwards Lifesciences, Medtronic, Abbott, and Actelion; and has received speaker fees from Edwards Lifesciences. Dr. Cavalcante has received a research grant from Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Annabi and Touboul contributed equally to this work and are joint first authors on this paper.

Manuscript received July 9, 2017; revised manuscript received November 2, 2017, accepted November 20, 2017.

FIGURE 1 Study Flowchart



The different subgroups derived from the main TOPAS (True or Pseudo-Severe Aortic Stenosis) cohort and for which analyses these subsets were used. AS = aortic stenosis; AVR = aortic valve replacement; DSE = dobutamine stress echocardiography; MDCT = multidetector computed tomography.

dobutamine infusion protocol consisted of 8-min stages with increments of 2.5 to 5 µg/kg/min up to a maximum dosage of 20 µg/kg/min (3). LV dimensions were measured at rest according to American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations (8). LV outflow tract diameter was measured at rest and considered constant during DSE. The following measurements were performed at rest and at each DSE stage: stroke volume was measured in the LV outflow tract; transvalvular flow rate (Q) was obtained by dividing stroke volume by the LV ejection time measured on the continuous-wave Doppler spectral envelope of aortic flow; AVA was calculated by the continuity equation; MG was obtained by the Bernoulli formula; and LVEF was measured using the biplane Simpson method. For all these parameters, we averaged the measures of 3 cycles in normal sinus rhythm and 5 cycles in the presence of irregular rhythm. The projected AVA (AVA_{Proj}) at a normal transvalvular flow rate (250 ml/min) was calculated using the equation (9):

$$AVA_{Proj} = AVA_{Rest} + \frac{AVA_{Peak} - AVA_{Rest}}{Q_{Peak} - Q_{Rest}} \times (250 - Q_{Rest})$$

where AVA_{Rest} and AVA_{Peak} are the AVA at rest and at peak stress, and Q_{Rest} and Q_{Peak} were Q at rest and at peak stress. To be consistent with the guideline criteria, peak stress values were obtained at the time when MG was maximal during DSE, which did not necessarily correspond to the last stage with a maximum dobutamine dose. Likewise, AVA_{Peak} and Q_{Peak} were the values of AVA and Q_{Peak} concomitant to MG_{peak}.

ASSESSMENT OF AS SEVERITY. AS severity was assessed in 87 patients by 1 of 2 methods: 1) macroscopic evaluation of the valve by the cardiac surgeon at the time of AVR; or 2) quantitation of aortic valve calcification by MDCT. For the macroscopic evaluation, the surgeon visually inspected

TABLE 1 Baseline Characteristics of the Population and the Subgroups of Patients

	Whole Cohort (n = 186)	Patients Under Medical Management (n = 88) (47%)	Patients Who Underwent AS Severity Assessment (n = 87)
Clinical data			
Age, yrs	73 ± 10	73 ± 10	72 ± 11
Male	145 (78)	69 (78)	68 (78)
Diabetes	75 (41)	30 (35)	39 (45)
Kidney failure	56 (30)	25 (28)	28 (32)
Hypertension	126 (68)	59 (68)	61 (70)
Hyperlipidemia	125 (68)	56 (64)	61 (70)
Chronic obstructive pulmonary disease	53 (29)	21 (24)	27 (31)
Coronary artery disease	140 (76)	65 (76)	61 (70)
Previous MI	100 (55)	55 (64)	38 (44)
Duke activity status index	21 ± 15	24 ± 16	17 ± 14
NYHA functional class ≥III	97 (52)	36 (40)	46 (52)
Atrial fibrillation/flutter	25 (13)	7 (8)	19 (22)
Rest echocardiographic data			
LV diameter, mm	61 ± 8	62 ± 10	59 ± 7
Mean gradient, mm Hg	23 ± 8	20 ± 8	25 ± 8
Aortic valve area, cm^2	0.88 ± 0.22	0.94 ± 0.25	0.83 ± 0.19
Stroke volume, ml	58 ± 17	58 ± 18	57 ± 15
Transvalvular flow rate, ml/s	190 ± 49	189 ± 55	191 ± 43
LV ejection fraction, %	28 ± 8	28 ± 9	27 ± 8
LV flow reserve, %	83 (44)	40 (45)	38 (43)
Increase in Q_{mean} ≥15%	164 (88)	80 (90)	75 (85)
Peak echocardiographic data			
Mean gradient, mm Hg	32 ± 12	27 ± 10	37 ± 11
Aortic valve area, cm^2	1.04 ± 0.27	1.11 ± 0.28	0.97 ± 0.24
Stroke volume, ml	68 ± 20	68 ± 20	68 ± 22
Transvalvular flow rate, ml/s	278 ± 80	274 ± 84	279 ± 78
LV ejection fraction, %	36 ± 10	35 ± 11	36 ± 10
Projected aortic valve area, cm^2	1.01 ± 0.21	1.09 ± 0.23	0.93 ± 0.20
Aortic valve intervention			
Surgical AVR	71 (38)	–	61 (70)
Transcatheter AVR	27 (15)	–	20 (23)

