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

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**Running title:** DSE criteria for low ejection fraction AS severity

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**Conflicts Of Interest:** None

**Abstract**

**Background:** Dobutamine stress echocardiography (DSE) is useful to differentiate true from pseudo severe aortic stenosis in patients with low left ventricular ejection fraction (LVEF), low-flow, low-gradient aortic stenosis (LF-LG AS). In the ACC/AHA guidelines, patients are considered having true-severe stenosis when the mean gradient (MG) is ≥40mmHg with an aortic valve area (AVA) ≤1cm2 during DSE. However these criteria have not been previously validated. 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 LFLG AS.

**Methods:** In the TOPAS (“True or Pseudo-Severe Aortic Stenosis”) study, 186 patients with low LVEF LF-LG AS were prospectively recruited and underwent DSE with measurement of the MG, AVA and projected AVA, an estimate of the AVA at a standardized normal flow rate (AVAProj). Severity of AS was independently corroborated by macroscopic evaluation of the valve at the time of valve replacement in 54 patients and by measurement of the aortic valve calcium by computed tomography in 25 patients and by both methods in 8. According to these assessments, 50/87 (57%) of the study cohort had true-severe stenosis.

**Results:** Peak stress MG ≥40 mmHg, peak stress AVA ≤1cm2, and the combination of peak stress MG ≥40 mmHg and peak stress AVA≤1cm2 correctly classified AS severity in 48%, 60%, and 47% of patients, respectively, whereas AVAProj ≤1cm2 was better than all the previous markers (p<0.007) with 70% of correct classification. Among the subset of 88 patients managed conservatively (47% of 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, AVAProj ≤1cm2 was a strong predictor of mortality under medical management (HR: 3.65; p=0.0003).

**Conclusion:** In patients with low LVEF LF-LG AS, the DSE criteria of peak stress MG≥40 mmHg, or the composite of peak stress MG≥40 mmHg and peak stress AVA≤1cm2 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, AVAProj better distinguishes true from pseudo-severe aortic stenosis and is strongly associated with mortality in patients under conservative management.

**Clinical Trial: Trial registration number**NC T01835028

**Key Words:** Aortic stenosis; Stress echocardiography; Survival; LV dysfunction

**Condensed Abstract**

Dobutamine stress echocardiography (DSE) criteria to assess aortic stenosis (AS) in patients with low ejection fraction are not validated. In the TOPAS study, 186 underwent DSE with measurement of mean gradient (MG), aortic valve area (AVA) and projected AVA (AVAProj). AVAProj≤1cm2 was the best marker (p<0.007) to assess AS severity with 70% of correct classification. After comprehensive adjustment, MG and AVA were not predictors of mortality under medical treatment, while AVAProj was (HR: 3.65; p=0.0003). Thus, AVAProj better distinguishes true from pseudo-severe AS and is strongly associated with mortality in patients under conservative management.

**abbreviations**

AS: Aortic stenosis

AVA: Aortic valve area; AVARest at rest - AVAPeak at peak stress

AVAProj: Projected aortic valve area

AVR: Aortic valve replacement

DSE: Dobutamine stress echocardiography

LF-LG: Low flow, low gradient

LV: Left ventricle/Left ventricular

LVEF: Left ventricular ejection fraction; LVEFRest at rest - LVEFPeak at peak stress

MG: Mean transvalvular gradient; MGRest at rest - MGPeak at peak stress

Q: Transvalvular flow rate; QRest at rest - QPeak at peak stress

**Introduction**

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 regards to the assessment of AS severity and the therapeutic decision making (1). In the presence of a low flow state, the mean transvalvular pressure gradient (MG) can underestimate the stenosis severity due to its flow dependence, whereas the AVA may overestimate the stenosis severity due to incomplete opening of the valve orifice due to reduced opening forces (pseudo-severe AS (PSAS)). Hence, at rest, the patient often presents with discordant grading of AS severity where the aortic valve area (AVA) is < 1.0 cm2 suggesting severe AS, but the MG is <40 mmHg suggesting non-severe AS. In the current ACC/AHA valve guidelines (1), this entity is labeled “classical LF-LG AS and is defined as an AVA< 1.0 cm2, a MG< 40 mmHg, and a LVEF < 50%. Dobutamine stress echocardiography (DSE) has been shown to be useful to overcome the discordant grading observed in these patients as it can identify the presence of true-severe AS (TSAS) (2). In the ACC/AHA valve guidelines (1), these patients are considered to have true-severe AS and thus an indication for aortic valve replacement (AVR) (Class IIa recommendation) if the MG is ≥40 mmHg with an AVA ≤ 1.0 cm2 during DSE (1). However, these DSE criteria to distinguish AS severity in low LVEF LF-LG AS have not been well validated.

