ORIGINAL RESEARCH

Contemporary Outcomes in Low-Gradient Aortic Stenosis Patients Who Underwent Dobutamine Stress Echocardiography

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***Background*—**Detection of flow reserve (FR) by dobutamine stress echocardiography is used for risk stratification in low-gradient aortic stenosis (AS). Prognostic significance of dobutamine stress echocardiography in the transcatheter aortic valve replacement era is unclear. We aimed to assess the current relevance of FR.

***Methods and Results*—**We studied 235 patients with low-gradient severe AS (rest aortic valve area ≤1.0 cm^2 or indexed aortic valve area ≤0.60 cm^2/m^2; mean aortic valve gradient <40 mm Hg) and left ventricular ejection fraction <50%) with dobutamine stress echocardiography done September 2010 through July 2016. FR was defined by ≥20% stroke volume increase. We diagnosed "true-severe AS" if peak aortic valve velocity ≥4 m/s occurred with aortic valve area ≤1.0 cm^2 (or indexed aortic valve area ≤0.6 cm^2/m^2). At a median time of 51 days, 128 patients underwent aortic valve replacement,either surgical aortic valve replacement (n=42) or transcatheter aortic valve replacement (n=86). FR was observed in 138 patients, while 86 patients had true-severe AS. During median follow-up of 2.3 years, 138 patients died. In a multivariable model, aortic valve replacement (hazard ratio 0.41, 95% CI: 0.29–0.58, P <0.001) and lower Society of Thoracic Surgeons score (hazard ratio 1.06, 95% CI: 1.04–1.09, P<0.001) were associated with better survival, while FR was not predictive. aortic valve replacement was associated with survival regardless of the presence or absence of FR or AS severity stratification.

***Conclusions*—**In low-gradient AS with reduced ejection fraction, FR or AS severity stratification by dobutamine stress echocardiography was not associated with survival. Aortic valve replacement was associated with better survival in low-gradient AS independent of FR. **(*J Am Heart Assoc*. 2019;8:e011168. DOI: 10.1161/JAHA.118.011168.)**

Key Words: aortic stenosis • dobutamine stress echocardiography • flow reserve • surgical aortic valve replacement • transcatheter aortic valve replacement

American College of Cardiology/American Heart Association Valve Guidelines endorse class IIa recommendations for low-dose dobutamine stress echocardiography (DSE) in aortic stenosis (AS) patients with left ventricular ejection fraction (LVEF) <50% to confirm AS severity and to assess flow reserve (FR), usually defined as stroke volume (SV) increase of ≥20%.[1–3] Based on FR presence and on measures of AS severity during DSE, patients are categorized as having true-severe AS with or without FR, pseudo-severe AS, and indeterminate AS.

FR was shown be a survival predictor in prior studies of low-gradient AS, whether treated conservatively or undergoing surgical aortic valve replacement (SAVR).[2,3] In addition, patients with pseudo-severe or indeterminate AS were deemed not to profit from SAVR. However, recent improvements in surgical procedures and the advent of transcatheter aortic valve replacement (TAVR) have enabled treatment of severe AS patients who were previously deemed inoperable. The utility of DSE, especially in risk stratification, in the TAVR era has not been studied. In addition, use of systolic function parameters such as LVEF, wall motion score index, cardiac power output (CPO), or global longitudinal strain (GLS) may improve the detection of FR.[4–10]

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Accompanying Tables S1, S2 and Figures S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011168

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Clinical Perspective

What Is New?

- Flow reserve (FR) assessed by dobutamine stress echocardiography was previously shown to be a survival predictor in low-gradient aortic stenosis patients who underwent surgical aortic valve replacement (AVR).
- The current study shows that FR (defined by stroke volume increase of ≥20% during dobutamine stress echocardiography) is not predictive of outcomes in low-gradient severe aortic stenosis.
- On the other hand, any type of AVR (ie, surgical or transcatheter) was independently associated with better survival, independent of the presence or absence of FR or aortic stenosis severity stratification.

What Are the Clinical Implications?

- Our results document limited ability of FR to predict outcome in the contemporary era even with surgical AVR.
- AVR improves outcome independent of the presence of FR or aortic stenosis severity, suggesting that absence of FR should not preclude patients from undergoing AVR.

In this study, we aim to assess the prognostic impact of FR in patients with low-gradient AS in the current era. Our main questions are: (1) Is FR associated with better survival?; (2) Does absence of FR decrease the beneficial impact of AVR?; and (3) Is classification of patients into subgroups of true-severe, pseudo-severe, and indeterminate AS relevant for decision making regarding AVR? We also assess the response of alternative markers of myocardial FR during DSE and compared their prognostic ability with SV increase to see if it improved risk stratification of low-gradient AS.

Methods

Study Sample

We identified consecutive patients who underwent low-dose DSE with peak dobutamine infusion of 20 μg/kg per minute for suspected low-gradient, severe AS with reduced ejection fraction (EF) at Cleveland Clinic from September 2010 to July 2016. The inclusion criteria were: (1) DSE study performed to define aortic stenosis severity; (2) Pretest echocardiogram that showed LVEF <50%, mean pressure gradient <40 mm Hg and aortic valve area (AVA) ≤1.0 cm^2 or indexed AVA ≤0.6 cm^2/m^2; and (3) Doppler interrogation of the aortic valve (AV) at each stage. Studies in which use of contrast for LV opacification or Doppler enhancement was deemed necessary were excluded to avoid signal overestimation caused by "blooming."[11] If the dobutamine infusion was terminated at the dobutamine dose of 5 μg/kg per minute, patients were also excluded. In 17 patients with multiple DSE, we used initial assessment only. We excluded patients with concomitant presence of restrictive cardiomyopathy.

We obtained demographic and clinical data at the time of DSE via manual extraction from electronic medical records. The survival status and presence of AVR were also collected. In this study, we grouped both SAVR and TAVR as AVR. The date of DSE was defined as the beginning of the observational period. Patients were followed via chart review with either the date of last follow-up or the date of death recorded. Mortality data were obtained from medical records or publicly available online sources (ie, nationally available databases, obituary websites), last queried November 18, 2017. We considered all-cause mortality the primary outcome. The study protocol was approved by the Cleveland Clinic Institutional Review Board, patient informed consent was waived, and data were de-identified.

Dobutamine Stress Echocardiography

All patients underwent a comprehensive echocardiographic assessment using commercial ultrasound systems. Dobutamine was delivered at a rate of 5, 10, and 20 μg/kg per minute with uptitration at 3-minute intervals. Systemic blood pressure and 12-lead ECG were monitored. DSE was terminated when maximum dose was reached or patients showed significant increase in blood pressure (systolic blood pressure >220 mm Hg or diastolic blood pressure >110 mm Hg), ischemia detected by ECG, complex ventricular arrhythmias, rapid new atrial arrhythmias, or chest discomfort. Measurements were performed at baseline and each stage of dobutamine protocol (5, 10, and 20 μg/kg per minute).

All DSE data were reviewed and measured by experienced readers blinded to clinical information according to the current guidelines.[12,13] Echocardiographic parameters included the following variables: peak AV velocity, peak and mean transvalvular gradient, aortic jet velocity-time integral (VTI), left ventricular outflow tract (LVOT) diameter, mean LVOT flow velocity, LVOT VTI, AVA, LVEF, LV end-diastolic volume, LV end-systolic volume, GLS, ejection time, SV, and CPO.

Peak AV velocity was measured using continuous-wave Doppler, and multiple acoustic windows were checked to determine the highest velocity at baseline. Transvalvular aortic gradients were calculated from velocity using a simplified Bernoulli equation. AVA was calculated using the continuity equation. SV was calculated from the cross-sectional area of the LVOT and VTI of LVOT flow:

SV_{LVOT}=cross sectional $area_{LVOT} \times VTI_{LVOT}$. We obtained LVOT VTI using pulsed-wave Doppler. In 30 patients with unreliable LVOT pulsed-wave Doppler signal, we calculated SV using LV volume measured by biplane Simpson's method throughout all stages from baseline to 20 μg/kg per minute.[14,15] Cardiac output (CO) was calculated as the product of SV and heart rate. CPO, a contractility parameter that incorporates pressure and flow generation into a single index, was calculated as follows: CPO (Watts)=(mean arterial pressure+mean AV gradient)$\times$CO$\times 2.22 \times 10^{-3}$, where mean arterial pressure=diastolic blood pressure+0.412 (systolic blood pressure−diastolic blood pressure).[7]

GLS was assessed offline using vendor-independent software (Velocity Vector Imaging, Siemens Medical Solutions).[16] The estimated peak systolic strain value from apical 4-chamber, 2-chamber, and long-axis views were averaged to obtain GLS. All strain measurements were performed by a single observer blinded to clinical, other echocardiographic data, and outcomes.