Values are mean ± SD or n (%).
AVR = aortic valve replacement; LV = left ventricular; NYHA = New York Heart Association.

the valve at the time of AVR and classified the valve stenosis severity as nonsignificant, mild, moderate, or severe using a standardized method described in previous publications (3,9). Briefly, each valve leaflet was evaluated for stiffness (scored from 0 to 3, 0 being entirely flexible) and degree of calcification (scored from 0 to 3, 0 being noncalcified). Scores for stiffness and calcification were summed and divided by the number of leaflets, giving an average per leaflet score. Among the 62 patients assessed visually by the surgeon, 36 valves were described as TSAS (AS graded as severe), whereas 26 valves were considered to be PSAS (AS graded as moderate or less) (**Figure 1**).

In 33 patients, AS severity was corroborated by the quantitation of aortic valve calcium load by MDCT (**Figure 1**). TSAS was considered present when the aortic valve calcium load was >1,200 Agatston units (AU) for women and >2,000 AU for men, as previously validated (10,11). Of the 33 patients in whom this method was used, 19 (58%) had TSAS according to MDCT assessment. In the 8 patients with both surgeon assessment and aortic valve calcium scoring, there was an 88% (7 or 8 patients) agreement in the classification of stenosis severity (**Figure 1**).

STATISTICAL ANALYSIS. **Figure 1** describes the subgroups that were used for each analysis. Results are expressed as mean ± SD, unless otherwise specified. Correlations among the assessment of AS severity and AVA_{Peak}, MG_{Peak}, and AVA_{Proj} were determined by simple logistic regression analysis. Receiver-operating characteristic curves were used to determine the area under the curve, sensitivity, specificity, positive and negative predictive values, and percentage of correct classification for these variables at several cutoff values. Based on previous studies that reported that estimation of AVA_{Proj} might not be reliable when the percent flow rate increase was <15% (3,9), we excluded such patients from the receiver-operating characteristic analysis in the present study.

Accuracy of mortality prediction was determined for the cutpoints proposed in the ACC/AHA guidelines for AVA_{Peak}, MG_{Peak}, and for AVA_{Proj} ≤1 cm^2 using Kaplan-Meier survival curves and Cox proportional hazards models, and the corresponding curves were adjusted for age, sex, functional capacity (as documented by the Duke activity status index), kidney failure, and $LVEF_{Peak}$ (LVEF at peak dobutamine stress) in patients who received medical management.

The net reclassification index using the category free net reclassification index and integrated discrimination agreement program codes downloaded online was used to determine the incremental predictive value of AVA_{Proj} ≤1 cm^2 beyond guideline parameters (AVA_{Peak} and MG_{Peak}) for predicting 1-year mortality under medical management. A p value <0.05 was considered statistically significant. Statistical analyses were performed with JMP version 13.0.0 (SAS Institute Inc., Cary, North Carolina, 1989-2007) and STATA version 11 (StataCorp, College Station, Texas) software.

RESULTS

STUDY POPULATION. The study population was a mean age of 73 ± 10 years and had a larger proportion of men (78%) (**Table 1**). There was a high prevalence of comorbidities, including diabetes (41%), hypertension (68%), coronary artery disease (76%), and previous myocardial infarction (55%) (**Table 1**). LVEF was

TABLE 2 Receiver-Operating Characteristic Curve Analyses and Percentage of Correct Classification for the DSE Parameters and Criteria Used to Identify TSAS in the Subgroup of 87 Patients With Flow-Independent Assessment of AS Severity

	AUC	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	% Correct Classification
AVA_{Peak}	0.60; p = 0.07	≤1 cm^2	63	56	66	58	60
		≤1.2 cm^2	84	21	58	50	56
MG_{Peak}	0.58; p = 0.12	≥40 mm Hg	35	65	57	44	48
		≥35 mm Hg	69	54	61	49	63
		≥30 mm Hg	78	37	61	56	60
MG_{Peak} ≥40 mm Hg and AVA_{Peak} ≤1 cm^2	N/A	N/A	22	81	61	42	47
AVA_{Proj}	**0.65; p = 0.01**	**≤1 cm^2**	**86**	**47**	**68**	**72**	**70**
		≤1.2 cm^2	100	13	60	100	61
Indexed AVA_{Proj}	**0.70; p = 0.002**	**≤0.60 cm^2/m^2**	**98**	**29**	**64**	**92**	**68**
		≤0.55 cm^2/m^2	**94**	**37**	**66**	**82**	**68**

Bold indicates variables that were found to significantly discriminate true from pseudo-severe aortic stenosis.

AS = aortic severity; AUC = area under the curve; AVA_{Peak} = aortic valve area at peak dobutamine stress; AVA_{Proj} = projected aortic valve area at normal transvalvular flow rate (250 ml/s); DSE = dobutamine stress echocardiography; MG_{Peak} = mean gradient at peak dobutamine stress; NPV = negative predictive value; PPV = positive predicted value; TSAS = true-severe AS.

28 ± 8%, Q_{Rest} was 190 ± 49 ml/s, MG_{Rest} was 23 ± 8 mm Hg, and AVA_{Rest} was 0.88 ± 0.22 cm^2. With DSE, the average transvalvular flow rate and hemodynamic parameters of AS severity increased significantly (Table 1). However, 26% of patients had a Q_{Peak} <220 ml/s and thus did not reach the normal flow rate despite dobutamine stress. In contrast, 32% achieved a supranormal flow rate (>300 ml/s) during DSE, whereas only 42% had a peak flow rate in the normal range (230 to 300 ml/s). Among the 186 patients included in this study, 98 (53%) underwent AVR, 71 (38%) by standard open-heart surgery, and 27 (15%) by transcatheter access.

ASSESSMENT OF AS SEVERITY. AVA_{Proj} and AVA_{Proj} indexed to body surface were significantly smaller in patients with TSAS versus PSAS (0.88 ± 0.16 cm^2 vs. 0.99 ± 0.23 cm^2; p = 0.01 and 0.45 ± 0.07 cm^2/m^2 vs. 0.54 ± 0.14 cm^2/m^2; p = 0.0005, respectively), whereas AVA_{Peak} and MG_{Peak} were not different (0.93 ± 0.24 cm^2 vs. 1.02 ± 0.23 cm^2; p = 0.07 and 38.2 ± 10.3 mm Hg vs. 34.5 ± 11.8 mm Hg; p = 0.12, respectively). MG_{Peak} ≥40 mm Hg had a low sensitivity of 35%, a positive predictive value of 57%, and a lower percentage of correct AS severity classification of 48% for the identification of TSAS (Table 2). Lowering the MG_{Peak} cutoff value to 35 mm Hg for identifying TSAS improved the sensitivity (69%), positive predictive value (61%), and percentage of correct classification (63%). A MG_{Peak} cutoff value of 30 mm Hg resulted in a percentage correct classification of 60%. AVA_{Peak} ≤1 cm^2 had a sensitivity of 63%, a positive

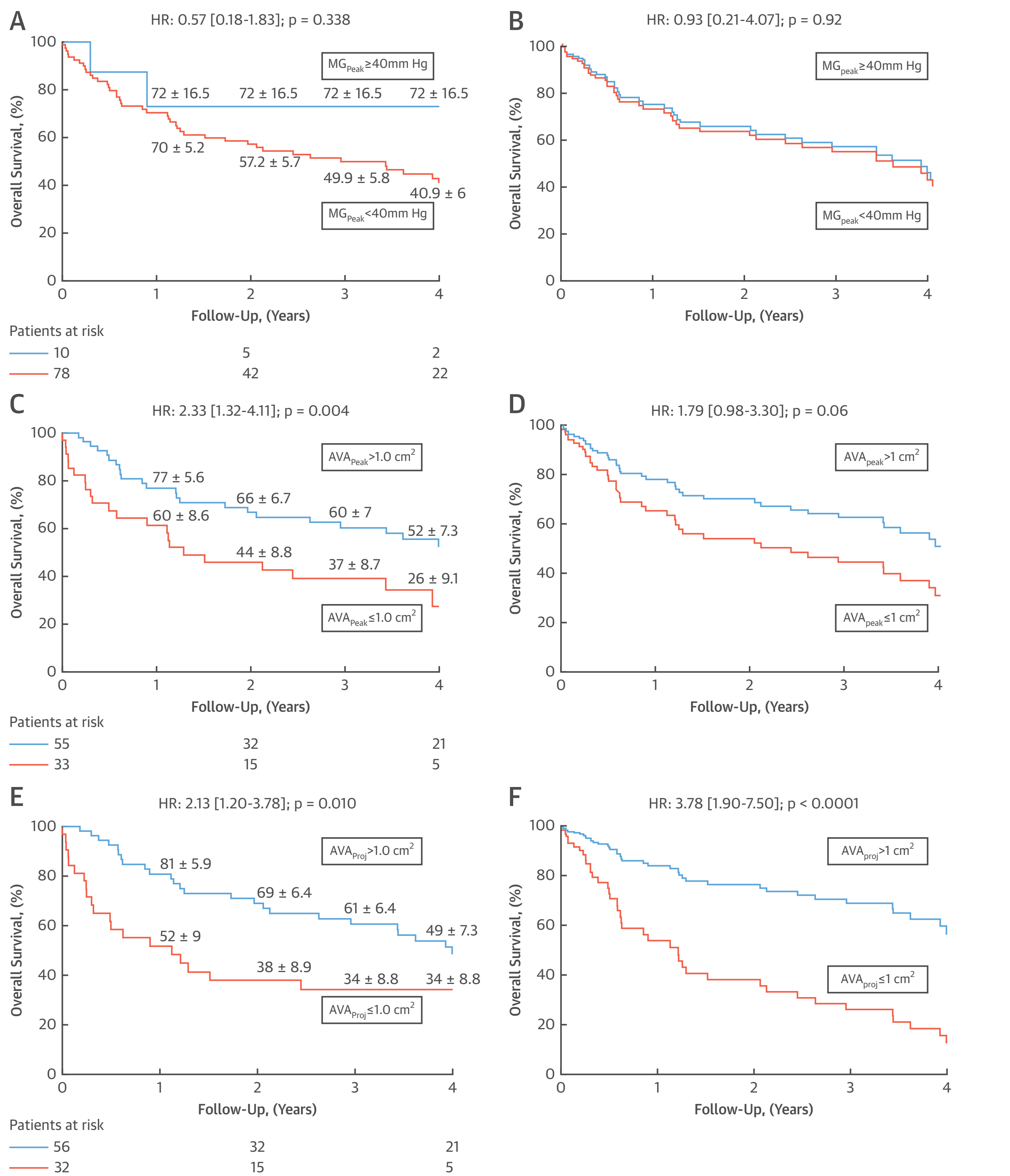
TABLE 3 Unadjusted and Adjusted HR (95% CI) of DSE Parameters of AS Severity to Predict Mortality in 87 Patients Under Medical Management

		Univariate Analysis			Multivariate Analysis		
	Increment/Threshold	Unadjusted HR	95% CI	p Value	Adjusted* HR	95% CI	p Value
MG_{Peak}	5 mm Hg	1.00	0.88–1.13	0.94	1.20	1.02–1.41	0.02
	≥40 mm Hg vs. <40 mm Hg	0.57	0.18–1.83	0.34	0.93	0.21–4.07	0.92
AVA_{Peak}	−0.1 cm^2	1.19	1.07–1.33	0.001	1.16	1.02–1.32	0.02
	≤1 cm^2 vs. >1 cm^2	2.33	1.32–4.11	0.004	1.79	0.98–3.3	0.06
	≤1.2 cm^2 vs. >1.2 cm^2	2.06	1.15–3.68	0.02	1.45	0.78–2.72	0.24
AVA_{Proj}	−0.1 cm^2	1.16	1.01–1.33	0.04	1.29	1.09–1.53	0.003
	≤1 cm^2 vs. >1 cm^2	2.13	1.20–3.78	0.01	3.78	1.90–7.50	<0.0001
	≤1.2 cm^2 vs. >1.2 cm^2	1.30	0.72–2.37	0.38	2.96	1.50–5.82	0.002
Indexed AVA_{Proj}	−0.1 cm^2	1.15	0.92–1.43	0.21	1.43	1.10–1.86	0.008
	≤0.55 cm^2/m^2 vs. >0.55 cm^2/m^2	1.60	0.89–2.87	0.12	2.59	1.35–4.95	0.004

*Adjusted for age, sex, functional capacity (Duke activity status index), kidney failure, and left ventricular ejection fraction at peak dobutamine stress.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

FIGURE 2 **Kaplan-Meier and Cox Curves of Survival Under Medical Management According to DSE Variables of AS Severity**



The survival according to DSE mean gradient (MG_{Peak} <40 mm Hg or ≥40 mm Hg) **(A)** unadjusted and **(B)** adjusted, DSE aortic valve area (AVA_{Peak} >1 cm^2 or ≤1 cm^2) **(C)** unadjusted and **(D)** adjusted, projected aortic valve area (AVA_{Proj} >1 cm^2 or ≤1 cm^2) **(E)** unadjusted and **(F)** adjusted, and indexed projected aortic valve area (AVA_{Proj} >0.6 cm^2/m^2 or ≤0.6 cm^2/m^2) **(G)** unadjusted and **(H)** adjusted. In **B**, **D**, **F**, **and H**, curves were adjusted for age, sex, functional capacity (Duke activity status index), kidney failure, and DSE left ventricular ejection fraction (LVEF) **(*)**. This analysis was performed in the subgroup of 88 patients followed under medical management. HR = hazard ratio. Other abbreviations as in Figure 1.

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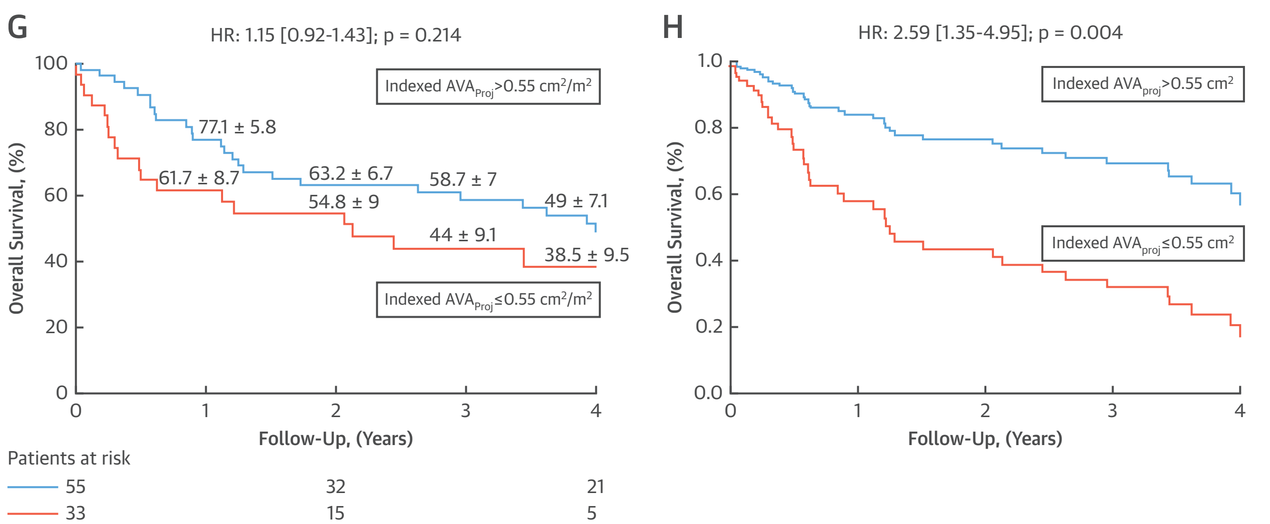
FIGURE 2 Continued



predictive value of 64%, and a percentage correct classification of 60%. The combination of MG_{Peak} ≥40 mm Hg and AVA_{Peak} ≤1 cm^2 had a lower percentage of correct classification (47%) compared with AVA_{Peak} ≤1 cm^2 alone. AVA_{Proj} and indexed AVA_{Proj} had the best area under the curve, sensitivity, and positive predictive value compared with the other DSE parameters (Table 2). Indexed AVA_{Proj} ≤0.6 cm^2/m^2 had the best performance to identify TSAS with an area under the curve of 0.70, sensitivity of 94%, positive predictive value of 66%, and a percentage correct classification of 68% (Table 2). An AVA_{Proj} ≤1 cm^2 provided similar results with a percentage correct classification of 70%.

PREDICTION OF PATIENT OUTCOME. In univariable analysis, MG_{Peak}, AVA_{Peak}, AVA_{Proj}, and indexed AVA_{Proj} as continuous variables were predictors of mortality (all $p \leq 0.02$). As dichotomous variables only AVA_{Proj} ≤1 cm^2 ($p < 0.0001$) and indexed AVA_{Proj} ≤0.55 cm^2/m^2, ($p = 0.004$) were predictors of mortality, whereas MG_{Peak} ≥40 mm Hg ($p = 0.69$) and AVA_{Peak} ≤1 cm^2 ($p = 0.06$) were not (Figure 2 and Table 3). The combination of AVA_{Peak} ≤1 cm^2 and MG_{Peak} ≥40 mm Hg as recommended in the guidelines to identify TSAS was not associated with all-cause mortality ($p = 0.21$).

After adjustment for age, sex, functional capacity, kidney disease, and $LVEF_{Peak}$, AVA_{Proj} and indexed AVA_{Proj} (as continuous or dichotomous variables), and MG_{Peak} and AVA_{Peak} (as continuous variables only) were independent predictors of mortality during medical management (all $p \leq 0.02$) (Figure 2).

There was a trend toward significance of AVA_{Peak} ≤1 cm^2 to predict mortality during medical management ($p = 0.06$) (Figure 2 and Table 3).

Models built with AVA_{Proj} or indexed AVA_{Proj} were more accurate in predicting mortality than those built with AVA_{Peak} or MG_{Peak} (all $p \leq 0.05$). AVA_{Proj} ≤1 cm^2 had a net reclassification index of predicting death under medical management at 1 year of 0.96 compared with AVA_{Peak} ≤1 cm^2 ($p < 0.0001$), 0.60 compared with MG_{Peak} ≥40 mm Hg ($p = 0.01$), and 0.88 compared with the composite of MG_{Peak} ≥40 mm Hg and AVA_{Peak} ≤1 cm^2 ($p = 0.0003$).

Adding atrial fibrillation in the models did not change the results of the Cox analyses. Flow reserve defined by a percent increase in stroke volume ≥20% during DSE was not associated with mortality ($p = 0.80$ and $p = 0.66$ in univariable and multivariable analyses, respectively).

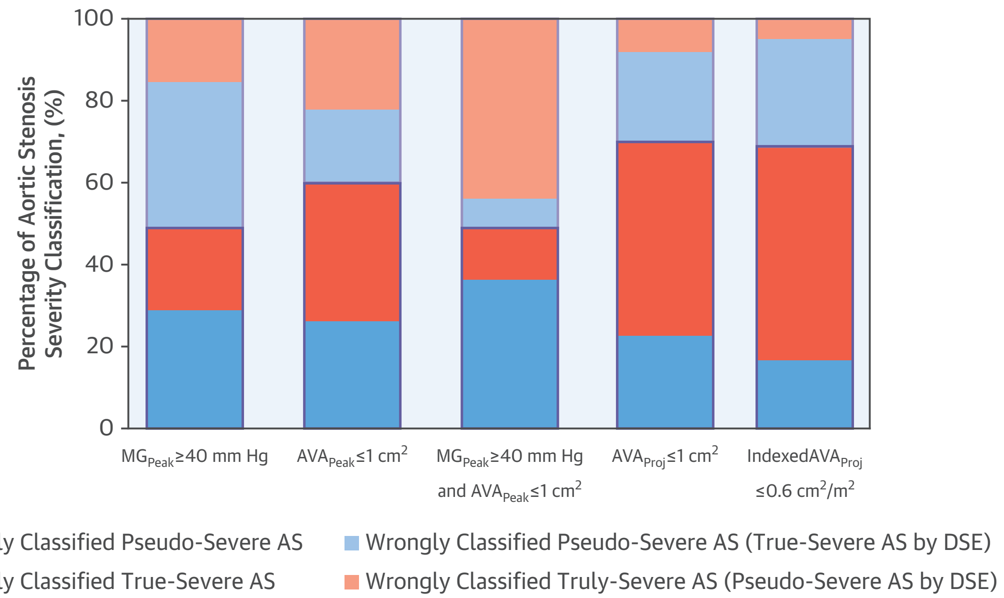
DISCUSSION

The main findings of this study are that in patients with low LVEF LF-LG AS: 1) a DSE criteria of MG_{Peak} ≥40 mm Hg has a low sensitivity for identifying TSAS and does not predict mortality in medically managed patients; lowering the cutoff value of MG_{Peak} to 35 mm Hg can improve the sensitivity; 2) a DSE criteria of AVA_{Peak} ≤1.0 cm^2 is superior to MG_{Peak} criteria to identify TSAS and predict mortality; 3) a combination of MG_{Peak} ≥40 mm Hg and AVA_{Peak} ≤1.0 cm^2 as proposed in the ACC/AHA valve guidelines has a low sensitivity for identifying TSAS and does not predict mortality in medically managed

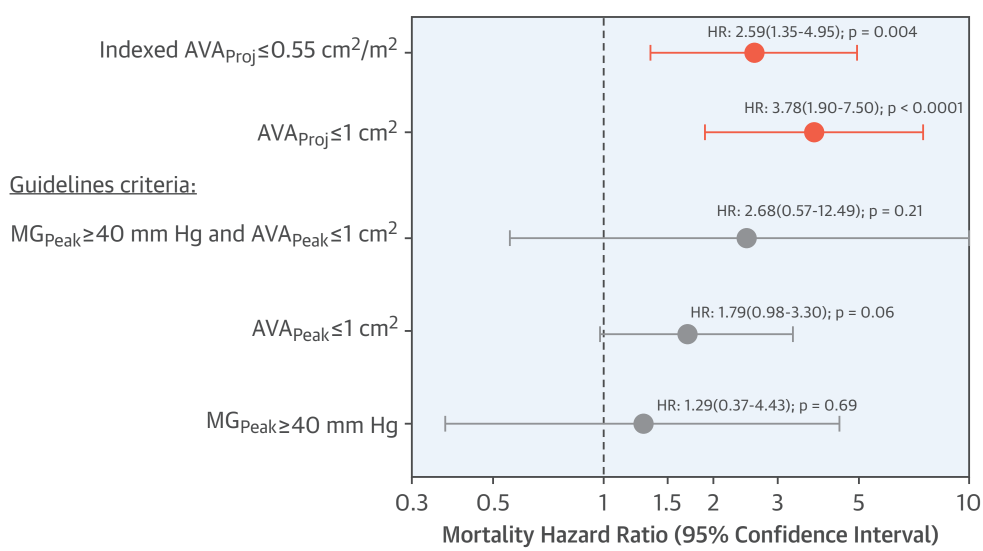
JACC VOL. 71, NO. 5, 2018
FEBRUARY 6, 2018:475–85

CENTRAL ILLUSTRATION **DSE Guideline Criteria for Low Ejection Fraction AS Severity**

A Identification of Aortic Stenosis Severity by Dobutamine Stress Echocardiographic Criteria



B Prediction of Mortality Under Medical Management



Annabi, M.-S. et al. J Am Coll Cardiol. 2018;71(5):475–85.

(A) Comparison of correct classification of aortic stenosis (AS) severity and **(B)** hazard ratio (HR) for survival prediction under medical treatment according to conventional dobutamine stress echocardiography (DSE) markers and projected aortic valve area at normal flow rate. **(A)** Bar graph of correct **(dark color)** or incorrect **(light color)** classification according to the actual severity of AS (i.e., true-severe **[orange]** of pseudo-severe **[blue]**). This analysis was performed in the subgroup of 87 patients with confirmation of AS severity by computed tomography (CT) and/or surgeon. **(B)** Forest plot of HRs of the different DSE criteria. Analyses were adjusted for age, sex, functional capacity (Duke activity status index), kidney failure, and DSE left ventricular ejection fraction. This analysis was performed in the subgroup of 88 patients followed under medical management.

patients; and 4) AVA_{Proj} provides the best accuracy to predict TSAS and clinical outcomes with an AVA_{Proj} ≤1.0 cm² (or indexed AVA_{Proj} ≤0.55 cm²/m²) providing the optimal cutoff value (**Central Illustration**).

FLOW DEPENDENCE OF PARAMETERS OF AS SEVERITY. Echocardiography or catheterization measures of AS severity such as MG and AVA are inherently flow dependent (3,12,13). Because the transvalvular flow response to dobutamine varies largely from one patient to another (12,13), peak DSE values of AVA and MG do not solely represent the severity of the valve stenosis, but may be influenced by the magnitude of the change in flow during dobutamine stress. In the present study, approximately one-half of patients did not have normal flow rate during dobutamine stress, which could potentially lead to persistence of the discordance in AS severity grade based on MG and AVA. In addition, 25% of patients achieved supranormal flow rates during dobutamine stress, which could lead to "reverse" discordant grading by AVA and MG (AVA >1 cm² and MG ≥40 mm Hg). The projected AVA at a normal flow rate has the advantage of being standardized for the transvalvular flow rate. This parameter provides an estimation of the AVA at a fixed normal flow rate that is identical for all patients (i.e., 250 ml/s) (3,9). This standardization for flow rate might explain why the AVA_{Proj} outperforms other DSE parameters for the prediction of stenosis severity and outcomes in low LVEF LF-LG AS.

CRITERIA TO DIFFERENTIATE TSAS AND PSAS IN LOW LVEF LF-LG AS. The DSE criteria of MG_{Peak} ≥40 mm Hg lacks sensitivity to differentiate TSAS and PSAS. Using a lower cutoff value of MG_{Peak} ≥35 mm Hg markedly improved the sensitivity from 35% to 69% while also improving the percentage of correct classification from 48% to 63%. The use of a cutoff of 30 mm Hg did not further improve the diagnostic performance of MG_{Peak}. The low sensitivity of MG_{Peak} criteria might be related to the fact that almost one-half of patients with low LVEF LF-LG AS did not achieve a normal flow rate with DSE, thus potentially precluding MG to reach 40 mm Hg despite the presence of TSAS. Using a DSE criteria of AVA_{Peak} ≤1.0 cm² had better sensitivity and percentage of correct classification compared with MG_{Peak}. Use of a cutoff value of <1.2 cm² as suggested in some studies (4,9,14) further improved the sensitivity (63% to 84%). However, the main limitation of AVA_{Peak} criteria was the relatively low specificity. Because achieving a normal flow rate of 250 ml/s with stress fails in a large proportion of patients, AVA_{Peak} might still be pseudo-severe due to a persistent LF state. Using the combination of MG_{Peak} ≥ 40 mm Hg and AVA_{Peak} ≤ 1.0 cm² as proposed in the ACC/AHA guidelines improved the specificity, but had a low sensitivity at only 22% and a percentage of correct classification of only 47% in our study cohort. The projected AVA at a normal flow overcomes the flow dependency of MG_{Peak} and AVA_{Peak}, and thereby improves the accuracy of DSE for the identification of TSAS and PSAS. However, a minimum 15% increase in mean transvalvular flow rate is required to obtain a reliable estimate of AVA_{Proj} during DSE (9). In patients with low LVEF LF-LG AS and no or minimal increase (<15%) in flow rate (11% of the patients in the present series), it is likely preferable to use aortic valve calcium scoring by computed tomography to corroborate stenosis severity (10).

DSE INDEXES OF AS SEVERITY AS PREDICTORS OF MORTALITY. There was no association between DSE MG_{Peak} ≥40 mm Hg and mortality in our low LVEF LF-LG AS patients who received medical management. This intriguing finding might be due to the fact that the increase in MG during DSE was not only related to the stenosis severity, but also influenced by LV contractile reserve (4,9,15,16). The presence of TSAS and lack of contractile reserve are known risk factors for mortality in low LVEF LF-LG AS (15,16), but have opposite effects on MG_{Peak}. A more severe stenosis is associated with a larger increase in MG during DSE, whereas a lack of contractile reserve, and thus flow reserve, due to advanced myocardial impairment, is associated with a smaller increase in MG. Hence, a lower MG_{Peak} does not necessarily indicate the presence of nonsevere AS, but may be observed in a patient with TSAS in whom the increase in MG_{Peak} has been blunted by poor flow reserve. Such patients would be at high risk of mortality under conservative management (15,16). Up to two-thirds of patients in our cohort with a MG_{Peak} <40 mm Hg and AVA_{Peak} ≤1.0 cm² had TSAS. Furthermore, there were several patients (n = 8) with a MG_{Peak} <40 mm Hg and AVA_{Peak} between 1.0 and 1.2 cm² who were found to have TSAS based on surgical inspection or aortic valve calcium load. Hence, the presence of a MG_{Peak} <40 mm Hg and/or an AVA_{Peak} >1.0 cm² on DSE does not exclude the presence of TSAS and a potential benefit from AVR.

As opposed to MG_{Peak}, the presence of TSAS and the lack of flow reserve both yield a smaller AVA_{Peak} (i.e., the effect of these 2 factors affect AVA_{Peak} in the same direction, as opposed to in opposite directions on MG_{Peak}). Hence, a small AVA_{Peak} may be a marker of a more severe AS, more advanced myocardial impairment, or both. This might explain why in univariable analyses, AVA_{Peak} was strongly associated with an increased risk of mortality in medically treated patients, whereas MG_{Peak} was not. After adjusting for other DSE markers of LV myocardial impairment (such as peak stress LVEF), the association between AVA_{Peak} and outcome was no longer significant.

As opposed to MG_{Peak} and AVA_{Peak}, AVA_{Proj} is standardized for flow and is a more precise marker of the actual AS severity. Furthermore, this parameter is independent of LV function and transvalvular flow. This might explain why a small AVA_{Proj}, which reflected the presence of TSAS, was independently associated with an increased risk of mortality in patients treated conservatively, even after adjustment for DSE parameters of LV function.

STUDY LIMITATIONS. Residual confounding factors could not be excluded in this observational study. The treatment was left to the discretion of the treating physician who was aware of the AVA rest/peak and MPG rest/peak, stroke volume rest/peak (i.e., data included in the guidelines), but not of the AVA_{Proj} or the aortic valve calcification score. Despite being a limitation, this aspect of the protocol further reinforced the robustness of the results and conclusions of the study. Patients with a $MG_{Peak} \geq 40$ mm Hg were underrepresented in the medical management group because they were more likely to undergo aortic valve replacement. However, even as continuous variable, MG_{Peak} appeared to be a weaker predictor of mortality than AVA_{Proj}.

We primarily used the assessment of the valve by the cardiac surgeon at the time of AVR as the reference standard. Although this process had been standardized among the different sites participating to the TOPAS study, the assessment performed by the surgeon was only semiquantitative and was predominantly based on the anatomic severity rather than the hemodynamic severity. In a subset of patients, we used the aortic valve calcium score measured by MDCT to corroborate AS severity. Aortic valve calcification is a marker of "anatomic" severity and not a direct marker of hemodynamic severity. Nonetheless, several studies demonstrated that MDCT aortic valve calcium score was strongly associated with AS hemodynamic severity, progression rate, and clinical outcomes (10,11,17). However, aortic valve calcium score thresholds were never validated in these low LVEF LF-LG AS patients.

CONCLUSIONS

The use of MG ≥40 mm Hg with or without an AVA ≤1 cm² during DSE leads to misclassification of AS severity in approximately one-half of patients with low LVEF LF-LG AS. The most important limitation of these DSE criteria is the low sensitivity due to persistence of a LF state during dobutamine stress and persistent discordant grading of AS severity using MG and AVA. Application of a lower cutoff value for peak stress MG ≥35 mm Hg improves the sensitivity of DSE for the identification of TSAS. Use of the projected AVA at a normal flow rate of 250 ml/s provides the best performance for correctly classifying AS severity and the best prediction of clinical outcome in patients with low LVEF LF-LG AS undergoing medical management. This parameter should be considered to guide patient management, especially when discordant AS grading persists despite DSE. Because of the major implications of accurate assessment of AS severity in these low LVEF LF-LG AS patients, other methods such as aortic valve calcium scoring by MDCT should be considered to corroborate AS severity in all cases. Further studies will be needed to validate aortic valve calcium thresholds in this population and to assess the complementarity of DSE and aortic valve calcium scoring.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with LF-LG AS and reduced LVEF who underwent DSE, calculation of AVA_{proj} at a normal transvalvular flow rate (250 ml/min) more accurately identified patients with truly severe AS than use of the combination of MG ≥40 mm Hg and AVA ≤1.0 cm².

TRANSLATIONAL OUTLOOK: Additional studies are needed to evaluate the complementary diagnostic value of aortic valve calcification assessed by MDCT imaging and calculation of the AVA_{proj} by DSE to improve selection of patients with LF-LG AS for valve replacement.

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KEY WORDS aortic stenosis, LV dysfunction, stress echocardiography, survival