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

**Methods**

*Population*

One hundred and eighty-six (186) patients were prospectively recruited in the True or Pseudo-Severe Aortic Stenosis (TOPAS) study. The design and methods of this prospective multicenter observational study have been previously described (https://clinicaltrials.gov; NCT 01835028) (3-5). Patients were included in the TOPAS study if they had a MG ≤ 40 mmHg, an indexed AVA ≤ 0.6 cm²/m² 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 subjects provided informed consent. At study entry, all patients underwent an echocardiogram at rest and with dobutamine stress. A subset of patients (those recruited beyond 2009) underwent multi-detector computed tomography (MDCT) for the quantitation of aortic valve calcification. Clinical data was collected and included age, gender, body surface area (BSA), 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 rest and DSE parameters of AS severity (rest and stress AVA and MG). Patients were followed, in accordance with protocol, yearly for 5 years.

*Doppler Echocardiography*

Resting Doppler echocardiograms and DSE were performed using commercially available ultrasound system. The dobutamine infusion protocol consisted of 8-minute 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). LVOT 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; 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 (AVAProj) at a normal transvalvular flow rate (250ml/min) was calculated using the equation (9):

where AVARest and AVAPeak are the AVA at rest and at peak stress, and QRest and QPeak were Q at rest and at peak stress. To be consistent with guidelines criteria, peak stress values were obtained at the time when MG was maximal during DSE, which does not necessarily correspond to the last stage with maximum dobutamine dose. Likewise, AVAPeak and QPeak were the values of AVA and QPeak concomitant to MGpeak.

*Assessment of AS severity*

AS severity was assessed in 87 patients by one of two 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 the valve at the time of AVR and classified the valve stenosis severity as non-significant, 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 non-calcified). 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) while 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 > 1200 Agatston units (AU) for women and >2000AU 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% (7/8 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 between the assessment of AS severity and AVAPeak, MGPeak and AVAProj were determined by simple logistic regression analysis. Receiver operating characteristic (ROC) curves were used to determine the AUC, sensitivity, specificity and % correct classification (%CC) for these variables at several cut-off values. Based on previous studies that reported that estimation of AVAProj may not be reliable when the percent flow rate increase is <15% (3,9), we excluded such patients from the ROC analysis in the present study.

Accuracy of mortality prediction was determined for the cut-points proposed in the ACC/AHA guidelines for AVAPeak and MGPeak, and for AVAProj ≤1cm2, using Kaplan-Meier survival curves and Cox proportional hazards models and the corresponding curves adjusted for age, sex, functional capacity (as documented by the Duke activity status index), kidney failure and LVEFPeak (LVEF at peak dobutamine stress), in patients receiving medical management.

The net reclassification index using the category free NRI & IDI program codes downloaded online (<http://personalpages.manchester.ac.uk/staff/mark.lunt>) was used to determine the incremental predictive value of AVAProj ≤1cm2 beyond guidelines parameters (AVAPeak and MGPeak) for predicting 1-year mortality under medical management t). A p-value <0.05 was considered statistically significant. Statistical analyses were performed with JMP v.12 and STATA v.11 software.

**Results**

*Study Population*

The study population had a mean age of 73 ±10 years and included a larger proportion of men (78%) (**Table 1**). There was a high prevalence of co-morbidities including diabetes (41%), hypertension (68%), coronary artery disease (76%) and previous myocardial infarction (55%) (**Table 1**). LVEF was 28 ±8%, QRest was 190±49ml/s, MGRest was 23±8mmHg and AVARest was 0.88±0.22 cm2. With DSE, the average transvalvular flow rate and hemodynamic parameters of AS severity increased significantly (**Table 1**). However, 26% of patients had a QPeak < 220 ml/s and thus did not reach the normal flow rate despite dobutamine stress. On the other hand, 32% achieved a supra-normal flow rate (>300ml/s) during DSE, while only 42% had a peak flow rate in the normal range (230-300 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*