Interpretation of Dobutamine Stress Echocardiography Results

We interpreted an increase in SV of ≥20% compared with baseline value as a presence of FR.[1,3,12] We defined significant AS as a maximum AV peak velocity ≥4 m/s with concomitant presence of AVA ≤1.0 cm^2 (or indexed AVA ≤0.6 cm^2/m^2) at any point during the test protocol.[1,12] Patients who reached significant AS criteria were classified into the true-severe AS group, independent from the presence of FR.

The patients who did not meet the criteria for significant AS were classified according to the presence of FR. Patients with FR were classified into the pseudo-severe AS group, while those without FR were classified as the indeterminate AS group (Figure S1A).

We also used stress echocardiography data to calculate projected valve area at a standardized flow rate of 250 mL/s using the formula[17]: $AVA_{proj}=AVA_{rest}+VC\times(250-Q_{rest})$, where VC is the valve compliance corresponding to the slope of the AVA-flow relationship.

Alternative FR Parameters

As SV may not be the best surrogate of myocardial FR, we used increase in mean LVOT velocity, CPO, EF, and GLS as alternative measures of FR. To determine the threshold for FR in each variable, we classified patients into tertiles according to the percentage change in these variables during DSE. Patients in the second and highest tertiles were defined as having FR. Patients in the lowest tertile were considered as low FR.

Statistical Analysis

Continuous data are expressed as mean±SD when normally distributed, and median (interquartile range) otherwise. Categorical data are presented as an absolute number and percentages. We used the unpaired *t* test, Mann–Whitney test, or Fisher exact test to compare the data between 2 groups. Kaplan–Meier curves were created to assess survival between groups and were compared by the log-rank test.

We performed Cox-proportional hazards analysis to assess association between echocardiographic variables and survival. The assumptions of proportional hazards were assessed by Schoenfeld residuals. In a multivariable model, relevant variables and possible confounding factors selected because of their known prognostic value were entered into the model using stepwise selection. To account for the time to AVR, we treated AVR as a time-dependent covariate. To assess whether the impact of AVR on survival was limited to patients with FR, we added an interaction term between AVR and presence or absence of FR into the multivariable model. Finally, Cox proportional hazards model analysis was done in the patients' subgroups, as detailed in Results.

In addition, we used the inverse probability of treatment weights (IPTW) derived from propensity scores to reduce potential imbalance in baseline variables between patients with and without AVR. The propensity scores were calculated using a multivariable logistic regression model with AVR as a dependent variable and known baseline characteristics associated with AVR (age, sex, body surface area, New York Heart Association class, creatinine, history of hypertension, end-stage renal disease, diabetes mellitus risk factors, chronic lung disease, coronary artery disease, congestive heart failure, prior myocardial infarction, and history of coronary artery bypass graft) as predictors. We also estimated the absolute standardized differences before and after propensity score adjustment.

A $P<0.05$ was considered statistically significant. All statistical analyses were performed with JMP 10.0 (SAS Institute Inc, Cary, NC), SPSS 25.0 software (SPSS Inc, Chicago, IL), and R software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows data of 235 patients who satisfied the entry criteria (Figure S1B). There was no ischemia detected by DSE. At peak stress, the AVA was 0.92 (0.74–1.08) cm^2, mean gradient was 34±11 mm Hg, and LVEF was 35 (27–45)%, showing significant increase compared with rest ($P<0.001$ for all). SV and indexed SV at peak stress were 58 (48–73) mL and 31 (25–38) mL/m^2, respectively. The median percent

increase in SV was 25 (11–40)%. FR defined by >20% increase in SV was present in 138 patients (59%) (Table 2). True-severe AS was present in 86 patients (37%), with 52 patients (60%) having preserved FR. Of the remaining 149 patients, 86 patients had preserved FR and were deemed to have pseudo-severe AS, and in 63 patients we were not able to determine AS.

Table 1. Baseline Clinical and Echocardiographic Characteristics

	All Patients (n=235)
Age, y	80 (73–85)
Male sex, n (%)	174 (74)
Body surface area, m^2	1.92±0.22
Heart rate, bpm	75 (65–85)
Systolic blood pressure, mm Hg	129 (110–150)
NYHA functional class (III/IV), n (%)	129/31 (55/13)
Hypertension, n (%)	176 (75)
End-stage renal disease, n (%)	11 (5)
Diabetes mellitus, n (%)	99 (42)
Chronic lung disease, n (%)	87 (37)
Atrial fibrillation, n (%)	126 (54)
STS score, %	5.5 (3.7–8.8)
Coronary artery disease, n (%)	172 (74)
Prior myocardial infarction, n (%)	87 (37)
History of CABG, n (%)	116 (49)
Prior SAVR or TAVR, n (%)	14 (6)
Congestive heart failure, n (%)	144 (61)
LVEDV index, mL/m^2	88±30
LVESV index, mL/m^2	62±27
Stroke volume, mL	49 (39–62)
Stroke volume index, mL/m^2	25 (20–33)
Stroke volume index <35 mL/m^2, n (%)	187 (80)
LVEF, %	29 (23–37)
LVEF<40%, n (%)	192 (82)
AVA, cm^2	0.75 (0.65–0.92)
Indexed AVA, cm^2/m^2	0.40 (0.33–0.48)
Peak velocity, m/s	3.08 (2.75–3.38)
Mean pressure gradient, mm Hg	22±7
MR ≥moderate, n (%)	95 (40)
AR ≥moderate, n (%)	32 (14)

Values are mean±SD, median (interquartile range), or n (%). AR indicates aortic regurgitation; AVA, aortic valve area; bpm, beats per minute; CABG, coronary artery bypass graft; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

The reference limits to detect FR using percent increase in CPO, mean LVOT velocity, EF, or GLS (defined by the cutoff values of the lowest tertile) were 38%, 26%, 11%, and 20%, respectively. We classified patients with increase that was less than the reference limits as having a low FR, with the other group treated as having preserved FR.

Clinical Outcomes

At a median time of 51 days (interquartile range 18–112 days) after DSE, 128 (54%) patients underwent either SAVR (42 patients [18%]) or TAVR (86 patients [37%]). Patients who had AVR of any kind had more severe AS than ones who did not (Table S1). Prevalence of FR was similar in patients who did or did not undergo AVR (58% versus 60%, P=0.76). AVR was performed in 74% of true-severe AS, 42% of pseudo-severe AS, and 44% of indeterminate AS patients after evaluation of clinical information by the heart valve team. Of note, pseudo-severe AS patients who underwent AVR showed significantly smaller projected AVA and higher mean gradient at baseline or maximum stress on DSE (Table 3). During a median follow-up period of 2.3 years (interquartile range 0.7–3.7 years), 138 patients (59%) died, with overall 2-year and 5-year survival of 61% and 30%, respectively.

Impact of FR on Survival

The lack of FR was not associated with increased risk of mortality (P=0.62 by log-rank statistics, Figure 1). The lack of association between FR, defined by SV increase or by alternative FR surrogates, and mortality was corroborated by uni- and multivariable Cox proportional hazards regression results (Table 4). In the multivariable model, lower Society of Thoracic Surgeons score and AVR were the only independent survival predictors.

Does Absence of FR Decrease the Beneficial Impact of AVR?

