

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 cm² 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 cm², and the combination of peak stress MG ≥ 40 mm Hg and peak stress AVA ≤ 1 cm² correctly classified AS severity in 48%, 60%, and 47% of patients, respectively, whereas AVA_{Proj} ≤ 1 cm² 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 cm² 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 cm² 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](https://doi.org/10.1016/j.jacc.2018.01.028)) (J Am Coll Cardiol 2018;71:475–85) © 2018 by the American College of Cardiology Foundation.



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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 $\leq 50\%$) 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 $< 1.0 \text{ cm}^2$, which suggests severe AS, but the MG is $< 40 \text{ mm Hg}$, 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 $\leq 1.0 \text{ cm}^2$, a MG $< 40 \text{ mm Hg}$, 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 $\geq 40 \text{ mm Hg}$ with an AVA $\leq 1.0 \text{ cm}^2$ during DSE (1). However, these DSE criteria to distinguish AS severity in low LVEF LF-LG AS have not been well validated.

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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 $< 40 \text{ mm Hg}$, an indexed AVA $\leq 0.6 \text{ cm}^2/\text{m}^2$, and a LVEF $\leq 40\%$ 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 $\geq 140/90 \text{ mm Hg}$]), diabetes, renal failure, hyperlipidemia, coronary artery disease (history of myocardial infarction or $\geq 50\%$ 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

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