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ORIGINAL RESEARCH

A Novel Echocardiographic Parameter to Confirm Low-Gradient Aortic Stenosis Severity

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ABSTRACT

BACKGROUND In patients with low-gradient (LG) aortic stenosis (AS), confirming disease severity and indication of intervention often requires dobutamine stress echocardiography (DSE) or aortic valve calcium scoring by computed tomography. We hypothesized that the mean transvalvular pressure gradient to effective orifice area ratio (MG/EOA, in mm Hg/cm^2) measured during rest echocardiography identifies true-severe AS (TSAS) and is associated with clinical outcomes in patients with low-flow, LG-AS.

OBJECTIVES The purpose of this study was to evaluate the diagnostic and prognostic value of MG/EOA ratio.

METHODS The diagnostic accuracy of MG/EOA ratio to identify TSAS was retrospectively assessed in: 1) an in vitro data set obtained in a circulatory model including 93 experimental conditions; and 2) an in vivo data set of 188 patients from the TOPAS (True or Pseudo-Severe Aortic Stenosis) study (NCT01835028). Receiver operating characteristic curves were used to assess the diagnostic accuracy of MG/EOA ratio for identifying TSAS, and Cox proportional hazards regression analyses were performed to assess its association with clinical outcomes.

RESULTS The optimal cutoff of MG/EOA ratio to identify TSAS in patients with low-flow, LG-AS was ≥25 mm Hg/cm^2 (correct classification 85%), as well as in vitro (100%). During a median follow-up of 1.41 ± 0.75 years, 146 (78%) patients met the composite endpoint of aortic valve replacement or all-cause mortality. A MG/EOA ratio ≥25 mm Hg/cm^2 was independently associated with an increased risk of the composite endpoint (adjusted HR: 2.36 [95% CI: 1.63-3.42], $P < 0.001$). The Harell's C-index of MG/EOA was 0.68, equaling projected EOA (0.67) measured by DSE.

CONCLUSIONS MG/EOA ratio can be useful in low-flow, LG-AS to confirm AS severity and may complement DSE or aortic valve calcium scoring. (JACC Adv. 2024;3:101245) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVC = aortic valve calcium

AVR = aortic valve replacement

CT = computed tomography

DSE = dobutamine stress echocardiography

EOA_{Proj} = projected effective orifice area

LG = low-gradient

LVEF = left ventricular ejection fraction

MG = mean transvalvular pressure gradient

SVi = stroke volume index

TSAS = true-severe aortic stenosis

Low-gradient (LG) aortic stenosis (AS) is a challenging clinical entity characterized by a discordant grading on rest echocardiography with an aortic valve effective orifice area (EOA) ≤1.0 cm^2 but a peak aortic jet velocity <4 m/s or mean transvalvular pressure gradient (MG) <40 mm Hg. Hence, in LG-AS, the true severity of AS and thus the indication of intervention cannot be reliably assessed by rest echocardiography. LG-AS includes 3 flow-gradient patterns: 1) classical low-flow, LG AS with a left ventricular ejection fraction (LVEF) < 50%; 2) paradoxical low-flow, LG AS with a LVEF ≥50% but a low-flow state defined as a stroke volume index (SVi) ≤35 mL/m^2; and 3) normal-flow, LG AS with a LVEF ≥50% and normal flow (ie SVi > 35 mL/m^2).

Current guidelines recommend performing low-dose dobutamine stress echocardiography (DSE) in patients with classical low-flow, LG-AS and aortic valve calcium scoring (AVC) by computed tomography (CT) in those with paradoxical low-flow, LG to adjudicate AS severity.[1,2] A peak stress MG (MG_{peak}) ≥40 mm Hg or peak stress EOA (EOA_{peak}) ≤1.0 cm^2 are the DSE criteria proposed in the guidelines to confirm the presence of true-severe AS (TSAS) and recommend intervention. In the True or Pseudo-Severe Aortic Stenosis (TOPAS) registry,[3] we previously reported that DSE is often inconclusive (up to 50% of the cases) and provides a suboptimal diagnostic accuracy (<60%) to identify TSAS, when using these criteria. We also reported that the projected aortic valve effective orifice area (EOA_{Proj}) at a normal flow rate is superior to the EOA_{peak} or MG_{peak} to identify TSAS and is associated with clinical outcomes in patients with LG-AS. All these parameters, however, have limitations since their measurement requires DSE, an additional diagnostic test that is not feasible for all patients, and which often results in inconclusive results due to a lack of or minimal flow reserve.[3]

Although the EOA and MG measurements are discordant on rest echocardiography for the grading of AS severity in LG-AS, we hypothesized that the ratio of these 2 parameters, ie, the MG/EOA ratio, is superior to the rest MG, MG_{peak}, rest EOA or EOA_{peak}, and at least equivalent to the best DSE parameter, (ie the EOA_{Proj}), to differentiate true severe vs pseudo-severe AS and is associated with clinical outcomes in patients with low-flow, LG-AS. From a pathophysiological standpoint, the MG/EOA ratio reflects the transvalvular pressure loss per 1 cm^2 of EOA and logically increases with degree of AS severity. Indeed, higher is the pressure gradient per cm^2 of valve orifice area, the higher is the magnitude of flow turbulence and thus of energy loss downstream to the valve. The objective of this study was thus to assess the diagnostic accuracy and prognostic value of the MG/EOA ratio in low-flow, LG-AS. To achieve this objective, we conducted an in vitro and an in vivo study (**Figure 1**).