It is possible that FR impacts survival only if patients undergo AVR. To assess whether impact of FR was limited to patients undergoing AVR, we forced an interaction term between FR and AVR into the multivariable model that already contained Society of Thoracic Surgeons score, true-severe AS, FR, and AVR as covariates. There was no impact of the interaction term (P=0.64), signifying that impact of AVR was observed regardless of presence or absence of FR. Survival curves show that the absence of FR was not associated with higher mortality in both subgroups of patients who underwent AVR, and who were managed by medical therapy (Figure 2; P>0.50 for both, log-rank statistics). Moreover, we treated AVR as a

Table 2. Echocardiographic Variables at Baseline and With Dobutamine Stress Echocardiography

	Baseline (n=235)	Peak Stress (n=235)	Delta Change (%)	*P* Value
Heart rate, bpm	75 (65to 85)	89 (77 to 103)	18 (7 to 32)	<0.001
Systolic blood pressure, mm Hg	129 (110 to 150)	137 (120 to 159)	6 (−2 to 16)	<0.001
Stroke volume, mL	49 (39 to 62)	58 (48 to 73)	25 (11 to 40)	<0.001
Stroke volume index, mL/m^2	25 (20 to 33)	31 (25 to 38)	17 (4 to 33)	<0.001
CPO, W	0.90 (0.69 to 1.13)	1.43 (1.05 to 1.80)	55 (33 to 88)	<0.001
Mean LVOT velocity, m/s	51±14	70±20	38 (20 to 58)	<0.001
LVEF, %	29 (23 to 37)	35 (27 to 45)	19 (7 to 35)	<0.001
GLS, %	−6.9 (−9.6 to −4.9)	−9.2 (−11.9 to −6.7)	29 (16 to 46)	<0.001
AVA, cm^2	0.75 (0.65 to 0.92)	0.92 (0.74 to 1.08)	17 (3 to 33)	<0.001
Peak velocity, m/s	3.08 (2.75 to 3.38)	3.91 (3.45 to 4.22)	24 (15 to 33)	<0.001
Mean pressure gradient, mm Hg	22±7	34±11	49 (30 to 74)	<0.001
Flow reserve (Δ SV≥20%), n (%)	…	138 (59)	…	…

Values are mean±SD, median (interquartile range), or n (%). AVA indicates aortic valve area; bpm, beats per minute; CPO, cardiac power output; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; SV, stroke volume; Δ, percent change of echo variables from baseline to peak stress during stress; W, Watts.

time-dependent covariate because it is known that dichotomizing patients according to treatment when there is a certain wait period leads to immortal time bias and overestimation of the beneficial effect of treatment. In this model, AVR was still a significant predictor of outcome (AVR as time-dependent covariate: hazard ratio [HR] 0.66, 95% CI: 0.44–0.90, *P*=0.011; Society of Thoracic Surgeons score [%]: HR 1.06, 95% CI: 1.03–1.08, *P*<0.001).

To elucidate whether these results were caused by confounding factors that drive selection for AVR in such a way that decreases the impact of FR results, we constructed propensity scores for AVR by using known characteristics to eliminate this potential bias in selecting patients for AVR. Table 5 shows the results from the original model and the results from the model using IPTW with propensity scores. The model adjusted by IPTW showed that AVR was independently associated with better survival (HR 0.40, 95% CI: 0.31–0.51, *P*<0.001). Application of IPTW resulted in balanced covariates between 2 groups (Table S2, Figure S2). The standardized differences for all covariates were below 0.25 threshold (with the exception of the standardized differences for end-stage renal disease and creatinine, they were even below 0.10 threshold), suggesting minimal differences in the weighted distributions between those who underwent AVR and those treated medically following application of IPTW.

To determine whether type of AVR affected the association between FR and survival, we compared the survival curves according to the presence of FR in patients who underwent TAVR and SAVR separately. We found out that there was no significant difference in survival between patients who

Table 3. Association Between AS Severity by DSE and Mortality (n=235)

	Diagnosis by DSE								
	True-Severe AS (n=86)			Pseudo-Severe AS (n=86)			Indeterminate AS (n=63)		
	AVR (n=64)	No AVR (n=22)	*P* Value	AVR (n=36)	No AVR (n=50)	*P* Value	AVR (n=28)	No AVR (n=35)	*P* Value
Baseline AVA	0.71 (0.58–0.81)	0.70 (0.59–0.91)	0.68	0.66 (0.57–0.98)	0.74 (0.66–0.93)	0.13	0.87 (0.78–1.03)	0.91 (0.76–1.09)	0.68
Baseline mean gradient	28±5	27±6	0.30	22±6	18±6	0.002	21±6	17±6	0.005
Peak AVA	0.81 (0.71–0.95)	0.93 (0.74–1.06)	0.12	0.95 (0.71–1.26)	0.98 (0.77–1.14)	0.64	0.93 (0.80–1.07)	0.95 (0.78–1.15)	0.49
Peak mean gradient	44±8	42±4	0.19	33±8	27±8	<0.001	29±9	23±8	0.006
Projected AVA	0.84 (0.74–0.93)	0.87 (0.79–0.98)	0.18	0.95 (0.78–1.09)	1.02 (0.89–1.21)	0.029	1.06 (0.90–1.20)	1.23 (0.84–1.43)	0.18
Death, n (%)	28 (44)	16 (73)	0.019	21 (58)	36 (72)	0.19	12 (43)	25 (71)	0.022

Values are mean±SD, median (interquartile range), or n (%). AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; DSE, dobutamine stress echocardiography.

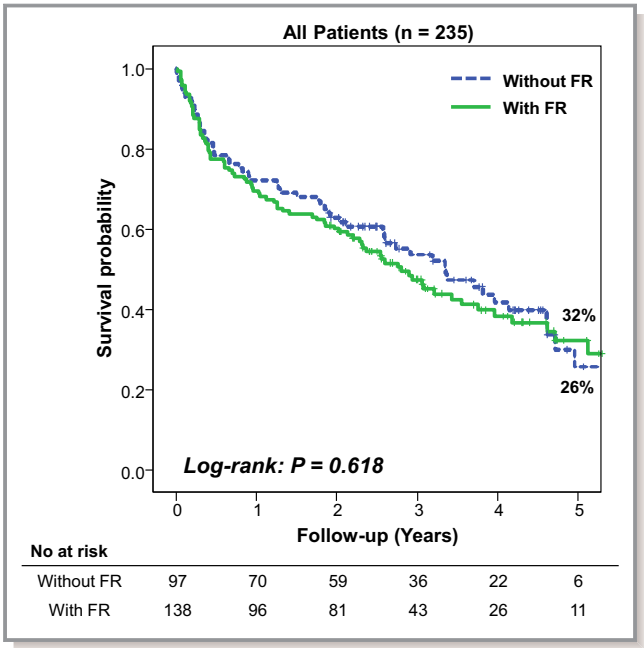


Figure 1. Impact of FR in low-gradient aortic stenosis patients (n=235). Kaplan–Meier curves according to the presence or absence of FR was performed. FR indicates flow reserve.

underwent SAVR and TAVR (5-year survival 46% versus 34%, respectively; *P*=0.102, Figure S3), and that FR had no impact on outcome in both patients who underwent SAVR (*P*=0.66) or TAVR (*P*=0.66) (Figures S4A and S4B).

Is Classification of Patients into Subgroups of True Severe, Pseudo-Severe, and Indeterminate AS Relevant for Decision Making?

It is possible that AVR is associated with improved survival only in patients with true-severe AS. We evaluated this possible association between the diagnosis of true-severe AS by DSE and overall mortality, separated by AVR status. Even in patients who were classified as pseudo-severe AS and indeterminate AS, patients who underwent AVR showed better survival than those treated medically (Figure 3; *P*<0.05 for all, log-rank statistics). Univariable HRs for the impact of AVR in these subgroups were numerically smaller for indeterminate AS and pseudo-severe AS compared with true-severe AS subgroup (true-severe AS: HR 0.32, 95% CI: 0.17–0.60, *P*<0.001; pseudo-severe AS: HR 0.55, 95% CI: 0.32–0.96, *P*=0.034; indeterminate AS: HR 0.47, 95% CI: 0.24–0.95, *P*=0.035), with the differences between 3 subgroups not statistically significant.

Projected AVA was analyzable in 233 patients, with 60% deemed to have true-severe AS (projected AVA <1.0 cm^2), while the remaining 40% were diagnosed as pseudo-severe AS. AVR was associated with better survival in patients with true-severe AS by projected AVA, while this was not true in patients with pseudo-severe AS by projected AVA (Figure S5). This result suggests that projected AVA better identifies AS patients who benefit from AVR when compared with standard criteria.