AVAProj and AVAProj indexed to body surface were significantly smaller in patients with TSAS vs. PSAS (0.88±0.16 vs. 0.99±0.23cm2; p=0.01 and 0.45±0.07 vs. 0.54±0.14 cm2/m2; p=0.0005, respectively), whereas AVAPeak and MGPeak were not (0.93±0.24 vs. 1.02±0.23cm2; p=0.07 and 38.2±10.3 vs. 34.5±11.8mmHg; p=0.12, respectively). MGPeak ≥40mmHg had low sensitivity of 35%, positive predictive value of 57% and lower percentage of correct AS severity classification of 48% for the identification of TSAS (**Table 2**). Lowering the MGPeak cut-off value to 35 mmHg for identifying TSAS improved the sensitivity (69%), positive predictive value (61%) and % correct classification (63%). A MGPeak cut-off value of 30 mmHg resulted in a % correct classification of 60%. AVAPeak≤1cm2 had a sensitivity of 63%, positive predictive value of 64%, and % correct classification of 60%. The combination of MGPeak ≥40mmHg and AVAPeak ≤1cm2 had a lower %correct classification (47%) compared to AVAPeak ≤1cm2 alone. AVAProj and indexed AVAProj had the best AUC, sensitivity and positive predictive value compared to the other DSE parameters (**Table 2**). Indexed AVAProj ≤ 0.6 cm2/m2 had the best performance to identify TSAS with an AUC of 0.70, sensitivity of 94%, positive predictive value of 66%, and % correct classification of 68% (**Table 2**). An AVAProj ≤ 1cm2 provided similar results with a % correct classification of 70%.

*Prediction of Patient Outcome*

In univariable analysis, MGPeak, AVAPeak, AVAProj and indexed AVAProj as continuous variables were predictors of mortality (all p≤0.02). As dichotomous variables only AVAProj ≤1cm2, (p<0.0001) and indexed AVAProj ≤0.55cm2/m2, (p=0.004) were predictors of mortality, while MGPeak ≥40 mmHg (p=0.69) and AVAPeak ≤1cm2 (p=0.06) were not (**Figure 2, Table 3**). The combination of AVAPeak ≤1cm2 and MGPeak ≥ 40mmHg 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 LVEFPeak, AVAProj and indexed AVAProj as continuous or dichotomous variables, and MGPeak and AVAPeak as continuous variables only, were independent predictors of mortality during medical management (all p≤0.02) (**Figure 2**). There was a trend toward significance of AVAPeak ≤1cm2 to predict mortality during medical management (p=0.06) (**Figure 2, Table 3**).

Models built with AVAProj or indexed AVAProj were more accurate to predict mortality than those built with AVAPeak or MGPeak (all p≤0.05). AVAProj≤1cm2 had a net reclassification index to predict death under medical management at one year of 0.96 compared to AVAPeak≤1cm2 (p<0.0001), 0.60 compared to MGPeak ≥ 40mmHg (p=0.01), and 0.88 compared to the composite of MGPeak ≥ 40mmHg and AVAPeak≤1cm2 (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 uni- and multi-variable analyses respectively).

**Discussion**

The main findings of this study are that in patients with low LVEF LF-LG AS: 1) A DSE criteria of MGPeak ≥40 mmHg has a low sensitivity for identifying TSAS and does not predict mortality in medically managed patients. Lowering the cut-off value of MGPeak to 35 mmHg can improve the sensitivity; 2) A DSE criteria of AVAPeak≤1.0 cm2 is superior to MGPeak criteria to identify TSAS and predict mortality; 3) A combination of MGPeak ≥40 mmHg and AVAPeak≤1.0 cm2 as proposed in the ACC/AHA valve guidelines has a low sensitivity for identifying TSAS and does not predict mortality in medically managed patients; and 4) AVAProj provides the best accuracy to predict TSAS and clinical outcomes with an AVAProj ≤1.0 cm2 (or indexed AVAProj ≤0.55 cm2/m2) providing the optimal cut-off value.