METHODS

IN VITRO STUDY. Cardiac pulse duplicator. The in vitro circulatory system was previously described.[4] Briefly, this system includes anatomically shaped silicone-made left heart cavities and aorta, and simulation of the pulmonary and systemic circulations. Contraction of the left ventricle is achieved by a piston pump (Vivitro Inc). Both pump activation and signal acquisition are controlled with LabVIEW8.2 (National Instruments) through a Compact RIO with field programmable gate array controller and data acquisition system. Controlling enables physiological flow through the aortic valve following the standards for heart valve testing in normal flow conditions (ISO 5840-part 3). The circulatory fluid was a saline mixture of water (53%) and glycerol (47%) mimicking blood viscosity (4 ± 0.2 cP) and maintained at 37 °C.

Doppler echocardiographic measurements. Doppler echocardiographic measurements were performed using a General Electric Vivid 7 (GE Health Medical) with a 3.5 MHz probe. The transvalvular flow velocities, MG, and aortic velocity-time integral were measured five times per condition by continuous-wave Doppler. Transvalvular flow was measured using an electromagnetic flowmeter (Model 501, Carolina Medical Electronics Inc) positioned immediately below the aortic valve and averaged over 100 cycles. Valve EOA was determined by the continuity

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

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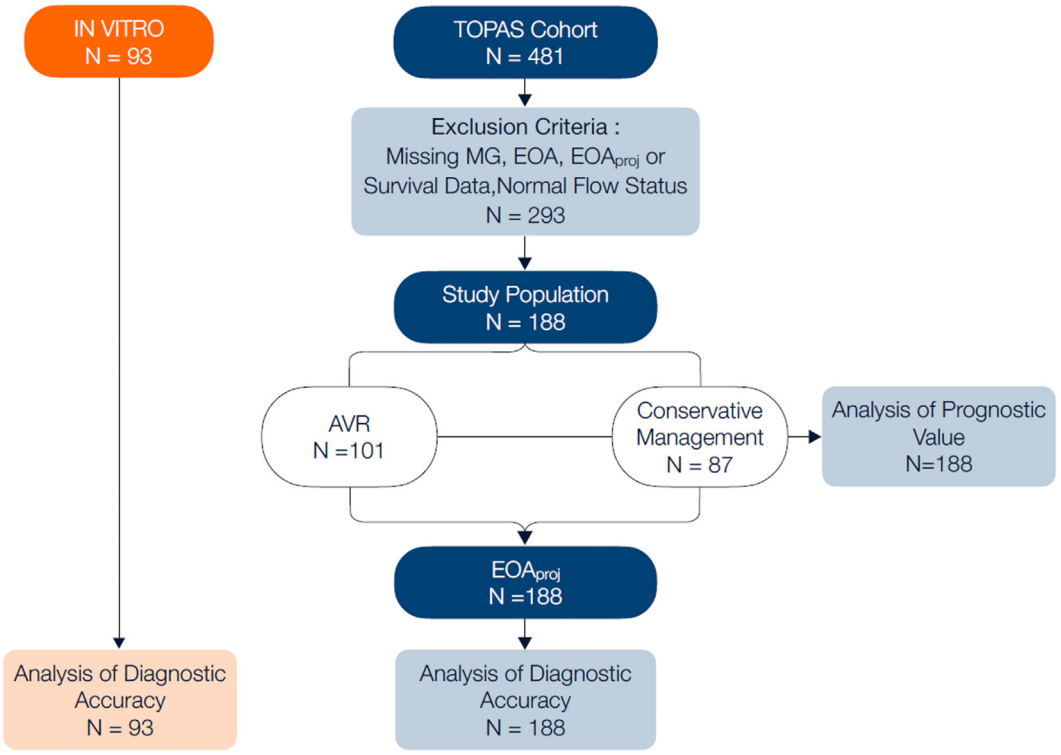
FIGURE 1 Study Flow Chart



AVR = aortic valve replacement; EOA = effective orifice area; EOA_{proj} = projected aortic valve area at normal flow rate; MG = mean transvalvular pressure gradient.

equation, by dividing the stroke volume measured with electromagnetic flowmeter by the echocardiographic aortic flow velocity-time integral. Mean transvalvular flow rate was calculated by dividing the stroke volume by the left ventricular ejection time.

Simulation of the aortic stenosis. To reproduce an AS, three clamp rings were inserted through the stent frame of a 23-mm Edwards SAPIEN transcatheter valve. Depending on the length of the clamp rings, different degrees of valve restriction and thus of AS severity were achieved. The aortic valve was then implanted in a 23 mm silicone annulus. Four degrees of stenosis were generated as follows: moderate, moderate to severe, severe, and very severe stenosis defined as an EOA of 1.3, 1.1, 0.9, and 0.8 cm^2, respectively. Severe AS was defined as an AVA ≤1.0 cm^2 at a normal transvalvular flow rate (mean transvalvular flow rate between 200 and 250 mL/s). For each degree of stenosis, 2 different heart rates (heart rate: 60, 80 beats/min), but 1 stroke volume (SV: 50 mL) were tested. Assuming an average body surface of 1.7 m^2, this stroke volume corresponded to low flow state (LF: ∼29 mL/m^2). Low-flow, LG-AS pattern was defined as: MG <40 mm Hg, EOA≤1.0 cm^2, and SVi ≤35 mL/m^2.