Table 4. Univariable and Multivariable Cox Proportional Hazards Model Analysis for All-Cause Mortality in Patients Who Underwent DSE (n=235)

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
STS score, %	1.05 (1.03–1.08)	<0.001	1.06 (1.04–1.09)	<0.001
Coronary artery disease	0.98 (0.67–1.43)	0.91		
Baseline AVA, cm^2	0.87 (0.43–2.06)	0.87		
Baseline mean gradient, mm Hg	0.98 (0.96–0.999)	0.04		
Baseline LVEF, %	0.99 (0.97–1.01)	0.28		
True-severe AS* (peak V ≥4 with AVA ≤1.0/AVAi ≤0.6)	0.60 (0.42–0.86)	0.005		
Peak aortic valve velocity >4 m/s	0.66 (0.47–0.93)	0.018		
FR by SV change ≥20%	1.09 (0.78–1.53)	0.62		
FR by CPO	1.10 (0.77–1.56)	0.61		
FR by mean LVOT velocity	1.01 (0.71–1.44)	0.97		
FR by EF	0.80 (0.56–1.14)	0.22		
FR by GLS	0.82 (0.57–1.17)	0.27		
AVR	0.44 (0.31–0.62)	<0.001	0.41 (0.29–0.58)	<0.001

AS indicates aortic stenosis; AVA, aortic valve area; AVAi, indexed aortic valve area; AVR, aortic valve replacement; CPO, cardiac power output; DSE, dobutamine stress echocardiography; EF, ejection fraction; FR, flow reserve; GLS, global longitudinal strain; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; peak V, peak aortic valve velocity; STS, Society of Thoracic Surgeons; SV, stroke volume.
*HR was assessed relative to those without true-severe AS (indeterminate and pseudo-severe AS).

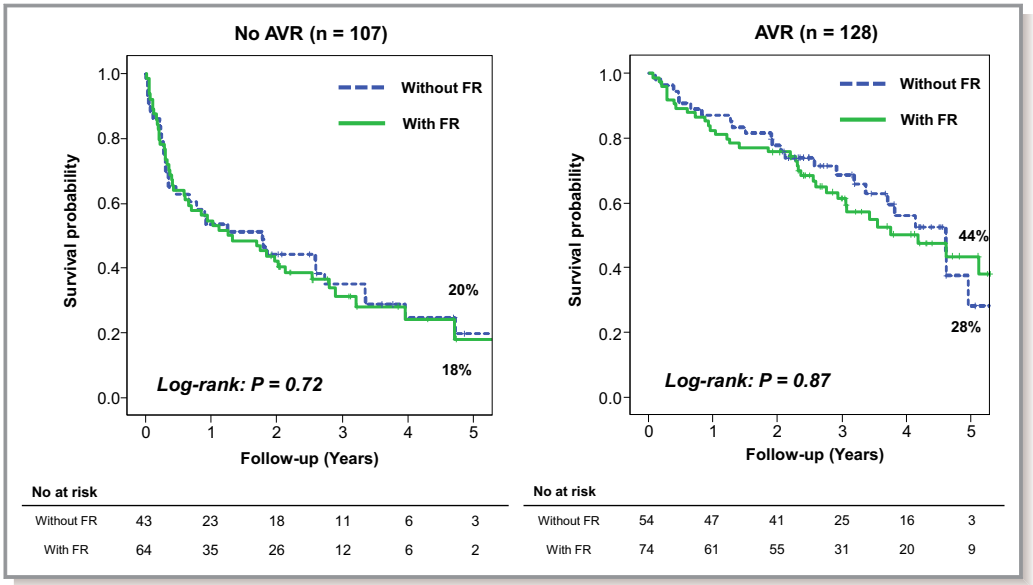


Figure 2. Impact of FR on survival in patients with AVR (n=107) and without AVR (n=128). Kaplan–Meier curves showed survival of low-gradient aortic stenosis patients stratified by flow reserve in the subgroup of patients who underwent AVR and who were treated medically. AVR included both surgical and transcatheter AVR. AVR indicates aortic valve replacement; FR, flow reserve.

Discussion

In this article, we showed that in patients with low-gradient AS undergoing DSE, FR by DSE was not associated with survival. Also, absence of FR did not eliminate the beneficial impact of AVR because even in patients with indeterminate AS severity and pseudo-severe AS, AVR was associated with improved survival. This favorable impact was observed with both SAVR and TAVR procedures. Of note, the impact of AVR was numerically smaller in indeterminate AS severity and pseudo-severe AS, with this difference not reaching statistical significance.

FR in AS

Monin et al[2,3] proposed increase in SV during low-dose DSE as a FR marker in patients with low-gradient low EF AS, and showed that thus defined, FR is associated with lower operative mortality. This may not necessarily extend to patients undergoing TAVR.[18,19] Our results show that, in our mix of patients that includes both TAVR and surgical AVR patients, FR by DSE was not associated with a survival advantage. Even if we only analyzed patients who underwent surgical AVR, FR was not associated with survival. This finding may reflect the improvements in perioperative management of patients after surgical AVR,[20] which mitigates the importance of FR, or less challenging stress caused by the TAVR procedure.

The link between SV and contractility is circuitous, as it stems from the SV being 1 of the 2 elements used to calculate stroke work, the other being the difference between mean LV systolic and diastolic pressures. To come up with a "load independent" contractility measure, stroke work has to be adjusted by preload to obtain preload recruitable stroke work.[21] In practical terms, increases in heart rate decrease SV, and SV does not capture increases in blood pressure, both of which occur with inotropic stimulation. To assess whether these issues are responsible for the lack of FR being associated with survival, we tried several other indices. We used mean LVOT velocity because it eliminates the impact of heart rate on LVOT VTI. We also used CPO because it also incorporates pressure generation by the LV, can represent cardiac pumping capability better than other hemodynamic variables, and is associated with survival in patients with heart failure.[6–8,22] Finally, LVEF and GLS are known surrogates of LV contractility and predictors of survival in patients with

Table 5. Multivariable Cox Proportional Hazards Model Analysis With and Without PS Adjustment

	No PS Adjustment		Inverse Probability Weighting	
	HR (95% CI)	*P* value	HR (95% CI)	*P* Value
STS score, %	1.06 (1.04–1.09)	<0.001	1.07 (1.05, 1.09)	<0.001
AVR	0.41 (0.29–0.58)	<0.001	0.40 (0.31, 0.51)	<0.001

AVR indicates aortic valve replacement; HR, hazard ratio; PS, propensity score; STS, Society of Thoracic Surgeons.

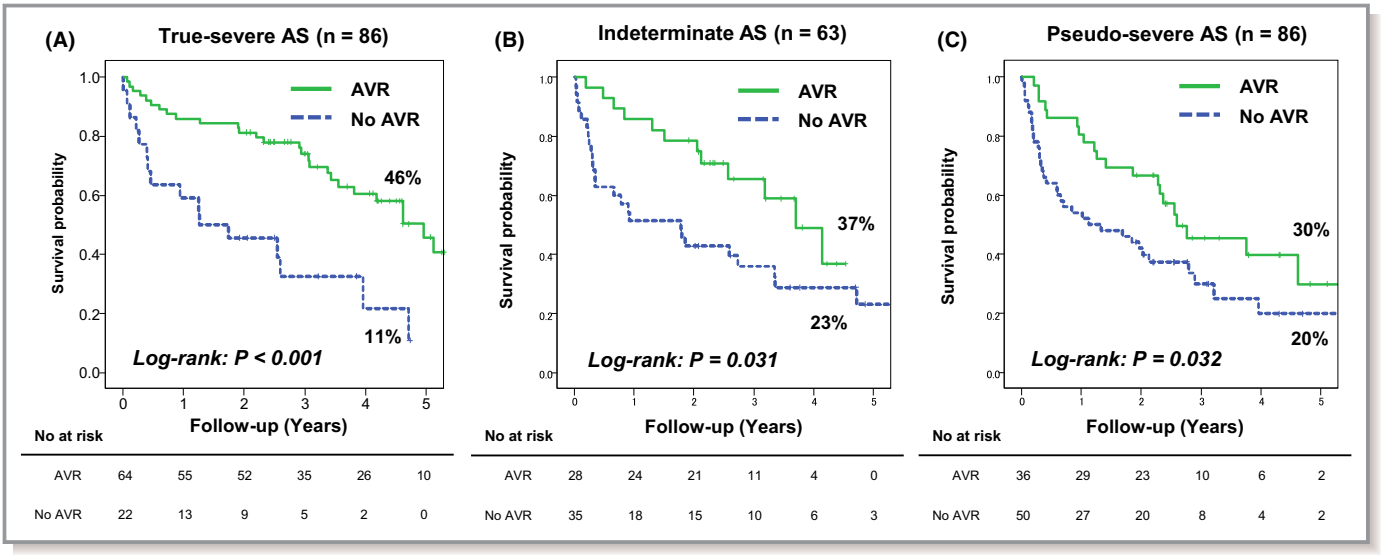


Figure 3. Impact of AVR on survival in patients diagnosed as (**A**) true-severe AS (n=86), (**B**) indeterminate AS severity (n=63), and pseudo-severe AS (n=86), and by dobutamine stress echocardiography. Kaplan–Meier curves showed survival of the low-gradient AS patients according to whether they underwent AVR. AS indicates aortic stenosis; AVR, aortic valve replacement.