*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). Since 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, about half of patients failed to normalize their flow rate during dobutamine stress, potentially leading to persistence of the discordance in AS severity grade based on the MG and AVA. Additionally, 25% of patients achieved supra-normal flow rates during dobutamine stress, which can lead to “reverse” discordant grading by AVA and MG (AVA>1cm2 and MG ≥40mmHg). The projected AVA at a normal flow rate has the advantage of being standardized for the transvalvular flow rate. Indeed, 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 may explain why the AVAProj 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 MGPeak≥ 40 mmHg lacks sensitivity to differentiate TSAS and PSAS. Using a lower cut-off value of MGPeak ≥35 mmHg markedly improved the sensitivity from 35 to 69% while also improving the % correct classification from 48% to 63%. The utilization of a cut-off of 30 mmHg did not further improve the diagnostic performance of MGPeak. The low sensitivity of MGPeak criteria may be related to the fact that almost half of patients with low LVEF LF-LG AS do not achieve a normal flow rate with DSE, thus potentially precluding the MG to reach 40 mmHg despite the presence of TSAS. Using a DSE criteria of AVAPeak ≤ 1.0 cm2 has better sensitivity and % correct classification compared to MGPeak. Utilization of a cut-off 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 AVAPeak criteria is the relatively low specificity. Given that a large proportion of patients fail to achieve a normal flow rate of 250 ml/s with stress, AVAPeak may still be pseudo-severe due to a persistent low flow state. Using the combination of MGPeak≥ 40 mmHg and AVAPeak ≤ 1.0 cm2 as proposed in the ACC/AHA guidelines improves the specificity, but has a low sensitivity at only 22% and % correct classification of only 47% in our study cohort. The projected AVA at a normal flow overcomes the flow-dependency of MGPeak and AVAPeak, 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 AVAProj 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 Indices of AS Severity as Predictors of Mortality*

There was no association between DSE MGPeak ≥40 mmHg and mortality in our low LVEF LF-LG AS patients receiving medical management. This intriguing finding may be due to the fact that the increase in MG during DSE is 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 MGPeak. Indeed, 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 MGPeak does not necessarily indicate the presence of non-severe AS, but may be observed in a patient with TSAS in whom the increase in MGPeak 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 MGPeak <40 mmHg and AVAPeak≤1.0 cm2 had TSAS. Furthermore, there were several patients (n=8) with a MGPeak <40 mmHg and AVAPeak between1.0 and 1.2 cm2 who were found to have TSAS based on surgical inspection or aortic valve calcium load. Hence, the presence of a MGPeak <40 mmHg and/or an AVAPeak>1.0 cm2 on DSE does not exclude the presence of TSAS and a potential benefit from AVR.

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

As opposed to MGPeak and AVAPeak, AVAProj 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 may explain why a small AVAProj, reflecting 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 cannot 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, SV rest/peak (i.e. data included in the guidelines), but not of the AVAProj or the aortic valve calcification score. Despite being a limitation, this aspect of the protocol further reinforces the robustness of the results and conclusions of the study. Patients with a MGPeak ≥ 40mmHg are underrepresented in the medical management group because they were more likely to undergo aortic valve replacement. However, even as continuous variable, MGPeak appears to be a weaker predictor of mortality than AVAProj.

We primarily used the assessment of the valve by the cardiac surgeon at the time 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 semi-quantitative 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 have demonstrated that MDCT aortic valve calcium score is strongly associated with AS hemodynamic severity, progression rate, and clinical outcomes (10,11,17). However, aortic valve calcium score thresholds were never validated in this low LVEF LF-LG AS patients.

**Conclusion**

The use of MG ≥40mmHg with or without an AVA≤1cm2 during DSE leads to mis-classification of AS severity in about 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 low flow state during dobutamine stress, and persistent discordant grading of AS severity using MG and AVA. Application of a lower cut-off value for peak stress MG ≥ 35 mmHg improves the sensitivity of DSE for the identification of TS AS. Utilization 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. Given 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 dobutamine stress echocardiography and aortic valve calcium scoring.

**Perspectives**

*COMPETENCY IN MEDICAL KNOWLEDGE:* In patients with low LVEF LF-LG AS, the current ACC/AHA valve guidelines propose using a combination of a MGPeak ≥ 40 mmHg and AVAPeak ≤ 1.0 cm2 during dobutamine stress to identify TSAS; however, these criteria correctly classify less than 50% of patients. A large proportion of patients (57% in our cohort) with a MGPeak < 40 mmHg actually have TSAS. However, patients with peak stress MG <40 mmHg and peak stress AVA >1.2 cm2 likely have non-severe AS and AVR is not indicated as per current guidelines.