IN VIVO STUDY. Patient population. The TOPAS prospective multicenter observational cohort protocol was previously described (NCT01835028).[3,5-7] Briefly, patients were eligible if they had an indexed EOA_{peak} ≤0.6 cm^2/m^2, a MG <40 mm Hg. The exclusion criteria were >mild mitral stenosis, acute coronary syndrome, or acutely decompensated heart failure within 3 months before inclusion, severe condition with a low likelihood of survival at 1 year, end-stage kidney disease (requiring dialysis), severe cognitive impairment, normal-flow status, and missing MG or EOA or survival data. The present analysis included 188 patients with classical (LVEF<50%) low-flow, LG-AS (**Figure 1**). The therapeutic management (aortic valve replacement [AVR] or conservative management) was left to the discretion of the caring heart team. The participants were followed up yearly until a minimum of 2 years. The Institutional Review Board committee of the

participating centers approved the study and the subjects provided written informed consent. Demographic and clinical data were collected at inclusion. Echocardiographic images were acquired and analyzed following established guidelines. Baseline resting EOA was calculated using the continuity equation and the MG was estimated using the simplified Bernoulli method.[8] The details of the resting and DSE and the measurement of the EOA_{proj} are provided in the Supplemental material.

In vivo study endpoints. To assess the diagnostic accuracy in the in vivo study, TSAS was defined as EOA_{proj} at normal flow rate (250 mL/s) ≤1.0 cm^2 on DSE as previously validated.[5] To assess the prognostic value in vivo, the primary study endpoint was a composite of all-cause mortality and AVR at 2 years and the secondary endpoint was all-cause mortality at 2 years.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (25th-75th percentile) for normally and not-normally distributed variables, respectively, and were compared using Student 2-sample, paired *t*-test or Wilcoxon-Mann-Whitney test, as appropriate. Proportions are expressed as percentages and compared using chi-squared test. Receiver operating characteristic curves were used to assess the diagnostic accuracy of the MG/EOA ratio for identifying TSAS. The areas under the receiver operating characteristic curve (AUC) (95% CI) were used to compare the diagnostic accuracy of the different echocardiographic parameters. The optimal cutoff value of each parameter in each condition was determined using the Youden's index, and its sensitivity, specificity, and percentage of overall correct classification were reported. Univariable and multivariable Cox proportional hazards regression analyses were performed to assess the association between clinical and echocardiographic parameters with all-cause mortality and the composite endpoint of AVR and all-cause mortality with results expressed as HRs [95% CI]. As the conservative treatment group was small and the number of events (ie all-cause mortality) during the follow-up was limited, comprehensive multivariable Cox analyses were constrained in the number of risk factors that could be included in a single model. The proportional hazards assumption was confirmed through the evaluation of scaled Schoenfeld residuals. To further investigate the relationship between MG/EOA and the HR change, a spline curve was fitted for both all-cause mortality and the composite endpoint of AVR and all-cause mortality, and the same methodology was applied for EOA_{proj}, the rest MG, the MG_{peak}, the rest EOA, and EOA_{peak} parameters. The incremental prognostic value of these echocardiographic parameters versus the multivariable clinical model (including diabetes, coronary artery disease, hyperlipidemia, peripheral artery disease, and New York Heart Association (NYHA) functional class III/IV) for the composite endpoint was assessed using the Harrell's C-index. The incremental prognostic value of the MG/EOA ratio was further assessed in the conservative treatment group versus the multivariable clinical model (diabetes, chronic kidney disease, and NYHA functional class III/IV) for all-cause mortality using the same approach. Likelihood ratio tests were also used to evaluate the prognostic value of MG/EOA ratio and EOA_{proj} by comparing the model fit of the multivariable model with and without MG/EOA or EOA_{proj}. Two-sided *P* value <0.05 was considered for statistical significance. Statistical analyses were performed with STATA (StataCorp, 2017) and R, version 4.3.1 (R Foundation for Statistical Computing).

RESULTS

DIAGNOSTIC ACCURACY OF THE MG/EOA RATIO.

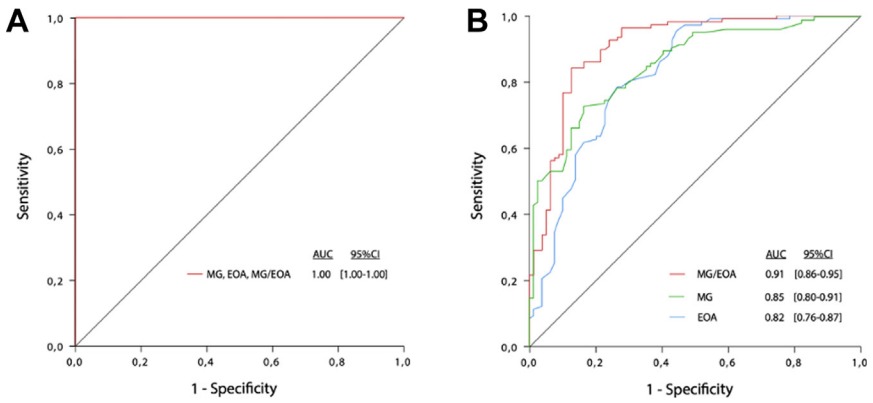
Echocardiographic characteristics. Supplemental Table 1 presents the average values of the echocardiographic parameters in the in vitro and in vivo data sets used in the diagnostic accuracy analysis.

In vitro study. In the in vitro study (**Figure 1**), the MG/EOA ratio had an excellent accuracy to identify TSAS in low-flow, LG-AS with an optimal cutoff at 25 mm Hg/cm^2, and a sensitivity, a specificity, and correct classification of 100% (**Figure 2A**, **Table 1**).

In vivo study. Baseline characteristics of the in vivo study cohort (**Figure 1**) are summarized in **Table 2**. The mean age was 74 ± 10 years, 78% of the patients were males. Baseline echocardiographic data are presented in **Table 2**. The prevalence of TSAS was 125 of 188 patients (66%). Baseline characteristics of the in vivo study cohort according to the optimal cutoff of 25 mm Hg/cm^2 are summarized in (Supplemental Tables 2 and 3).

In patients with low-flow, LG-AS, the MG/EOA ratio measured at rest demonstrated excellent accuracy to identify TSAS confirmed by DSE (ie EOA_{Proj} ≤1.0 cm^2) with an AUC of 0.91 [95% CI: 0.86-0.95], an optimal

FIGURE 2 Diagnostic Accuracy of MG/EOA Ratio, MG, and EOA Measured at Rest Echocardiography to Identify TSAS in the In Vitro and In Vivo Data Sets



Diagnostic accuracy of MG/EOA (red line), MG (green line), and EOA (blue line) to identify TSAS in the in vitro and in vivo data sets using ROC curve analyses, a red line was used when MG/EOA, MG, and EOA had identical accuracy to determine the presence of TSAS. (A) The diagnostic ability of these echocardiographic parameters in vitro to discriminate TSAS in low-flow, LG-AS (MG <40 mm Hg, EOA ≤1.0 cm^2, and stroke volume index ≤35 mL/m^2). (B) The diagnostic accuracy in vivo of the MG/EOA ratio, MG, and EOA to identify TSAS (defined as EOA_{proj} at normal flow rate measured by DSE ≤1.0 cm^2) in low-flow, LG-AS patients. AS = aortic stenosis; AUC = area under the receiver operating characteristic curve; LG = low-gradient; MG = mean transvalvular gradient; ROC = receiver operating characteristic curves; TSAS = true-severe aortic stenosis; other abbreviation as in Figure 1.

cutoff at 25 mm Hg/cm^2, and a sensitivity of 84%, specificity of 88%, and correct classification of 85%, respectively (Figure 2B, Table 1).

PROGNOSTIC VALUE OF MG/EOA RATIO IN LG-AS PATIENTS.

Follow-up and clinical outcomes. During a mean follow-up of 1.41 ± 0.75 years, 101 (54%) patients underwent AVR (73 [72%] surgical AVR and 28 [28%] transcatheter aortic valve implantation), 87 (46%) received conservative treatment, 74 (39%) died (45 [24%] patients in the conservative group, 29 [15%] in the AVR group) and 146 (78%) met the composite endpoint of AVR or all-cause mortality.

Composite endpoint of AVR and all-cause mortality. Using univariable and multivariable Cox regression analyses, the MG/EOA ratio was associated with an increased risk of the composite end point of AVR and all-cause mortality (all $P < 0.001$) (Supplemental Table 4). Based on spline curve analysis, the optimal prognostic cutoff for the composite endpoint at 2 years was close to 25 mm Hg (Figure 3). This association was confirmed using multivariable Cox proportional analysis (adjusted HR: 2.36 [95% CI: 1.63-3.42], $P < 0.001$; Table 3, Figure 4) with a Harrell's C-index of 0.68, which was similar to the DSE-derived EOA_{Proj} ≤1 cm^2 (C-index = 0.67), and the rest MG (C-index = 0.66) and EOA (C-index = 0.65) when compared with the multivariable model adjusted for diabetes, coronary artery disease, hyperlipidemia,

TABLE 1 Diagnostic Accuracy of MG/EOA to Identify TSAS

	AUC (95% CI)	Optimal Threshold	Se	Sp	CC
In vitro study					
MG/EOA	1.00 (1.00-1.00)	25 mm Hg/cm^2	100%	100%	100%
In vivo study (n = 188)					
MG/EOA	0.91 (0.86-0.95)				
Optimal		25 mm Hg/cm^2	84%	88%	85%
Highly sensitive		13 mm Hg/cm^2	100%	26%	68%
More specific		30 mm Hg/cm^2	49%	74%	54%
Highly specific		45 mm Hg/cm^2	21%	100%	55%

AUC = area under the receiver operating characteristic curve; CC = correct classification; EOA = effective orifice area; MG = mean gradient; Se = sensitivity; Sp = specificity; TSAS = true severe aortic stenosis.

TABLE 2 Baseline Clinical and Echocardiographic Characteristics of the Cohort (N = 188)

Clinical characteristics	
Age, y	74 ± 10
Males	147 (78%)
Body mass index, kg/m^2	27 ± 5
Diabetes	71 (38%)
Hypertension	131 (70%)
Hyperlipidemia	125 (66%)
Chronic kidney disease	54 (29%)
COPD	50 (27%)
Previous coronary artery bypass grafting	59 (31%)
Previous myocardial infarction	96 (51%)
Coronary artery disease	128 (68%)
Previous stroke or TIA	26 (14%)
Peripheral artery disease	14 (7%)
Atrial fibrillation/flutter	27 (14%)
Heart rate, beats/min	72 ± 13
Systolic blood pressure, mm Hg	120 ± 20
Diastolic blood pressure, mm Hg	71 ± 11
Congestive heart failure	125 (66%)
NYHA functional class III/IV	106 (56%)
EuroSCORE II	6.6 ± 5.2
Echocardiographic characteristics	
EOA, cm^2	0.87 ± 0.21
MG, mm Hg	23 ± 8
True severe AS	125 (66%)
Stroke volume, mL	59 ± 16
Stroke volume index, mL/m^2	31 ± 8
Mean systolic flow rate, mL/s	191 ± 47
LV ejection fraction, %	31 ± 10
Aortic regurgitation ≥ moderate	2 (1%)
Mitral regurgitation ≥ moderate	25 (13%)
Tricuspid regurgitation ≥ moderate	32 (17%)

Values are mean ± SD or n (%).

AS = aortic stenosis; Bpm = beats per minute; COPD = chronic obstructive pulmonary disease; EOA = effective orifice area; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; LG = low-gradient; LV = left ventricle; MG = mean transvalvular gradient; TIA = transient ischemic attack; other abbreviation as in Table 1.

peripheral artery disease, and NYHA functional class ≥II (Table 3).

Moreover, the addition of MG/EOA ratio to the baseline model improved the model's ability to estimate the risk for the composite endpoint of AVR and all-cause mortality: C-index increased from 0.63 to 0.68 and chi-squared from 20.0 to 41.8 (change 21.8; $P < 0.001$) using MG/EOA ≥25 mm Hg/cm^2 and C-index increased from 0.63 to 0.67 and chi-squared increased from 20.0 to 43.9 (change 23.9; $P < 0.001$) using MG/EOA as a continuous variable. The addition of the EOA_{proj} instead of the MG/EOA to the baseline model improved the model's ability to estimate the risk for the composite of AVR and all-cause mortality: C-index increased from 0.63 to 0.67 and chi-squared from 20.0 to 40.3, change 20.3; $P < 0.001$ using EOA_{proj} ≤1.0 cm^2 and C-index increased from 0.63 to 0.69 and chi-squared from 20.0 to 50.7, change 30.7 ($P < 0.001$) using EOA_{proj} as a continuous variable (Table 3).

All-cause mortality. Based on spline curve analysis, the optimal prognostic cutoff for all-cause mortality at 2 years was close to 20 mm Hg/cm^2 (Supplemental Figure 1). In univariable analyses, the MG/EOA ratio was not associated with increased risk of all-cause mortality in the whole cohort (data not shown). However, a MG/EOA >20 mm Hg/cm^2 was associated with an increased risk of mortality in the conservative treatment group after adjustment for diabetes, chronic kidney disease, and NYHA functional class III/IV (adjusted HR: 1.99 [1.03-3.84], $P = 0.04$) (Supplemental Table 5).

DISCUSSION

The main findings of the present study are: 1) a MG/EOA ≥25 mm Hg/cm^2 obtained on rest echocardiography accurately identifies the presence of TSAS determined by DSE in patients with low-flow, LG-AS; 2) a MG/EOA ratio ≥25 mm Hg/cm^2 is also independently associated with an increased risk of the composite clinical endpoint of AVR and all-cause mortality and provides incremental prognostic value versus the baseline clinical risk factors and standard rest echocardiographic parameters; 3) although a MG/EOA ratio ≥20 mm Hg/cm^2 was associated with higher rates of all-cause mortality after adjustment for baseline clinical risk factors, it did not provide significant incremental prognostic value versus these factors as well as versus the standard rest echocardiographic parameters.

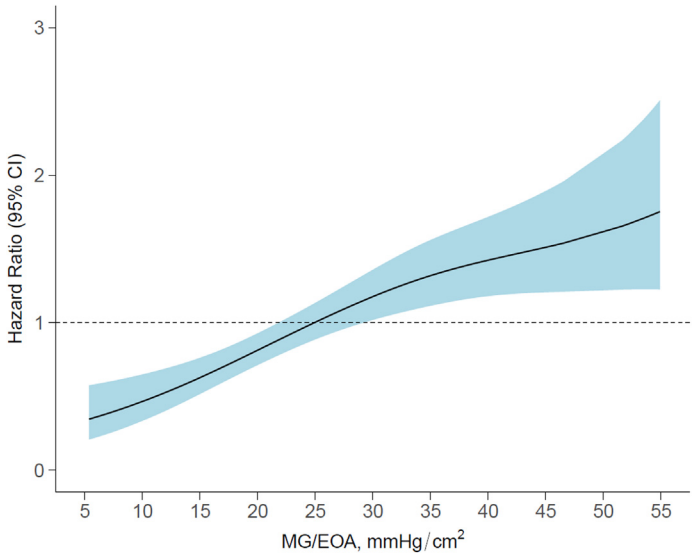
DIAGNOSTIC VALUE OF THE MG/EOA RATIO. In patients with LG-AS, there is a discordance on rest echocardiography between the gradient or peak aortic jet velocity, suggesting nonsevere AS, and the EOA, suggesting severe AS. In this context, the actual severity of the stenosis and thus the indication for AVR cannot be determined. Hence, accurate confirmation of AS severity using additional echocardiographic parameters, or an additional imaging modality is key for therapeutic decision-making. To our knowledge, this is the first study that proposes to differentiate TSAS versus nonsevere AS in patients with low-flow, LG-AS using the MG/EOA ratio. From a pathophysiological standpoint, this ratio reflects the transvalvular pressure loss per 1 cm^2 of EOA and logically increases with degree of AS severity. Indeed, higher is the pressure gradient per cm^2 of valve orifice area, the higher is the magnitude of flow turbulence and thus of energy loss downstream to the valve.

Both gradient and EOA are flow dependent: ie, the gradient decreases and thus underestimates AS severity with decreasing flow, whereas the EOA decreases and thus overestimates AS severity.[9-12] Given that these flow-dependent changes in gradient and EOA results in opposite effects on the estimation of AS severity, the ratio of these 2 parameters may actually cancel or dampened these effects, and therefore provide a more accurate estimate of the true AS severity, even if assessed in low flow conditions. For example, among 2 patients with low-flow, LG-AS, the one presenting with a MG of 35 mm Hg, an EOA of 0.8 cm^2, and thus a MG/EOA ratio of 44 mm Hg/cm^2 is very likely to have TSAS, whereas the other one with a MG of 16 mm Hg, an EOA of 0.95 cm^2 and thus a ratio of 17 mm Hg/cm^2 is unlikely to have TSAS (**Central Illustration**, Supplemental Figure 2). One of the major strengths of the MG/EOA ratio is that it can easily be obtained from the rest echocardiogram using parameters that are routinely measured and this parameter therefore does not require any additional measure or test.

In this study, we included patients with classical low-flow, LG-AS with reduced LVEF. The LG-AS entity also includes the subset of patients with preserved LVEF and paradoxical low-flow, LG AS and those with normal flow, LG-AS. For patients with paradoxical low-flow, LG-AS guidelines recommend using CT AVC scoring to determine the presence of TSAS and confirm the indication of AVR. For normal-flow, LG-AS, the American guidelines[2] do not specifically address this challenging subset of patients and the European guidelines indicate that severe AS is unlikely in these patients. Nevertheless, several studies reported that a substantial proportion of these patients may have TSAS and benefit of AVR.[13-15] Further studies are needed to determine if the MG/EOA ratio would be useful to confirm AS severity in these patients with paradoxical low-flow, LG-AS and in those with normal-flow, LG-AS. We expect the optimal cutoff value of MG/EOA associated with TSAS and prognosis will be similar (ie ≥25 mm Hg/cm^2) in paradoxical vs classical low-flow, LG-AS, whereas higher cutoff values (~30 mm Hg/cm^2) may have to be applied for patients with normal-flow, LG-AS. Indeed, given that the MG is more flow-dependent than the EOA, the MG/EOA ratio may still exhibit some flow dependency.

The purpose of the MG/EOA ratio obtained from the rest echocardiography is not to replace but rather to complement the DSE or CT parameters of AS severity. Indeed, in this challenging subset of patients with low-flow, LG-AS, it is more robust to apply a multimodality, multiparameter integrative approach rather than relying on a single modality and parameter to determine the severity of AS and the indication of AVR.

FIGURE 3 Spline Curves Analyses of the Composite EndPoint of AVR and All-Cause Mortality According to MG/EOA Ratio



Association between the MG/EOA ratio and the composite endpoint of AVR and all-cause mortality at 2 years using spline curve analysis. Abbreviations as in **Figure 1**.

PROGNOSTIC VALUE OF MG/EOA IN LG-AS. The present study also demonstrated the powerful incremental prognostic value of the MG/EOA ratio in patients with low-flow, LG-AS. This new parameter appeared to be superior to standard resting echocardiographic parameters of AS severity and equal to DSE parameters in association with prognosis. Further studies are needed to confirm the prognostic value of the MG/EOA ratio in the other subtypes of LG-AS: ie, paradoxical low-flow and normal-flow. Another interesting future direction is to apply this novel and simple Doppler echocardiographic parameter to assess the effect of bioprosthetic valve hemodynamics following AVR on postprocedural mid- and long-term outcomes. There have been conflicting results regarding the impact of high residual gradients (ie, MG ≥20 mm Hg) following surgical or transcatheter AVR.[16-18] These discrepancies may be related to the fact that the MG is highly flow dependent and that the flow status may vary extensively depending on the baseline risk profile of the population and the type of AVR. A normalization of the MG to the EOA by calculating the MG/EOA ratio may help to better identify suboptimal bioprosthetic valve

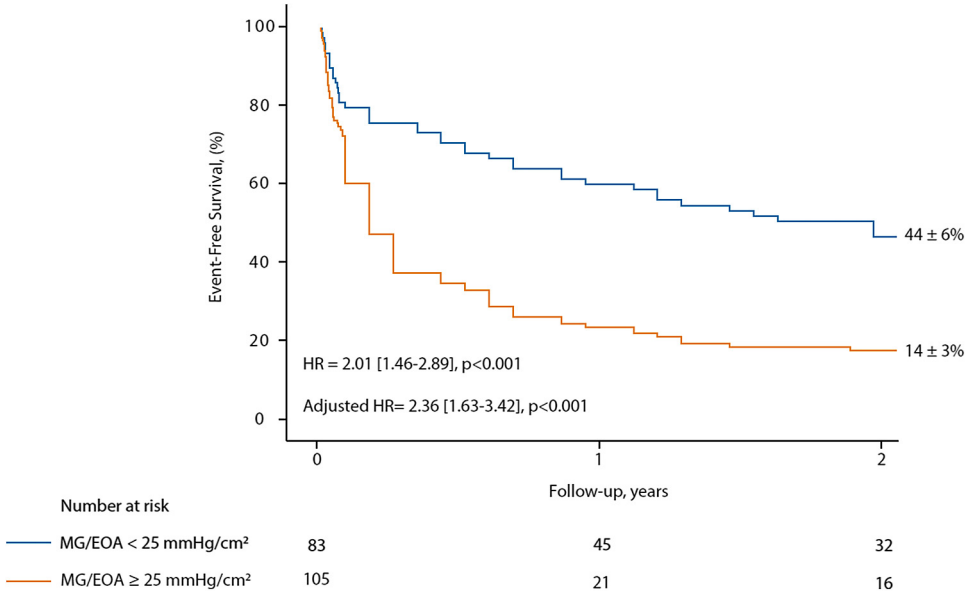
TABLE 3 Association of Echocardiographic Parameters With the Composite EndPoint of AVR and All-Cause Mortality Using Univariable and Multivariable Cox Regression Analyses

		Univariable	Multivariable	
	Prognostic Cutoff	HR (95% CI), *P* Value	HR[a] (95% CI), *P* Value	C-Index
Composite of AVR and mortality				
MG, (continuous)	-	1.04 (1.02-1.06), $P < 0.001$	1.05 (1.03-1.07), $P < 0.001$	0.66
MG	21 mm Hg	1.89 (1.35-2.66), $P < 0.001$	2.15 (1.43-2.90), $P < 0.001$	0.66
MG_{peak}, (continuous)	-	1.02 (1.01-1.04), $P < 0.001$	1.03 (1.01-1.05), $P < 0.001$	0.67
MG_{peak}	27 mm Hg	1.94 (1.38-2.76), $P < 0.001$	2.21 (1.51-3.22), $P < 0.001$	0.67
EOA, (continuous)	-	6.25 (2.77-14.28), $P < 0.001$	7.30 (2.77-17.54), $P < 0.001$	0.67
EOA	1.0 cm^2	5.30 (1.95-14.36), $P = 0.001$	5.88 (2.15-16.66), $P = 0.001$	0.65
EOA_{peak}, (continuous)	-	47.6 (9.90-232.53), $P < 0.001$	42.2 (7.94-227.27), $P < 0.001$	0.67
EOA_{peak}	0.55 cm^2/m^2	2.87 (1.81-4.56), $P < 0.001$	2.81 (1.75-4.50), $P < 0.001$	0.68
MG/EOA, (continuous)	-	1.03 (1.02-1.04), $P < 0.001$	1.03 (1.02-1.04), $P < 0.001$	0.67
MG/EOA	25 mm Hg/cm^2	2.01 (1.46-2.89), $P < 0.001$	2.36 (1.63-3.42), $P < 0.001$	0.68
MG/EOA	30 mm Hg/cm^2	1.87 (1.34-2.61), $P < 0.001$	1.97 (1.38-2.80), $P < 0.001$	0.65
EOA_{proj}, (continuous)	-	14.2 (5.55-36.63), $P < 0.001$	14.0 (5.38-36.9), $P < 0.001$	0.69
EOA_{proj}	1.0 cm^2	2.23 (1.57-3.16), $P < 0.001$	2.31 (1.59-3.35), $P < 0.001$	0.67

C-index refers to the comparison between MG, EOA, MG/EOA, and EOA_{proj} with the multivariable model[a]. [a]Adjusted for: diabetes, coronary artery disease, hyperlipidemia, peripheral artery disease, and NYHA functional class III/IV.

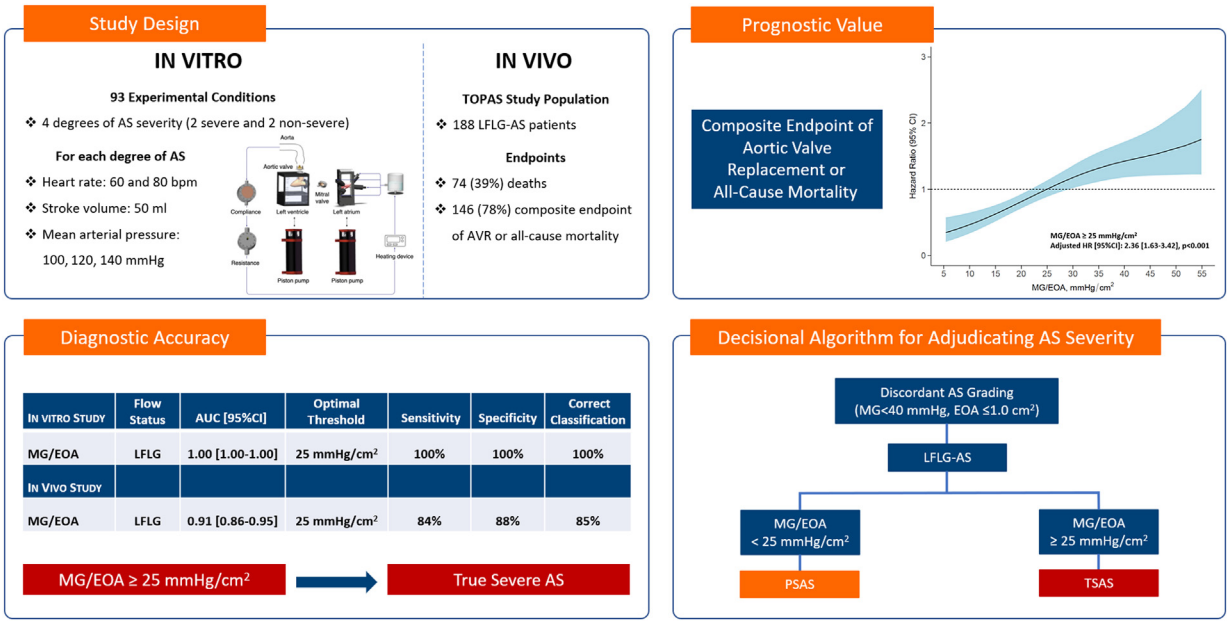
C-index = the Harrell's C-index; EOA_{proj} = projected effective orifice area; other abbreviations as in Table 1.

FIGURE 4 Prognostic Impact of MG/EOA Ratio on the Composite End Point



Kaplan-Meier curves analysis assessing the prognostic impact of MG/EOA ratio in the whole cohort. The blue line represents patients with a MG/EOA ratio below 25 mm Hg/cm^2. The orange line represents patients with a MG/EOA ratio equal or above 25 mm Hg/cm^2. Adjusted for EuroSCORE II, diabetes, coronary artery disease, hyperlipidemia, and congestive heart failure. EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **The Transvalvular Pressure Gradient to Aortic Valve Area Ratio to Adjudicate True Severe Aortic Stenosis and Association With Clinical Outcomes**



Hecht S, et al. JACC Adv. 2024;3(10):101245.

The hazard ratio in the spline curve presented in the top right panel is adjusted for: EuroSCORE II, diabetes, coronary artery disease, hyperlipidemia, and congestive heart failure. LFLG = low-flow low-gradient; PSAS = pseudo-severe aortic stenosis; TOPAS = the True or Pseudo-Severe Aortic Stenosis; TSAS = true-severe aortic stenosis; other abbreviations as in Figures 1, 2, and 4.

hemodynamics following AVR and therefore to better predict prognosis.

STUDY LIMITATIONS. This study has several limitations. The in vivo study was a retrospective analysis conducted in the prospective TOPAS registry and may thus have included biases inherent to retrospective analyses. CT AVC score was not available in all patients and could thus not be used to assess the diagnostic value of the MG/EOA ratio. However, the in vitro data and the in vivo DSE data were consistent in confirming the high accuracy of the MG/EOA ratio to identify TSAS. One limitation of our study is the overfit of the model for the in vitro data, which may be due to the low noise levels inherent to the in vitro experiments.

In the TOPAS registry, there were not enough patients with paradoxical low-flow or normal-flow, LG-AS to assess the usefulness of the MG/EOA ratio. Thus, further studies are necessary to assess the diagnostic accuracy and optimal cutoff value of the MG/EOA ratio to differentiate severe from nonsevere AS and its association with prognosis in these other subtypes of LG-AS. Furthermore, the utility of the MG/EOA ratio in low-flow LG-AS patients requires additional validation in other cohorts. In the present study, a cutoff of MG/EOA ≥25 mm Hg/cm^2 appeared to provide the best performance both in terms of diagnostic accuracy and prognostic value. However, a cutoff ≥30 mm Hg/cm^2 provides better specificity for the identification of TSAS and may thus be more suitable for clinical use.

The robustness of the MG/EOA ratio depends on the accuracy of the measures that are used in its calculation and a particular attention should be paid to confirm the validity of the gradient and EOA measures. In particular, an underestimation of left ventricular outflow tract diameter will translate into overestimation of the ratio and thus of AS severity and, vice versa, a misalignment of the probe leading toward an underestimation of the gradient will result in underestimation of the ratio and thus of AS severity.

The measurement of the MG/EOA ratio on the rest echocardiogram was feasible in 99% of the patients included in the TOPAS study. However, the

diagnostic accuracy and prognostic value was tested only in the subset (n = 188) of patients for whom the EOA_{Proj}, used for adjudication of AS severity, was available. Consequently, the analyses of the association between MG/EOA and all-cause mortality were underpowered, particularly in the conservative treatment group, and further studies with larger number of patients are required to confirm the association between this ratio and all-cause mortality.

CONCLUSIONS

The MG/EOA ratio measured on rest echocardiography is a novel and robust parameter to differentiate true versus pseudo-severe AS in patients with discordant grading and low-flow, LG-AS. The optimal cutoff value of MG/EOA to identify TSAS and therefore confirm the current guideline indication of AVR is ≥ 25 mm Hg/cm^2. This parameter may provide a valuable additional measure to DSE parameters or CT AVC score to confirm AS severity and guide intervention in low-flow, LG-AS. Further analyses are required to assess and validate the utility of the MG/EOA ratio in the LG AS population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with LG-AS, the actual AS severity and thus the indication of AVR cannot be determined from classical rest echocardiography parameters. A MG/EOA ratio ≥25 mm Hg/cm^2 allows the differentiation of TSAS from nonsevere AS with high accuracy and is associated with increased risk of AVR or all-cause mortality at 2 years in patients with low-flow, LG-AS.

TRANSLATIONAL OUTLOOK: This novel and simple parameter may provide an additional measure to DSE parameters or CT AVC scoring to confirm AS severity. The utility of MG/EOA in paradoxical low-flow and normal-flow LG AS patients need to be further evaluated.

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KEY WORDS aortic stenosis, dobutamine stress, echocardiography, low-flow low-gradient

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.