AS.[23] Despite all our effort, we could not show that any FR index was predictive of survival.

Which Patients Profit From AVR?

In the present study, AS severity was indeterminate in 63 patients (27%) because of lack of FR. The beneficial impact of AVR was numerically larger in patients with true-severe AS. However, patients with indeterminate AS by DSE and those with pseudo-severe AS also benefited from AVR. A possible reason for this is that these patients have heart failure and signs of cardiac dysfunction, and that elimination of excessive afterload by AVR, even if AS is not deemed "severe" by DSE, may be beneficial. A patient with low-gradient, very low EF AS can occasionally profit from AVR even with no FR by DSE.[24] This is not surprising because a recent study showed that the amount of DSE-defined FR was not associated with degree of LV functional recovery. At least some LV reverse remodeling and contractile recovery can be expected after TAVR even in high-risk patients with severely reduced LV function preoperatively.[16] Another possible explanation of beneficial effect of AVR observed in indeterminate-AS and pseudo-severe AS is lack of accuracy in conventional DSE criteria. As shown in the Results, projected AVA successfully stratified the patients who have benefit from AVR and those who did not, suggesting the limited ability of the current definition and assessing FR to predict outcome in low-gradient AS. Finally, AS severity invariably progresses,[25] so what is deemed pseudo-severe AS may become severe AS even in a matter of a few months. In sum, prediction of myocardial contractile recovery is challenging because pressure overload may play a critical role in LV dysfunction in advanced AS, and conventional LV systolic function indices do not reflect myocardial plasticity.

Clinical Implication

Our results document a limited ability of FR to predict outcome in the contemporary era even with SAVR. In addition, our results suggest that the DSE parameters and criteria currently used to differentiate true- versus pseudo-severe AS are often not conclusive and lack accuracy to identify true-severe AS. Application of projected AVA better differentiates AS patients who may benefit from AVR.

Limitations

This was a retrospective observational study conducted at a large tertiary referral center. Therapeutic decisions were made by the physicians who were aware of DSE data. Because of the retrospective nature of our study, physicians can bring together all clinical information and recommend interventional or medical treatment accordingly. One can argue that the beneficial effect of AVR may be, at least in part, attributed to the relevant selection bias. Our data showed that 28% of patients who had confirmed true-severe AS did not undergo surgery. In addition, there were some significant differences in baseline characteristics between patients with AVR and with medical treatment, suggesting that lower-risk candidates for surgery might undergo AVR and higher-risk candidates did not. Although we confirmed survival benefit by multiple statistical approaches, this selection bias might not be eliminated completely. We also defined cutoffs for the FR

absence as lowest tertile of each alternative measure to FR. These cutoffs might be dependent on the study population, and generalizability of this reference range might be limited. Finally, biplane Simpson's method was used to evaluate SV in 30 patients, because pulsed-wave Doppler signals of LVOT flow were not analyzable and a prior study suggested usefulness of biplane Simpson's method in this setting.[14] Furthermore, to minimize inconsistency, biplane Simpson's method was used at all stages in those 30 patients.

Conclusions

In this article we show that, in patients with low-gradient AS, FR or AS severity stratification by DSE in the current era was not associated with survival. AVR was associated with outcomes independent from the presence of FR or true-severe AS.

Disclosures

None.

References

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–e643.
2. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. *J Am Coll Cardiol*. 2001;37:2101–2107.
3. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319–324.
4. Pratali L, Picano E, Otasevic P, Vigna C, Palinkas A, Cortigiani L, Dodi C, Bojic D, Varga A, Csanady M, Landi P. Prognostic significance of the dobutamine echocardiography test in idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2001;88:1374–1378.
5. Eichhorn EJ, Grayburn PA, Mayer SA, St John Sutton M, Appleton C, Plehn J, Oh J, Greenberg B, DeMaria A, Frantz R, Krause-Steinrauf H. Myocardial contractile reserve by dobutamine stress echocardiography predicts improvement in ejection fraction with beta-blockade in patients with heart failure: the Beta-Blocker Evaluation of Survival Trial (BEST). *Circulation*. 2003;108:2336–2341.
6. Tan LB, Bain RJ, Littler WA. Assessing cardiac pumping capability by exercise testing and inotropic stimulation. *Br Heart J*. 1989;62:20–25.
7. Cooke GA, Marshall P, al-Timman JK, Wright DJ, Riley R, Hainsworth R, Tan LB. Physiological cardiac reserve: development of a non-invasive method and first estimates in man. *Heart*. 1998;79:289–294.
8. Tan LB. Cardiac pumping capability and prognosis in heart failure. *Lancet*. 1986;2:1360–1363.
9. deFilippi CR, Willett DL, Brickner ME, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol*. 1995;75:191–194.
10. Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, Grimm RA, Griffin BP, Desai MY. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. *Circ Cardiovasc Imaging*. 2014;7:938–945.
11. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, Burns PN, Castello R, Coon PD, Hagen ME, Jollis JG, Kimball TR, Kitzman DW, Kronzon I, Labovitz AJ, Lang RM, Mathew J, Moir WS, Nagueh SF, Pearlman AS, Perez JE, Porter TR, Rosenbloom J, Strachan GM, Thanigaraj S, Wei K, Woo A, Yu EH, Zoghbi WA. American society of echocardiography consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. *J Am Soc Echocardiogr*. 2008;21:1179–1201; quiz 1281.
12. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
14. Sato K, Seo Y, Ishizu T, Nakajima H, Takeuchi M, Izumo M, Suzuki K, Akashi YJ, Otsuji Y, Aonuma K. Reliability of aortic stenosis severity classified by 3-dimensional echocardiography in the prediction of cardiovascular events. *Am J Cardiol*. 2016;118:410–417.
15. Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M, Szymanski C, Cosyns B, Pierard LA. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol*. 2012;59:235–243.
16. Sato K, Kumar A, Jones BM, Mick SL, Krishnaswamy A, Grimm RA, Desai MY, Griffin BP, Rodriguez LL, Kapadia SR, Obuchowski NA, Popovic ZB. Reversibility of cardiac function predicts outcome after transcatheter aortic valve replacement in patients with severe aortic stenosis. *J Am Heart Assoc*. 2017;6:e005798. DOI: 10.1161/JAHA.117.005798.
17. Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, Baumgartner H, Beanlands RS, Chayer B, Kadem L, Garcia D, Durand LG, Pibarot P. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. *Circulation*. 2006;113:711–721.
18. Barbash IM, Minha S, Ben-Dor I, Dvir D, Magalhaes MA, Torguson R, Okubagzi P, Satler LF, Pichard AD, Waksman R. Relation of preprocedural assessment of myocardial contractility reserve on outcomes of aortic stenosis patients with impaired left ventricular function undergoing transcatheter aortic valve implantation. *Am J Cardiol*. 2014;113:1536–1542.
19. Ribeiro HB, Lerakis S, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, Windecker S, Enriquez-Sarano M, Cheema AN, Nombela-Franco L, Amat-Santos I, Munoz-Garcia AJ, Garcia Del Blanco B, Zajarias A, Lisko JC, Hayek S, Babaliaros V, Le Ven F, Gleason TG, Chakravarty T, Szeto WY, Clavel MA, de Agustin A, Serra V, Schindler JT, Dahou A, Puri R, Pelletier-Beaumont E, Cote M, Pibarot P, Rodes-Cabau J. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: the TOPAS-TAVI Registry. *J Am Coll Cardiol*. 2018;71:1297–1308.
20. Barreto-Filho JA, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, Krumholz HM. Trends in aortic valve replacement for elderly patients in the United States, 1999–2011. *JAMA*. 2013;310:2078–2085.
21. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation*. 1985;71:994–1009.
22. Chantler PD, Clements RE, Sharp L, George KP, Tan LB, Goldspink DF. The influence of body size on measurements of overall cardiac function. *Am J Physiol Heart Circ Physiol*. 2005;289:H2059–H2065.
23. Sato K, Seo Y, Ishizu T, Takeuchi M, Izumo M, Suzuki K, Yamashita E, Oshima S, Akashi YJ, Otsuji Y, Aonuma K. Prognostic value of global longitudinal strain in paradoxical low-flow, low-gradient severe aortic stenosis with preserved ejection fraction. *Circ J*. 2014;78:2750–2759.
24. Sperry BW, Jacob MS, Menon V, Soltesz EG, Rodriguez ER, Popovic ZB. Defying dogma: recovery after left ventricular assist device implantation and aortic valve replacement for bicuspid aortic valve. *Circ Heart Fail*. 2015;8:832–835.
25. Aksoy O, Cam A, Goel SS, Houghtaling PL, Williams S, Ruiz-Rodriguez E, Menon V, Kapadia SR, Tuzcu EM, Blackstone EH, Griffin BP. Do bisphosphonates slow the progression of aortic stenosis? *J Am Coll Cardiol*. 2012;59:1452–1459.