*COMPETENCY IN PATIENT CARE 1:* AVAProj ≤1.0 cm2 (or indexed AVAProj ≤0.55 cm2/m2) provides the best accuracy for predicting TSAS and predicting clinical outcome of low LVEF LF-LG AS under medical treatment. We would recommend calculating AVAProj to guide the management of patients with low LVEF LF-LG AS, especially in those patients with persistent discordant grading of AS severity during DSE (i.e. low MGPeak but small AVAPeak).

*COMPETENCY IN PATIENT CARE 2:* In patients with only a small increase in transvalvular flow rate (< 15%) during dobutamine stress, estimation of AVAProj may not be reliable and should not be used to guide therapeutic decision. Moreover, as no parameter provided a 100% correct classification, and given the crucial impact of aortic valve intervention in presence of true severe AS, it may be useful to perform MDCT to quantitate aortic valve calcification load and confirm AS severity.

*TRANSLATIONAL OUTLOOK:* Future larger studies are needed to evaluate the complementarity of aortic valve calcification by MDCT and AVAProj calculation by DSE, given that the combination of these two exams may improve patients’ stratification and thus outcome.

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**Figure Legends**

**Central Illustration: Comparison of correct classification of aortic stenosis severity (upper panel) and hazard ratio for survival prediction under medical treatment (lower panel) according to conventional DSE markers and projected aortic valve area at normal flow rate**. *Upper panel* shows the bar graph of correct (dark color) or incorrect (light color) classification according to the actual severity of aortic stenosis, i.e. truly severe (orange) of pseudo severe (blue). This analysis was performed in the subgroup of 87 patients with confirmation of AS severity by CT and/or surgeon. ***Lower panel*** shows the forest plot of hazard ratios of the different DSE criteria. This analysis was performed in the subgroup of 88 patients followed under medical management.

**Figure 1: Study flow chart.** This figure shows the different subgroups derived from the main TOPAS cohort and for which analyses these subsets were used. AVR: aortic valve replacement; AS: aortic stenosis; MDCT: multidetector computed tomography; DSE: dobutamine stress echocardiography.

**Figure 2: Kaplan-Meier and Cox curves of survival under medical management according to DSE variables of AS severity.** This figure shows the survival according to DSE mean gradient (MGPeak <40mmHg or ≥40mmHg) unadjusted (***Panel A***) and adjusted (***Panel B***), DSE aortic valve area (AVAPeak >1cm2 or ≤1cm2) unadjusted (***Panel C***) and adjusted (***Panel D***), projected aortic valve area (AVAProj >1cm2 or ≤1cm2) unadjusted (***Panel E***) and adjusted (***Panel F***),and indexed projected aortic valve area (AVAProj >0.6cm2/ m2 or ≤0.6cm2/ m2) unadjusted (***Panel G***) and adjusted (***Panel H***). In panels B, D, F, H, curves were adjusted for age, sex, functional capacity (Duke activity status index), kidney failure and DSE LVEF (\*). This analysis was performed in the subgroup of 88 patients followed under medical management.

**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, years | 73 ± 10 |  | 73 ± 10 | 72±11 |
| Male gender, n (%) | 145 (78) |  | 69 (78) | 68(78) |
| Diabetes, n (%) | 75 (41) |  | 30 (35) | 39(45) |
| Kidney failure, n (%) | 56 (30) |  | 25 (28) | 28(32) |
| Hypertension, n (%) | 126 (68) |  | 59 (68) | 61(70) |
| Hyperlipidemia, n (%) | 125 (68) |  | 56 (64) | 61(70) |
| Chronic obstructive pulmonary disease, n (%) | 53 (29) |  | 21 (24) | 27(31) |
| Coronary artery disease, n (%) | 140 (76) |  | 65 (76) | 61(70) |
| Previous MI, n (%) | 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, mmHg | 23 ±8 |  | 20 ±8 | 25±8 |
| Aortic valve area, cm2 | 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 Qmean ≥ 15%, n(%) | 164(88) |  | 80(90) | 75(85) |
|  |  |  |  |  |
| *Peak echocardiographic data* | |  |  |  |
| Mean gradient, mmHg | 32 ±12 |  | 27 ±10 | 37±11 |
| Aortic valve area, cm2 | 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, cm2 | 1.01 ± 0.21 |  | 1.09 ±0.23 | 0.93±0.20 |
|  |  |  |  |  |
| *Aortic valve intervention* |  |  |  |  |
| Surgical AVR, n(%) | 71 (38) |  | - | 61(70) |
| Transcatheter AVR, n(%) | 27 (15) |  | - | 20(23) |

Legend: AVR: Aortic valve replacement, LV: Left ventricular, NYHA: New-York heart association

**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**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **AUC** | **Cut-off** | **Sensitivity (%)** | **Specificity (%)** | **PPV (%)** | **NPV (%)** | **% Correct Classification** |
| AVAPeak | 0.60;  p = 0.07 | ≤1 cm2 | 63 | 56 | 66 | 58 | 60 |
| ≤1.2 cm2 | 84 | 21 | 58 | 50 | 56 |
| MGPeak | 0.58;  p = 0.12 | ≥40 mmHg | 35 | 65 | 57 | 44 | 48 |
| ≥35 mmHg | 69 | 54 | 61 | 49 | 63 |
| ≥30 mmHg | 78 | 37 | 61 | 56 | 60 |
| MGPeak ≥ 40mmHg  and AVAPeak ≤ 1cm2 | N/A | N/A | 22 | 81 | 61 | 42 | 47 |
| **AVAProj** | **0.65;**  **p = 0.01** | **≤ 1 cm2** | **86** | **47** | **68** | **72** | **70** |
| ≤1.2 cm2 | 100 | 13 | 60 | 100 | 61 |
| **Indexed AVAProj** | **0.70;**  **p=0.002** | **≤0.60 cm2/m2** | **98** | **29** | **64** | **92** | **68** |
| **≤0.55 cm2/m2** | **94** | **37** | **66** | **82** | **68** |

Legend: AVAPeak: Aortic valve area at peak dobutamine stress; MGPeak: Mean gradient at peak dobutamine stress; AVAProj: Projected aortic valve area at normal transvalvular flow rate (250ml/s)

**Table 3: Unadjusted and adjusted\* hazard ratio [95% confidence interval] of DSE parameters of AS severity to predict mortality in 87 patients under medical management**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate Analysis** | | |  | **Multivariate Analysis** | | |
| **Variables** | **Increment/**  **threshold** | **Unadjusted**  **HR** | **95% confidence interval** | **p-value** |  | **Adjusted\***  **HR** | **95% confidence interval** | **p-value** |
| MGPeak | 5 mmHg | 1.00 | 0.88-1.13 | 0.94 |  | 1.20 | 1.02-1.41 | 0.02 |
| ≥ vs. <40mmHg | 0.57 | 0.18-1.83 | 0.34 |  | 0.93 | 0.21-4.07 | 0.92 |
| AVAPeak | -0.1cm2 | 1.19 | 1.07-1.33 | 0.001 |  | 1.16 | 1.02-1.32 | 0.02 |
| ≤ vs. >1cm2 | 2.33 | 1.32-4.11 | 0.004 |  | 1.79 | 0.98-3.3 | 0.06 |
| ≤ vs. >1.2cm2 | 2.06 | 1.15-3.68 | 0.02 |  | 1.45 | 0.78-2.72 | 0.24 |
| AVAProj | -0.1cm2 | 1.16 | 1.01-1.33 | 0.04 |  | 1.29 | 1.09-1.53 | 0.003 |
| ≤ vs. >1cm2 | 2.13 | 1.20-3.78 | 0.01 |  | 3.78 | 1.90-7.50 | <0.0001 |
| ≤ vs. >1.2cm2 | 1.30 | 0.72-2.37 | 0.38 |  | 2.96 | 1.50-5.82 | 0.002 |
| Indexed AVAProj | -0.1cm2 | 1.15 | 0.92-1.43 | 0.21 |  | 1.43 | 1.10-1.86 | 0.008 |
| ≤ vs. > 0.55cm2/m2 | 1.60 | 0.89-2.87 | 0.12 |  | 2.59 | 1.35-4.95 | 0.004 |

Legend: AVAPeak: Aortic valve area at peak dobutamine stress; MGPeak: Mean gradient at peak dobutamine stress; AVAProj: Projected aortic valve area at normal transvalvular flow rate (250ml/s)

\* Adjusted for age, sex, functional capacity (Duke activity status index), kidney failure and LVEF at peak dobutamine stress