SUPPLEMENTAL MATERIAL

Table S1. Comparison of baseline clinical characteristics and echocardiographic variables between patients with AVR and without AVR.

	No	No AVR (n= 107)	AVR (n= 128)	P value
Age, years	235	78±9	77±12	0.77
Male sex, n(%)	235	74 (69)	100 (78)	0.12
Body surface area, m^2	235	1.88±0.21	1.95±0.22	0.02
NYHA functional class (III/IV), n(%)	235	61/20 (57/19)	68/11 (53/9)	0.03
Hypertension, n(%)	235	82 (77)	94 (73)	0.57
End stage renal disease, n(%)	235	5 (5)	6 (5)	0.996
Diabetes mellitus, n(%)	235	41 (38)	58 (45)	0.28
Chronic lung disease, n(%)	235	28 (26)	59 (46)	0.002
STS score, %	235	7.1±4.8	7.2±5.7	0.85
Coronary artery disease, n(%)	235	75 (70)	97 (76)	0.33
Prior myocardial infarction, n(%)	235	31 (29)	56 (44)	0.02
History of CABG, n(%)	235	48 (45)	68 (53)	0.21
Congestive heart failure, n(%)	235	76 (71)	68 (53)	0.005
Heart rate, bpm	235	76±13	75±14	0.87
Systolic blood pressure, mmHg	235	128±24	133±25	0.11
LVEDV index, ml/m^2	235	91±30	85±31	0.11
LVESV index, ml/m^2	235	66±27	59±27	0.054
Stroke volume index, ml/m^2	235	26±9	28±9	0.32
Stroke volume index < 35%, n(%)	235	85 (79)	102 (80)	0.96
LVEF, %	235	28±9	32±10	0.005

LVEF < 40%, n(%)	235	93 (87)	99 (77)	0.06
AVA, cm^2	235	0.84±0.24	0.76±0.20	0.006
Indexed AVA, cm^2	235	0.45±0.12	0.39±0.11	<0.001
Peak velocity, m/s	235	2.86±0.53	3.21±0.43	<0.001
Mean pressure gradient, mmHg	235	19±7	25±6	<0.001
Projected valve area	235	1.08±0.33	0.91±0.27	< 0.001

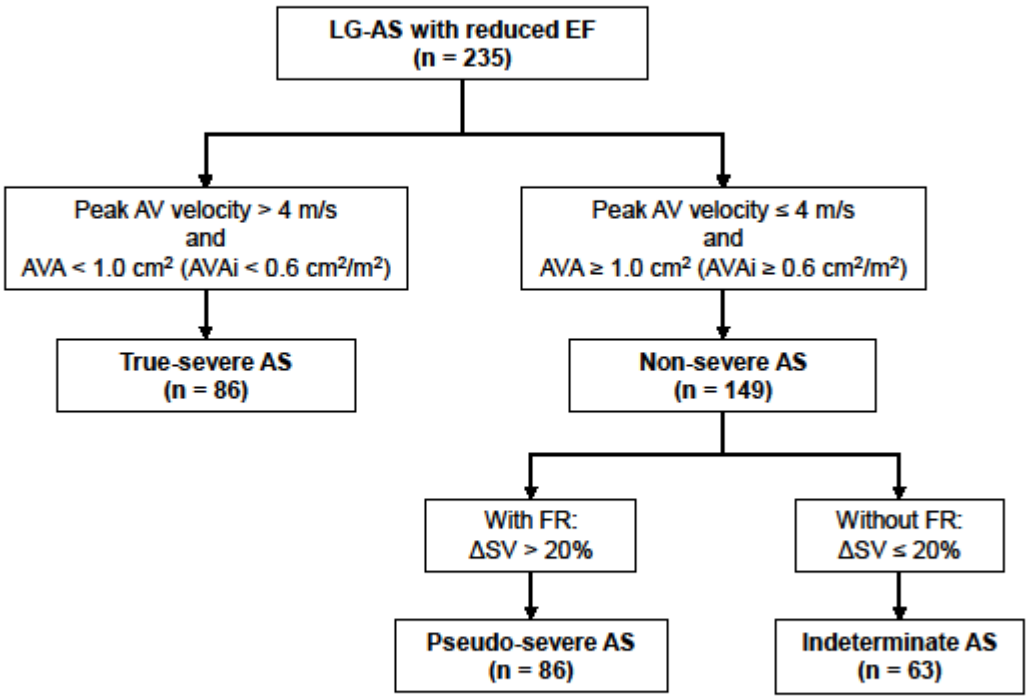
AVA, aortic valve area; AR, aortic regurgitation; CABG, coronary artery bypass graft; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

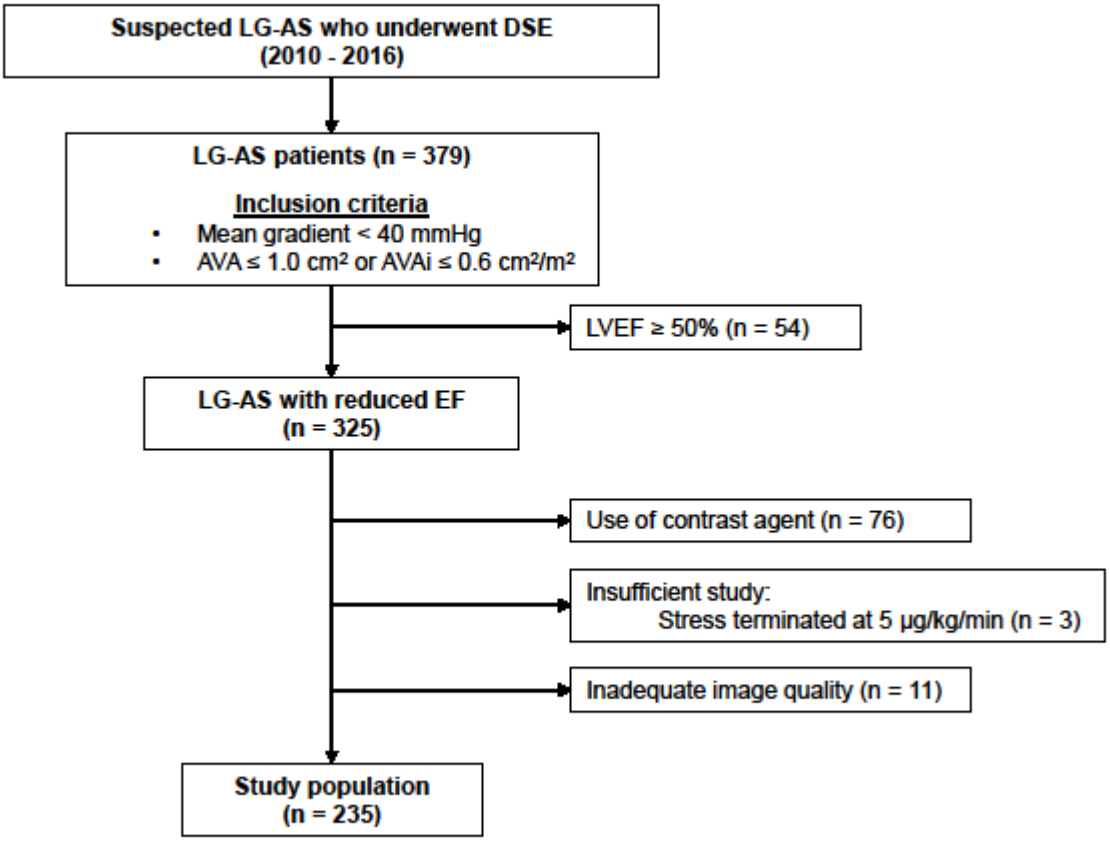
Table S2. Standardized differences between those who underwent aortic valve replacement and those treated medically before and after propensity score adjustment.

Variable	Absolute STD before PS adjustment	Absolute STD after PS adjustment
Age	0.04	0.06
Sex	0.20	0.01
Body surface area	0.31	0.00
NYHA functional class	0.32	0.01
Hypertension	0.07	0.06
End stage renal disease	0.00	0.13
Creatinine	0.27	0.13
Diabetes mellitus	0.14	0.01
Chronic lung disease	0.42	0.01
Coronary artery disease	0.13	0.03
Congestive heart failure	0.38	0.02
Prior myocardial infarction	0.31	0.06
History of CABG	0.17	0.02

CABG, coronary artery bypass graft; NYHA, New York Heart Association.

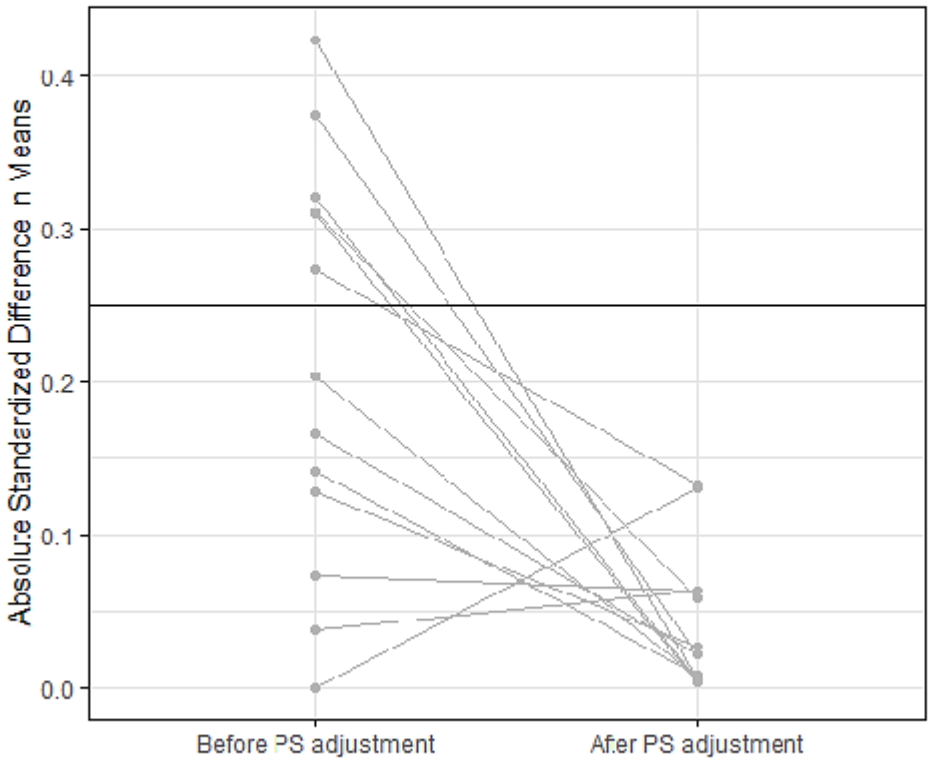
Figure S1. Flow diagram of A) diagnosis of dobutamine stress echocardiography and B) patient selection.





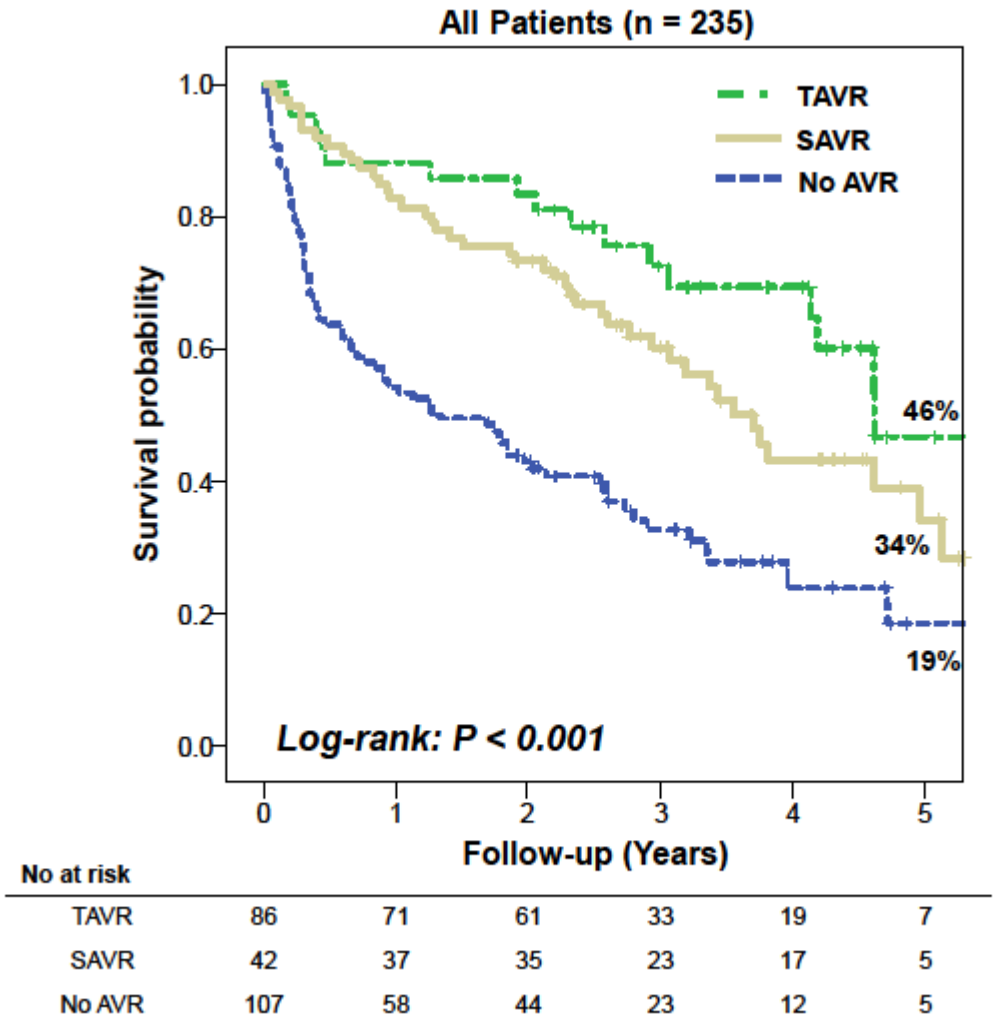
AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; AVAi, indexed aortic valve area; FR, flow reserve; DSE, dobutamine stress echocardiography; EF, ejection fraction; LG, low-gradient, ΔSV, change in strike volume.

Figure S2. Standardized differences between those who underwent aortic valve replacement and those treated medically before and after propensity score adjustment.



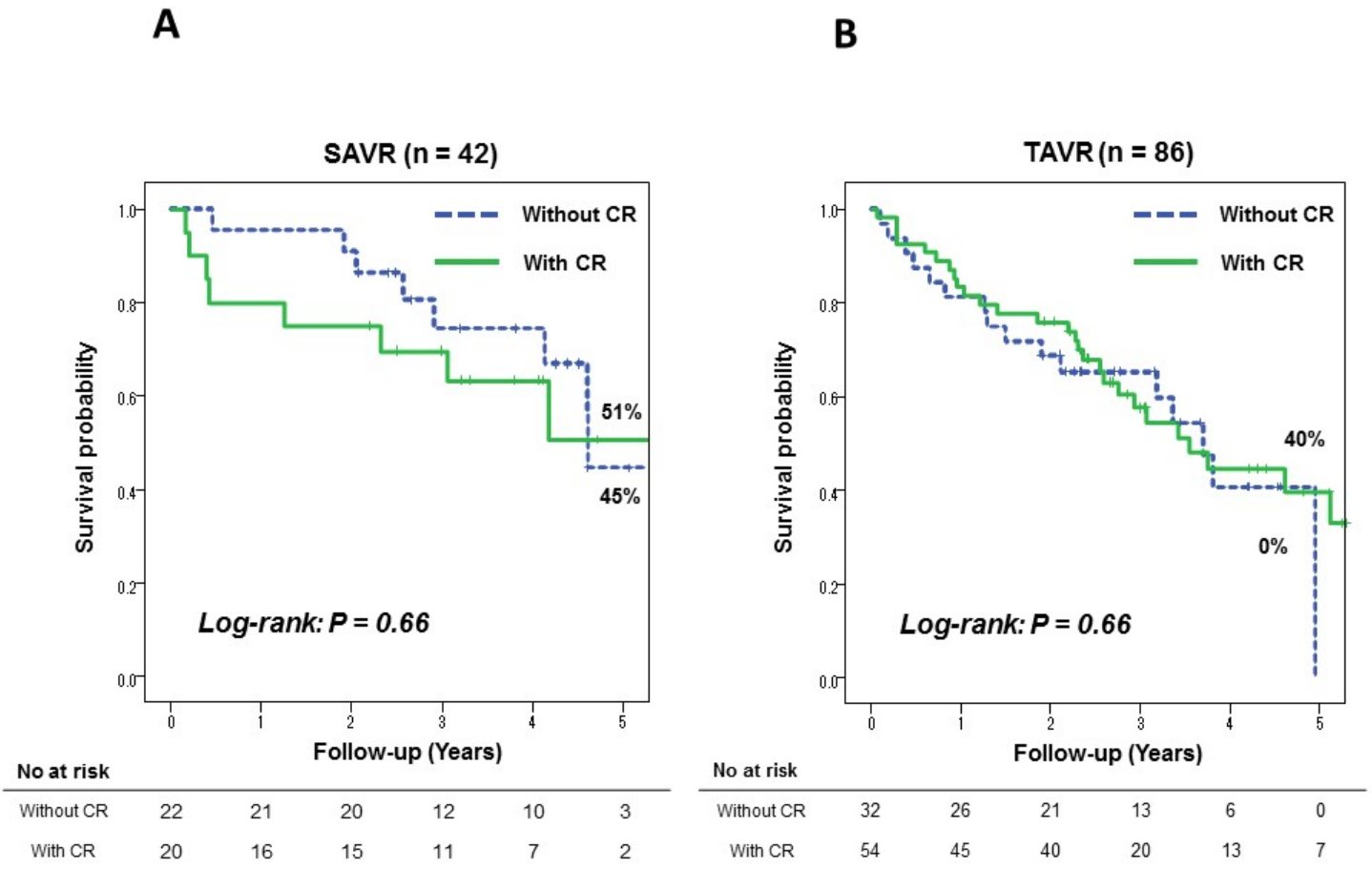
Application of inverse probability treatment weight (IPWT) resulted in balanced covariates between 2 groups. The absolute standardized differences (STD) after adjustment were below 0.25 threshold. IPWT, inverse probability treatment weight; PS, propensity score; STD, standardized differences.

Figure S3. Impact of surgical or transcatheter aortic valve replacement in low-gradient aortic stenosis patients.



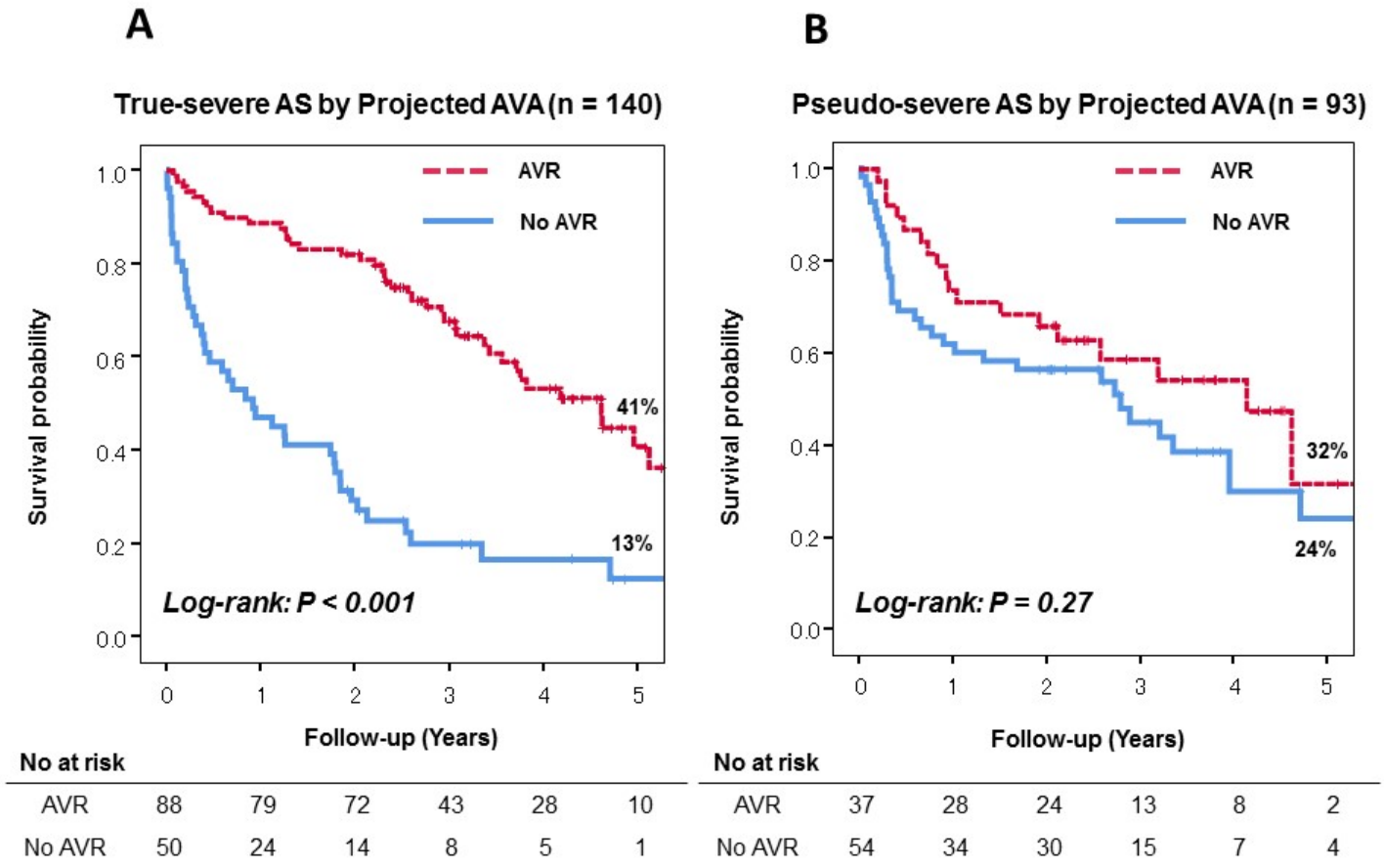
Kaplan-Meier curves according to treatment: medical therapy (n=107), transcatheter aortic valve replacement (TAVR; n = 86), surgical aortic valve replacement (SAVR; n = 42). AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure S4. Impact of flow reserve on survival in low-gradient aortic stenosis patients who underwent dobutamine stress echocardiography and A) surgical aortic valve replacement (SAVR; n = 42) and B) transcatheter aortic valve replacement (TAVR; n = 86).



Kaplan-Meier curves according to the presence of flow reserve (FR) on dobutamine stress echocardiography in patients who underwent SAVR and TAVR. FR, flow reserve; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure S5. Impact of aortic valve replacement on survival in patients diagnosed as A) true-severe aortic stenosis (AS) (n = 140) and B) pseudo-severe AS (n = 93) by projected aortic valve area (AVA).



Kaplan-Meier curves showed survival of the true-severe AS and pseudo-severe AS by projected AVA according to if they underwent aortic valve replacement (AVR). AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement.