JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2021

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

# Prognosis of Severe Low-Flow, Low-Gradient Aortic Stenosis by Stroke Volume Index and Transvalvular Flow Rate

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## ABSTRACT

**OBJECTIVES** This study determined whether flow state classified by stroke volume index (SVi) or transvalvular flow rate (FR) improved risk stratification of all-cause mortality, hospitalization due to heart failure, and aortic valvular interventions for patients with severe aortic stenosis (AS).

**BACKGROUND** SVi is a widely accepted classification for flow state in severe low-flow, low-gradient (LFLG) AS. Recent studies suggest that FR more closely approximates true AS severity and provides more useful prognostication than SVi.

**METHODS** Patients with severe AS over a 7-year period were subclassified by echocardiographic parameters. LFLG-AS was defined as severe AS (aortic valve area index [AVAi]: $<0.6$ cm$^2$/m$^2$), with a mean transvalvular pressure gradient of $<40$ mm Hg in the setting of low flow state: SVi of $<35$ ml/m$^2$ and/or FR of $<200$ ml/s and subclassified into preserved ($\geq 50\%$; paradoxical) or reduced ($<50\%$; classical) left ventricular ejection fraction (LVEF).

**RESULTS** Among 621 consecutive patients with severe AS, the proportions of patients classified as LFLG-AS were different between SVi and FR ($p < 0.001$). Classification using SVi, FR, and LVEF was a strong predictor of the composite endpoint at the 2-year follow-up. The addition of SVi to the echocardiographic and clinical model provided significant improvement in reclassification (net reclassification improvement: 0.089; 95% confidence interval [CI]: 0.045 to 0.133; $p = 0.04$), whereas addition of FR did not (net reclassification improvement: 0.061; 95% CI: 0.016 to 0.106; $p = 0.17$). C-statistics indicated improved risk discrimination when AVAi, LVEF, and SVi or FR were added as predictive variables to the clinical model ($p = 0.006$).

**CONCLUSIONS** Low SVi or FR was associated with adverse cardiovascular events and showed improvement in discrimination, but only SVi, not FR, significantly improved risk reclassification compared to other conventional clinical and echocardiographic predictors. This suggests that FR is not superior to SVi in distinguishing true severe from pseudosevere forms of AS and identification of patients with LFLG-AS who have worse outcomes.
(J Am Coll Cardiol Img 2021;■:■–■) © 2021 by the American College of Cardiology Foundation.

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Philippe Pibarot, MD, served as Guest Editor for this paper.
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.

Manuscript received August 17, 2020; revised manuscript received December 10, 2020, accepted December 21, 2020.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.12.029

**ABBREVIATIONS AND ACRONYMS**

**AS** = aortic stenosis

**AVAi** = indexed aortic valve area

**CI** = confidence interval

**FR** = flow rate

**HF** = heart failure

**HR** = hazard ratio

**LFLG** = low-flow, low-gradient

**LVEF** = left ventricular ejection fraction

**LVOT** = left ventricular outflow tract

**MPG** = mean transvalvular pressure gradient

**SVi** = stroke volume index

**VTI** = velocity-time integral

Aortic stenosis (AS) is the most common valvulopathy in elderly patients (1-3). Echocardiography is pivotal in the diagnosis of AS and in evaluating disease severity, prognostication, and management (4). Severe low-flow, low-gradient (LFLG) AS is first defined based on indexed aortic valve area (AVAi), followed by low-gradient and low-flow states (2,4,5).

Stratifying AS severity and determining the optimal timing of interventions is particularly challenging in patients who have discordant echocardiographic parameters (6,7). Patients with AS with AVAi of $<0.6$ cm$^2$/m$^2$ (severe AS criterion) may have a mean pressure gradient (MPG) of $<40$ mm Hg due to low flow. Low flow has been defined on the basis of a stroke volume index (SVi) $<35$ ml/m$^2$ (7-10) or aortic transvalvular flow rate (FR) of $<200$ ml/s (11). Discrepancies in phenotypic classification and conflicting outcome results make evaluation of LFLG-AS challenging (12). Paradoxical LFLG occurs with normal left ventricular ejection fraction (LVEF), whereas classical LFLG occurs with reduced LVEF ($<50\%$) (2,4,13,14). LFLG-AS accounts for up to 40% of AS in tertiary hospitals. Because many patients with low gradients may not be referred to tertiary hospitals, this proportion may be an underestimate of community prevalence. In this study, we used the echocardiography database of a large suburban hospital without onsite cardiac surgery to assess the frequency of these AS phenotypes based on the FR and SVi classifications of flow and compared outcomes.

## METHODS

**STUDY DESIGN AND PARTICIPANTS.** This was a cohort study of consecutive patients at Western Health (Melbourne, Australia) between January 2013 and July 2019 with a diagnosis of severe AS (AVAi: $<0.6$ cm$^2$/m$^2$) based on transthoracic echocardiograms. Severe LFLG-AS was defined as AVAi of $<0.6$ cm$^2$/m$^2$ with MPG of $<40$ mm Hg and SVi of $<35$ ml/m$^2$ and/or FR of $<200$ ml/s. Patients were subclassified based on LVEF into paradoxical LFLG (LVEF: $\geq 50\%$) or classical LFLG (LVEF: $<50\%$). We excluded patients who had aortic valvular intervention before diagnosis.

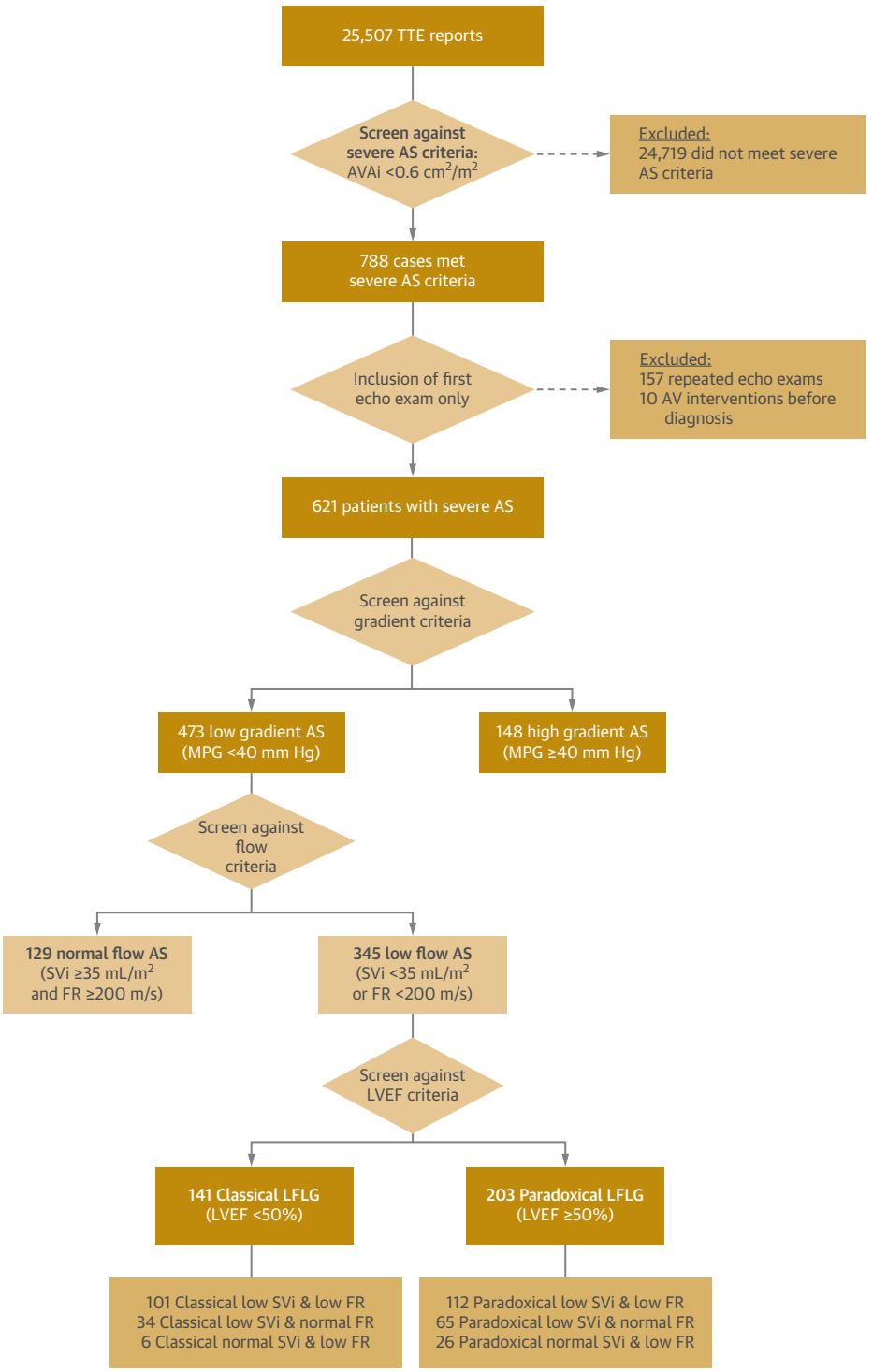
This study was approved by the Melbourne Health Human Research Ethics Committee, the Western Health Office for Research, and the Alfred Health Office of Ethics and Research Governance and was conducted in accordance with the National Health and Medical Research Council (Australia) Statement on Ethical Conduct in Human Research (2007) and the International Conference on Harmonization Guidelines for Good Clinical Practice.

**DATA COLLECTION.** To identify the study cohort, consecutive transthoracic echocardiograms from all patients in the echocardiographic picture archives at Western Health were obtained and filtered for severe AS based on AVAi of $<0.6$ cm$^2$/m$^2$. Patients were subclassified into classical LFLG, paradoxical LFLG, and non-LFLG based on their first available echocardiographic. Selected echocardiographic parameters as well as demographic and clinical information were obtained from the Western Health echocardiography database, electronic medical records, Alfred Health transcatheter aortic valve replacement registry, and BioGrid Australia platform (https://www.biogrid.org.au/).

**TRANSTHORACIC ECHOCARDIOGRAPHY PARAMETERS.** The left ventricular outflow tract (LVOT) diameter, LVOT velocity-time integral (VTI), LVOT peak velocity, LVOT diameter, and MPG were measured. Aortic valvular area was calculated from the continuity equation using the VTI. SVi was calculated from LVOT diameter and LVOT VTI and indexed to body surface area. FR was calculated based on MPG, peak velocity, and aortic valvular mean velocity as described previously (15,16). The distribution of summary output data and outliers was also scanned for missing and incorrect values, and the validity of values was also confirmed by comparing extracted values with expected values from the dataset. Outliers and missing values were investigated through manual validation of echocardiographic video clips and images in the study cohort.

**OUTCOME DATA.** The primary outcome was a composite outcome of all-cause mortality, hospitalization due to heart failure (HF), and aortic valvular interventions after diagnosis with severe AS. Secondary outcomes include the individual components of the composite outcomes. Survival status was determined from Western Health's electronic medical records, which included data from date of death, inpatient episodes, and emergency presentation from the echocardiographic examination date through March 16, 2020. HF readmission after the echocardiographic examination date was defined as the occurrence of hospitalization from diagnosis-related group codes, the principal diagnosis, and the discharge specialty in the inpatient episode database. Aortic valvular intervention was defined as transcatheter aortic valve replacement or surgical aortic valve replacement.

**FIGURE 1** **Flow Chart Summarizing Case Selection and Classification**




Stratification of flow state was based on stroke volume index or transvalvular flow rate. AS = aortic stenosis; AV = aortic valvular; AVAi = indexed aortic valve area; echo = echocardiography; FR = transvalvular flow rate; LFLG = low flow-low gradient; LVEF = left ventricular ejection fraction; MPG = mean pressure gradient; SVi = stroke volume index; TTE = transthoracic echocardiogram.

**TABLE 1 Baseline Characteristics of Patients With Severe Aortic Stenosis According to Standard Phenotypes, Stratified by Low Flow (SVi: <35 ml/m$^2$) Versus Normal Flow (SVi: ≥35 ml/m$^2$) and LVEF (<50% vs. ≥50%)**

| | All Patients With AS (N = 621) | Classical LFLG (n = 135) | Paradoxical LFLG (n = 177) | Normal Flow-Low Gradient (n = 161) | p Value* |
|---|---|---|---|---|---|
| Age, yrs | 76.4 ± 11.2 | 76.8 ± 10.9 | 75.0 ± 12.5 | 76.3 ± 10.3 | 0.36 |
| Male | 351 (57.0) | 92 (68.1) | 82 (46.3) | 103 (64.0) | <0.001 |
| Weight, kg | 83.4 ± 22.8 | 87.1 ± 26.5 | 88.9 ± 25.3 | 81.3 ± 19.7 | 0.01 |
| Moderate/severe aortic regurgitation | 47 (8.0) | 9 (6.7) | 8 (4.5) | 13 (8.1) | 0.40 |
| Heart rate, beats/min | 76.7 ± 19.5 | 81.9 ± 20.2 | 81.5 ± 22.2 | 67.5 ± 12.4 | <0.001 |
| Hypertension | 415 ± 67 | 91 ± 67.9 | 113 ± 63.8 | 112 ± 69.6 | 0.52 |
| Atrial fibrillation | 169 (27) | 56 (41.5) | 67 (37.9) | 17 (10.6) | <0.001 |
| AVA, cm$^2$ | 0.9 ± 0.2 | 0.9 ± 0.2 | 0.9 ± 0.2 | 1.0 ± 0.2 | 0.02 |
| AVAi, cm$^2$/m$^2$ | 0.4 ± 0.1 | 0.4 ± 0.1 | 0.5 ± 0.1 | 0.5 ± 0.1 | <0.001 |
| MPG, mm Hg | 29.8 ± 16.3 | 18.1 ± 8.7 | 19.9 ± 8.8 | 29.2 ± 7.1 | <0.001 |
| Peak gradient, mm Hg | 48.5 ± 25.3 | 29.6 ± 13.8 | 33.9 ± 13.8 | 49.1 ± 14.2 | <0.001 |
| DI | 0.3 ± 0.7 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.002 |
| SVi, ml/m$^2$ | 32.7 ± 10.7 | 23.2 ± 6.9 | 26.9 ± 5.8 | 41.6 ± 6.2 | <0.001 |
| FR, m/s | 206.6 ± 62.8 | 165.0 ± 49.1 | 187.9 ± 57.1 | 237.0 ± 46.6 | <0.001 |
| E/e′ | 20.7 ± 9.2 | 24.0 ± 9.3 | 18.2 ± 7.7 | 20.1 ± 9.5 | <0.001 |
| LV hypertrophy | 212 (34.0) | 57 (42.2) | 39 (22.0) | 47 (29.2) | <0.001 |
| AV intervention | 26 (4.0) | 4 (3.0) | 6 (3.4) | 11 (6.8) | 0.19 |
| Heart failure | 318 (51.0) | 66 (49.3) | 90 (50.8) | 87 (54.0) | 0.70 |
| Angina pectoris | 134 (22.0) | 29 (21.6) | 33 (18.6) | 38 (23.6) | 0.53 |
| Diabetes mellitus | 237 (38.0) | 50 (37.3) | 67 (37.9) | 61 (37.9) | 0.99 |
| Chronic kidney disease | 158 (25.0) | 30 (22.4) | 48 (27.1) | 41 (25.5) | 0.63 |
| Coronary angiography | 163 (26.0) | 29 (21.6) | 38 (21.5) | 52 (32.3) | 0.04 |
| BAV | 7 (1.0) | 0 (0.0) | 2 (1.1) | 2 (1.2) | 0.45 |

Values are mean ± SD or n (%). *Analysis of variance for continuous variables or Pearson chi-square test for categorical variables.

AV = aortic valvular; AVA = aortic valve area; AVAi = indexed aortic valve area; BAV = percutaneous aortic balloon valvuloplasty; DI = dimensionless index; FR = transvalvular flow rate; LFLG = low flow and low gradient; LV = left ventricular; LVEF = left ventricular ejection fraction; MPG = aortic valvular mean pressure gradient; SVi = stroke volume index.

**STATISTICAL ANALYSIS.** Descriptive statistics were used to examine the distribution of patient characteristics, echocardiographic parameters, and comorbidities. Means and standard deviations (or medians and interquartile ranges where appropriate) were computed for continuous variables and frequencies with percentages for categorical variables. Characteristics were compared between the 2 AS subtypes (e.g., classical or paradoxical LFLG-AS) using a 2-way *t*-test for continuous variables or Pearson' chi-square test for categorical variables. Analysis of variance was used to compare characteristics among 3 or more groups.

Cumulative hazard functions for time to events were used to describe the hazard functions of different AS subtypes. The log rank test was used to provide comparison between the survival data between AS subtypes. Multivariable analysis in Cox proportional hazards models was used to assess the significance of different severe AS subtype classifications in predicting 2-year composite outcome and all-cause mortality alone. For HF readmission, mortality before the first readmission was considered a competing risk in the models, and we determined the subdistribution hazard derived from cumulative incidence function and corrected for competing risk (17). Analyses were performed separately for LVEF, FR, and/or SVi criteria. All multivariable analyses were adjusted for age, sex, obesity, hypertension, dyslipidemia, diabetes, atrial fibrillation/flutter, stroke/transient ischemic attack, coronary artery disease, endocarditis, left ventricular mass index, moderate-severe tricuspid insufficiency, moderate-severe mitral regurgitation, chronic kidney disease, and percutaneous aortic balloon valvuloplasty. For all-cause mortality and HF readmission, models were also adjusted for aortic valvular intervention. We also conducted sensitivity analyses using different cutoff points for SVi of 34 or 36 ml/m$^2$ and FR of 210 and 220 ml/s. Harrell C-statistics were computed to compare discrimination of severe AS classifications based on clinical parameters, AVAi, LVEF, and SVi or FR. The net reclassification improvement (NRI) assessed correct reassignment among risk subgroups and compared base model (clinical parameters), echocardiographic model (base model with AVAi and

**TABLE 2 Baseline Characteristics of Patients With Classical LFLG-AS, According to Flow State Classified Using SVi and/or Transvalvular FR**

| | Classical LFLG-AS | | | | |
|---|---|---|---|---|---|
| | Overall Low SVi or Low FR (N = 141) | Low SVi and Low FR (n = 101) | Normal SVi and Low FR (n = 6) | Low SVi and Normal FR (n = 34) | p Value* |
| Age, yrs | 76.4 ± 11.2 | 77.2 ± 10.4 | 75.8 ± 12.8 | 75.4 ± 12.4 | 0.71 |
| Male | 97 (68.8) | 67 (66.3) | 5 (83.3) | 25 (73.5) | 0.54 |
| Weight, kg | 83.4 ± 22.8 | 83.0 ± 21.5 | 75.7 ± 14.6 | 99.3 ± 35.3 | 0.004 |
| Moderate/severe aortic regurgitation | 10 (7.1) | 5 (5.0) | 1 (16.7) | 4 (11.8) | 0.26 |
| Heart rate, beats/min | 76.7 ± 19.5 | 80.7 ± 20.1 | 64.7 ± 7.2 | 85.3 ± 20.4 | 0.06 |
| Hypertension | 94 (67.1) | 68 (68.0) | 3 (50.0) | 23 (67.6) | 0.66 |
| Atrial fibrillation | 57 (40.4) | 44 (43.6) | 1 (16.7) | 12 (35.3) | 0.33 |
| AVA, $cm^2$ | 0.9 ± 0.2 | 0.8 ± 0.2 | 0.8 ± 0.1 | 1.0 ± 0.2 | <0.001 |
| AVAi, $cm^2/m^2$ | 0.4 ± 0.1 | 0.4 ± 0.1 | 0.4 ± 0.0 | 0.5 ± 0.1 | 0.0043 |
| MPG, mm Hg | 29.8 ± 16.3 | 16.1 ± 8.2 | 28.7 ± 8.5 | 24.2 ± 7.3 | <0.001 |
| Peak gradient, mm Hg | 48.5 ± 25.3 | 26.7 ± 13.4 | 46.2 ± 13.1 | 38.2 ± 11.1 | <0.001 |
| DI | 0.3 ± 0.7 | 0.3 ± 0.1 | 0.2 ± 0.1 | 0.3 ± 0.1 | 0.35 |
| SVi, $ml/m^2$ | 32.7 ± 10.7 | 21.3 ± 6.5 | 38.0 ± 1.8 | 28.7 ± 4.7 | <0.001 |
| FR, m/s | 206.6 ± 62.8 | 143.6 ± 34.0 | 186.9 ± 6.4 | 228.4 ± 26.9 | <0.001 |
| E/e′ | 20.7 ± 9.2 | 25.1 ± 9.6 | 22.1 ± 7.8 | 20.9 ± 7.8 | 0.06 |
| LV hypertrophy | 62 (44.0) | 44 (43.6) | 5 (83.3) | 13 (38.2) | 0.12 |
| AV intervention | 5 (3.5) | 3 (3.0) | 1 (16.7) | 1 (2.9) | 0.21 |
| Heart failure | 68 (48.6) | 48 (48.0) | 2 (33.3) | 18 (52.9) | 0.66 |
| Angina pectoris | 30 (21.4) | 24 (24.0) | 1 (16.7) | 5 (14.7) | 0.50 |
| Diabetes mellitus | 52 (37.1) | 34 (34.0) | 2 (33.3) | 16 (47.1) | 0.39 |
| Chronic kidney disease | 31 (22.1) | 22 (22.0) | 1 (16.7) | 8 (23.5) | 0.93 |
| Coronary angiography | 32 (22.9) | 21 (21.0) | 3 (50.0) | 8 (23.5) | 0.26 |
| BAV | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NA |

Values are mean ± SD or n (%). *Analysis of variance for continuous variables or Pearson chi-square test for categorical variables.
Abbreviations as in Table 1.

LVEF), and echocardiographic model plus SVi or FR. The risk categories or thresholds used were based on the distribution of patients over the range of predicted scores, which included <20% (low risk), 20% to <40% (intermediate risk), 40% to <60% (high risk), and ≥60% (very high risk).

Bootstrapping was used to determine 95% confidence intervals (CIs). A p value of <0.05 was considered statistically significant. Competing risk analysis, Harrell C-statistics, and NRI were performed by using Stata, version 15 (StataCorp, College Station, Texas). All other data analyses were performed by using the R statistical software package, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

**BASELINE PATIENT CHARACTERISTICS.** Over the study period, severe AS (AVAi: <0.6 $cm^2/m^2$) was identified in 621 consecutive unique patients (age: 76 ± 11 years; 57% male) from 25,507 transthoracic echocardiograms. There were 473 (76%) patients with low-gradient AS, including 129 (27%) with normal flow and 345 (73%) with low flow based on SVi or FR (Figure 1). The proportions of patients classified as having LFLG-AS were different between SVi and FR (50% of 621 with severe AS had low SVi vs. 39% with low FR; p < 0.001). Among patients with a low-gradient and low-flow state defined by SVi, 43% had classical and 57% had paradoxical LFLG. Baseline demographic, clinical, and echocardiographic characteristics of the patient population stratified by conventional classification (flow state by SVi) are presented in Table 1. The classical LFLG group had significantly lower AVAi, MPG, peak gradient, SVi, and FR and greater proportions of male patients, as well as atrial fibrillation, left ventricular hypertrophy, and higher E/e′ than the paradoxical LFLG or normal SVi-low-gradient groups. Baseline characteristics were stratified by SVi and/or FR among classical (Table 2) or paradoxical LFLG (Table 3) subtypes; most patients with a low-flow state had both low SVi and low FR. Supplemental Table 1 provides additional baseline characteristics of all patients with severe AS stratified by MPG, LVEF, SVi, and FR.

**THE 2-YEAR OUTCOMES.** The median follow-up was 11.6 months, and the longest follow-up was 74 months. The overall survival of patients with

**TABLE 3** Baseline Characteristics of Patients With Paradoxical LFLG-AS, According to Flow State Classified by Using SVi and/or Transvalvular FR

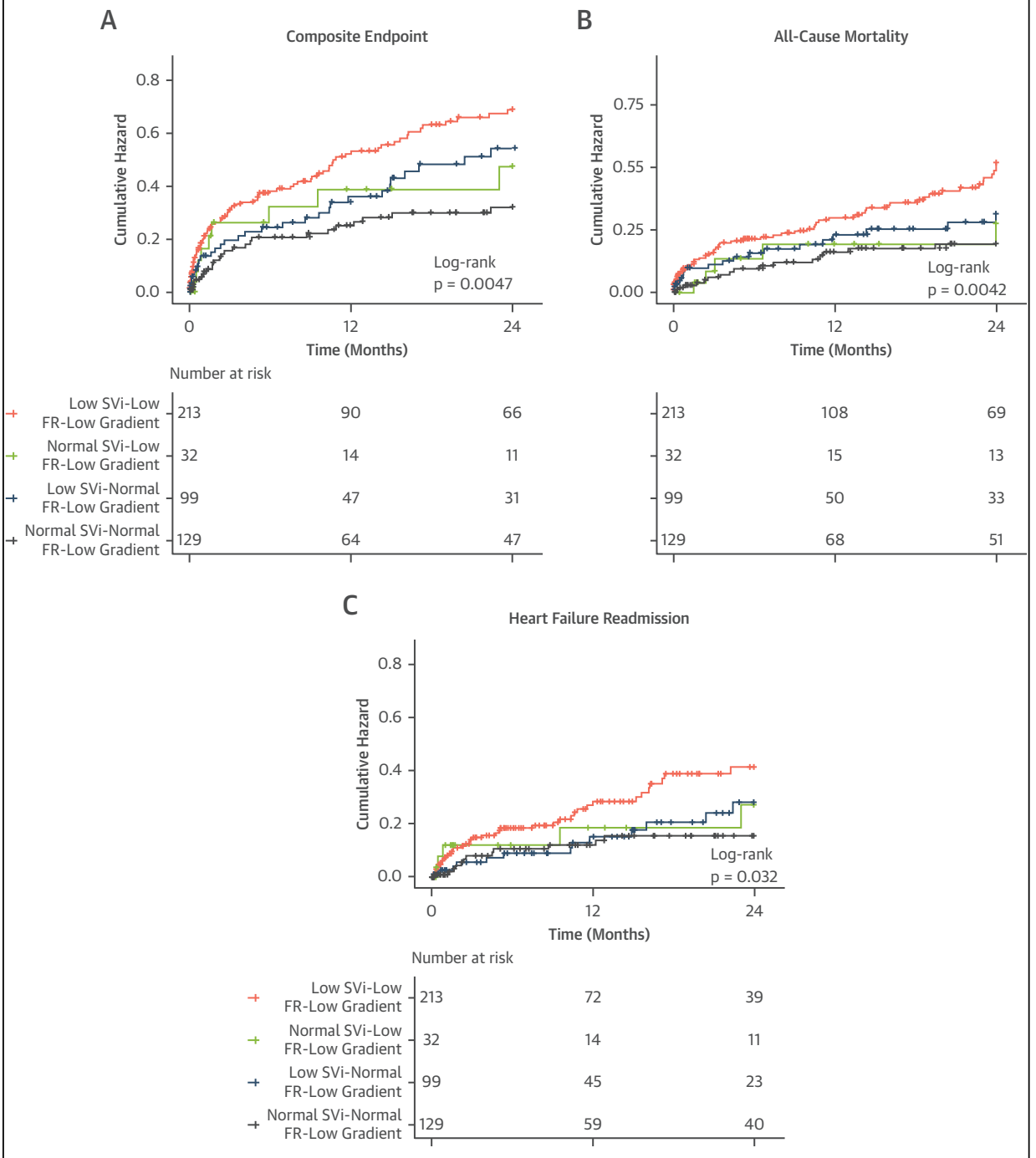
| | Paradoxical LFLG AS | | | | |
|---|---|---|---|---|---|
| | Overall Low SVi or Low FR (N = 203) | Low SVi and Low FR (n = 112) | Normal SVi and Low FR (n = 26) | Low SVi and Normal FR (n = 65) | p Value* |
| Age, yrs | 76.4 ± 11.2 | 76.8 ± 12.1 | 75.6 ± 18.1 | 71.8 ± 12.6 | 0.05 |
| Male | 92 (45.3) | 39 (34.8) | 10 (38.5) | 43 (66.2) | <0.001 |
| Weight, kg | 83.4 ± 22.8 | 78.9 ± 18.4 | 67.6 ± 12.2 | 106.1 ± 26.3 | <0.001 |
| Moderate/severe aortic regurgitation | 11 (5.4) | 4 (3.6) | 3 (11.5) | 4 (6.2) | 0.26 |
| Heart rate, beats/min | 76.7 ± 19.5 | 79.5 ± 22.5 | 65.8 ± 11.0 | 84.8 ± 21.3 | <0.001 |
| Hypertension | 132 (65.0) | 72 (64.3) | 19 (73.1) | 41 (63.1) | 0.65 |
| Atrial fibrillation | 69 (34.0) | 49 (43.8) | 2 (7.7) | 18 (27.7) | <0.001 |
| AVA, $cm^2$ | 0.9 ± 0.2 | 0.9 ± 0.2 | 0.8 ± 0.1 | 1.1 ± 0.2 | <0.001 |
| AVAi, $cm^2/m^2$ | 0.4 ± 0.1 | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.5 ± 0.1 | 0.005 |
| MPG, mm Hg | 29.8 ± 16.3 | 17.8 ± 8.8 | 26.4 ± 7.8 | 23.5 ± 7.5 | <0.001 |
| Peak gradient, mm Hg | 48.5 ± 25.3 | 30.5 ± 13.7 | 50.4 ± 15.5 | 39.7 ± 11.8 | <0.001 |
| DI | 0.3 ± 0.7 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.12 |
| SVi, $ml/m^2$ | 32.7 ± 10.7 | 25.1 ± 5.9 | 40.3 ± 8.0 | 30.1 ± 3.9 | <0.001 |
| FR, m/s | 206.6 ± 62.8 | 154.6 ± 37.2 | 173.7 ± 34.7 | 245.3 ± 35.7 | <0.001 |
| E/e′ | 20.7 ± 9.2 | 18.7 ± 7.9 | 23.7 ± 9.9 | 17.2 ± 7.2 | 0.002 |
| LV hypertrophy | 44 (21.7) | 29 (25.9) | 5 (19.2) | 10 (15.4) | 0.25 |
| AV intervention | 7 (3.4) | 1 (0.9) | 1 (3.8) | 5 (7.7) | 0.06 |
| Heart failure | 103 (50.7) | 53 (47.3) | 13 (50.0) | 37 (56.9) | 0.47 |
| Angina pectoris | 37 (18.2) | 21 (18.8) | 4 (15.4) | 12 (18.5) | 0.92 |
| Diabetes mellitus | 78 (38.4) | 42 (37.5) | 11 (42.3) | 25 (38.5) | 0.90 |
| Chronic kidney disease | 57 (28.1) | 29 (25.9) | 9 (34.6) | 19 (29.2) | 0.65 |
| Coronary angiography | 47 (23.2) | 24 (21.4) | 9 (34.6) | 14 (21.5) | 0.33 |
| BAV | 3 (1.5) | 2 (1.8) | 1 (3.8) | 0 (0.0) | 0.36 |

Values are mean ± SD or n (%). *Analysis of variance for continuous variables or Pearson chi-square test for categorical variables.
Abbreviations as in Table 1.

severe AS was 80.4% (95% CI: 76.9 to 84.2) at 1 year and 70.8% (95% CI: 66.5 to 75.5) at 2 years. The estimated probability of being free from HF readmission in severe AS was 82.8% (95% CI: 79.1 to 86.6) at 1 year and 75.7% (95% CI: 71.2 to 80.6) at 2 years. The estimated probability of freedom from composite outcomes at 2 years was highest in patients with normal SVi, normal FR, and low gradient (72.5%; 95% CI: 63.9 to 82.3) and lowest in patients with low SVi, low FR, and low gradient (50.2%; 95% CI: 43.1 to 58.4). Cumulative hazard curves for patients with severe AS with low gradient and stratified by SVi and FR are shown in Figure 2. Low flow, defined as low SVi and low FR, was associated with the highest risk of composite outcomes, mortality, and HF readmissions ($p < 0.05$). This association remained despite separate alternative analyses using combinations of LVEF, SVi, and/or FR (Supplemental Figure 1). In patients with low or high gradient, the subgroup with low SVi and low FR was also significantly associated with composite outcomes ($p = 0.047$), and all-cause mortality alone ($p = 0.025$), but not HF readmissions alone ($p = 0.087$).

**MULTIVARIABLE MODELS.** Multivariable analyses with Cox proportional hazard models adjusted for demographic data and comorbidities are summarized in Table 4. SVi of <35 $ml/m^2$ and FR <200 ml/s were both strongly and independently associated with the composite endpoint in patients with low gradient AS (HR: 2.15; 95% CI: 1.36 to 3.41; $p = 0.001$). This association was still significant among overall patients with severe AS regardless of MPG (HR: 1.54; 95% CI: 1.06 to 2.22; $p = 0.023$). When SVi, FR, and/or LVEF were added to the models, the HRs for any of the outcomes for the highest risk subgroup were increased. When risk was stratified by all 3 echocardiographic parameters (LVEF, SVi, and FR), classical low SVi, low FR, and low gradient had the highest risk of the composite endpoints (HR: 2.65; 95% CI: 1.61 to 4.38; $p < 0.001$), all-cause mortality (HR: 3.07; 95% CI: 1.65 to 5.69; $p < 0.001$), and HF readmissions (HR: 1.83; 95% CI: 1.00 to 3.37; $p = 0.048$) using competing risk analysis. Patients with paradoxical low SVi, low FR, and low-gradient AS were also associated with increased risk of composite endpoints and all-cause mortality. Sensitivity analyses using other cutoff

**FIGURE 2** **Cumulative Hazard Curves**




**(a)** Composite endpoint (all-cause mortality, hospitalization for heart failure, and aortic valvular intervention), **(b)** all-cause mortality, or **(c)** hospitalization for heart failure in patients with severe aortic stenosis and low gradient, grouped according to transvalvular flow rate (low: <200 ml/s; normal: ≥200 ml/s), stroke volume index (low: <35 ml/m$^2$; normal: ≥35 ml/m$^2$). Abbreviations as in Figure 2.

**TABLE 4** HRs of Composite Endpoint at 2 Years, All-Cause Mortality at 2 Years, and Heart Failure Readmission After Accounting for Competing Risk of All-Cause Mortality in Patients With Severe Aortic Stenosis, With Flow Based on Transvalvular Flow and/or SVi

| Multivariable Models | Composite Endpoint* | All-Cause Mortality* | Heart Failure Readmission† |
|---|---|---|---|
| Model 1: LVEF + SVi + FR (reference group: normal SVi/normal FR-LG) | | | |
| Low FR-LG | | | |
| Classical low SVi | 2.65 (1.61-4.38), <0.001 | 3.07 (1.65-5.69), <0.001 | 1.83 (1.00-3.37), 0.048 |
| Paradoxical low SVi | 1.71 (1.01-2.91), 0.047 | 1.74 (0.89-3.39), 0.10 | 1.45 (0.77-2.85), 0.21 |
| Classical normal SVi | 1.99 (0.45-8.74), 0.40 | 0 (0.00-infinity), >0.90 | 2.45 (0.58-10.53), 0.22 |
| Paradoxical normal SVi | 1.16 (0.49-2.74), 0.70 | 1.21 (0.43-3.42), 0.70 | 0.96 (0.32-2.88), 0.94 |
| Normal FR-LG | | | |
| Classical low SVi | 1.88 (0.94-3.74), 0.074 | 1.52 (0.61-3.82), 0.40 | 1.91 (0.89-4.09), 0.097 |
| Paradoxical low SVi | 1.9 (1.01-3.55), 0.045 | 2.59 (1.18-5.71), 0.018 | 0.66 (0.25-1.70), 0.39 |
| Model 2: SVi + FR (reference group: normal SVi/normal FR-LG) | | | |
| Low FR-LG | | | |
| Low SVi | 2.15 (1.36-3.41), 0.001 | 2.41 (1.35-4.29), 0.003 | 1.84 (1.06-3.18), 0.029 |
| Normal SVi | 1.32 (0.61-2.89), 0.50 | 1.12 (0.40-3.14), 0.80 | 1.23 (0.43-3.49), 0.70 |
| Normal FR-LG | | | |
| Low SVi | 1.88 (1.10-3.21), 0.021 | 2.06 (1.03-4.10), 0.04 | 1.15 (0.59-2.26), 0.68 |
| Model 3: LVEF + SVi (reference group: normal SVi-LG) | | | |
| Classical LFLG-low SVi | 2.29 (1.47-3.55), <0.001 | 2.62 (1.50-4.55), <0.001 | 1.90 (1.12-3.23), 0.017 |
| Paradoxical LFLG-low SVi | 1.66 (1.07-2.59), 0.025 | 1.92 (1.09-3.40), 0.024 | 1.25 (0.73-2.15), 0.41 |
| Model 4: LVEF + FR (reference group: normal FR-LG) | | | |
| Classical LFLG-low FR | 1.94 (1.29-2.91), 0.001 | 2.1 (1.28-3.44), 0.003 | 1.89 (1.11-3.21), 0.019 |
| Paradoxical LFLG-low FR | 1.19 (0.78-1.83), 0.40 | 1.18 (0.70-1.99), 0.50 | 1.47 (0.83-2.61), 0.19 |
| Model 5: SVi (reference group: normal SVi-LG) | | | |
| Low SVi-LG | 1.94 (1.31-2.88), 0.001 | 2.25 (1.35-3.74), 0.002 | 1.55 (0.97-2.49), 0.067 |
| Model 6: FR (reference group: normal FR-LG) | | | |
| Low FR-LG | 1.52 (1.07-2.16), 0.02 | 1.58 (1.03-2.44), 0.038 | 1.66 (1.05-2.64), 0.031 |

Values are hazard ratio (95% confidence interval), p value. All multivariate analyses were adjusted for age, sex, obesity, hypertension, dyslipidemia, diabetes, atrial fibrillation/flutter, stroke/transient ischemic attack, coronary artery disease, endocarditis, left ventricular mass index, moderate-severe tricuspid insufficiency, moderate-severe mitral regurgitation, chronic kidney disease, and percutaneous aortic balloon valvuloplasty. For separate outcomes (all-cause mortality and heart failure readmission), models were also adjusted for aortic valvular intervention (transcatheter aortic valvular intervention vs. surgical aortic valve replacement). LVEF was analyzed as a categorical variable: classical (<50%) vs. paradoxical (≥50%). SVi was analyzed as categorical variable: low (<35 ml/m$^2$) vs. normal (≥35 ml/m$^2$). FR was analyzed as a categorical variable: low (<200 ml/s) vs. normal (≥200 ml/s). *Cox proportional hazard models were used to estimate the HRs for composite endpoint or all-cause mortality. †For heart failure readmission outcome, competing risk analysis was conducted with death as a competing risk.

Abbreviations as in Table 1.

values for FR and SVi produced similar findings for composite endpoints (Supplemental Table 2). When FR and SVi were analyzed as continuous variables, SVi and LVEF were independently associated with composite endpoint (HR: 0.97 [95% CI: 0.94 to 0.99; p = 0.006] and HR: 1.46 [95% CI: 1.05 to 2.04; p = 0.026], respectively), whereas FR and MPG were not significant.

**COMPARISON OF DISCRIMINATION AND RECLASSIFICATION OF DIFFERENT AS SUBTYPES.** A clinical base model consisting of age, sex, obesity, hypertension, dyslipidemia, diabetes, atrial fibrillation, stroke/transient ischemic attack, coronary artery disease, endocarditis, moderate/severe tricuspid regurgitation, and chronic kidney disease had a C-statistic of 0.68 (95% CI: 0.63 to 0.72). The echocardiographic model that included AVAi and LVEF in addition to clinical parameters had a C-statistic of 0.71 (95% CI: 0.66 to 0.75), which showed significant improvement from the base model alone (p = 0.018). Adding SVi or FR to the echocardiographic model with LVEF, AVAi, and clinical parameters had a higher C statistic (SVi: 0.71 [95% CI: 0.67 to 0.76] and FR: 0.715 [95% CI: 0.67 to 0.76]) than the base model (p = 0.006, both) but was not significantly different from the echocardiographic model (p = 0.25 and p = 0.24, respectively).

The overall proportions of individuals reclassified to a new category were 25.8% (27.1% in events and 25% in nonevents) when adding SVi and 26% (29.1% in events and 24.5% in nonevents) when adding FR (Tables 5 and 6). Adding SVi to the clinical and echocardiographic model significantly improved classification accuracy based on an NRI of 0.089 (95% CI: 0.045 to 0.133; p = 0.04). However, there was no improvement in classification when FR was added based on an NRI of 0.061 (95% CI: -0.016 to 0.106; p = 0.17).

**TABLE 5 Reclassification of 2-Year Predicted Risk for Composite Endpoint Based on Net Reclassification Improvement: Stroke Volume Index**

| | | Stroke Volume Index + Base Model | | | | |
|---|---|---|---|---|---|---|
| | **Risk** | **<20%** | **20% to 40%** | **40% to 60%** | **≥60%** | **Total** |
| Base model* | | | | | | |
| Event | <20% | 15 | 12 | | | 27 |
| | 20% to 40% | 6 | 59 | 13 | | 78 |
| | 40% to 60% | | 9 | 41 | 9 | 59 |
| | ≥60% | | | 5 | 30 | 35 |
| | Total | 21 | 80 | 59 | 39 | 199 |
| Nonevent | <20% | 136 | 25 | | | 161 |
| | 20% to 40% | 40 | 125 | 15 | | 180 |
| | 40% to 60% | | 14 | 39 | 9 | 62 |
| | ≥60% | | | 3 | 15 | 18 |
| | Total | 176 | 164 | 57 | 24 | 421 |

*Base model includes indexed aortic valve area; left ventricular ejection fraction; and clinical parameters: age, sex, obesity, hypertension, dyslipidemia, diabetes, atrial fibrillation, stroke/transient ischemic attack, coronary artery disease, endocarditis, moderate/severe tricuspid regurgitation, and chronic kidney disease. The new models included additional flow state classification by stroke volume index as a binary variable (<35 vs. ≥35 ml/m$^2$) or transvalvular flow rate as a binary variable (<200 vs. ≥200 ml/s).

## DISCUSSION

Accurate evaluation of the severity of AS using echocardiographic parameters is essential for risk stratification and management. However, inconsistencies and discordant gradings can lead to suboptimal treatment of AS. In this study from a community hospital, with a relatively low rate of aortic intervention, FR, and SVi, classifications led to differences in the prevalence of LFLG-AS, and the SVi showed significant reclassification improvement, whereas FR did not (**Central Illustration**).

**FREQUENCY OF THE LFLG PHENOTYPES.** In our cohort of patients with severe AS, 56% had LFLG (low SVi or FR), which corresponds to a higher frequency of patients with LFLG-AS compared to previous reports of between 30% and 50%, where patients with LFLG were identified by using SVi (9,10,14,18-22). Of note, these studies were different with respect to patient selection and classification strategies. Previous studies focused on subgroups, such as patients with transcatheter aortic valve replacement or patients with reduced LVEF, rather than an unselected community group.

**TABLE 6 Reclassification of 2-Year Predicted Risk for Composite Endpoint Based on Net Reclassification Improvement: Transvalvular Flow Rate**

| | | Transvalvular Flow Rate + Base Model | | | | |
|---|---|---|---|---|---|---|
| | **Risk** | **<20%** | **20% to 40%** | **40% to 60%** | **≥60%** | **Total** |
| Base model* | | | | | | |
| Event | <20% | 17 | 10 | | | 27 |
| | 20% to 40% | 8 | 57 | 13 | | 78 |
| | 40% to 60% | | 8 | 41 | 10 | 59 |
| | ≥60% | | | 9 | 26 | 35 |
| | Total | 25 | 75 | 63 | 36 | 199 |
| Nonevent | <20% | 143 | 18 | | | 161 |
| | 20% to 40% | 35 | 127 | 18 | | 180 |
| | 40% to 60% | | 16 | 35 | 11 | 62 |
| | ≥60% | | | 5 | 13 | 18 |
| | Total | 178 | 161 | 58 | 24 | 421 |

*Base model includes indexed aortic valve area; left ventricular ejection fraction; and clinical parameters: age, sex, obesity, hypertension, dyslipidemia, diabetes, atrial fibrillation, stroke/transient ischemic attack, coronary artery disease, endocarditis, moderate/severe tricuspid regurgitation, and chronic kidney disease. The new models included additional flow state classification by stroke volume index as a binary variable (<35 vs. ≥35 ml/m$^2$) or transvalvular flow rate as a binary variable (<200 vs. ≥200 ml/s).

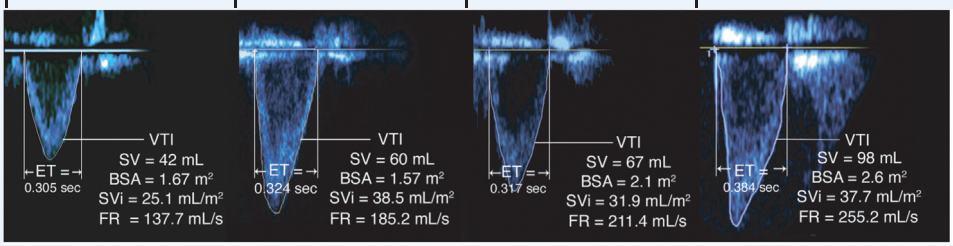
**CENTRAL ILLUSTRATION** **Flow State-Based Risk Model for Prediction of Mortality and Heart Failure Readmissions in Patients With Low-Gradient Severe Aortic Stenosis**

| Phenotype | Low SVi and Low FR | Normal SVi and Low FR | Low SVi and Normal FR | Normal SVi and Normal FR |
|---|---|---|---|---|
| Proportion, n (%) | 213 (45.0) | 32 (6.8) | 99 (20.9) | 129 (27.3) |
| 2-year composite<br>2-year mortality<br>2-year HF re-admissions<br>HR (95% CI) | 2.15 (1.36-3.41)<br>2.41 (1.35-4.29)<br>1.84 (1.06-3.18) | 1.32 (0.61-2.89)<br>1.12 (0.40-3.14)<br>1.23 (0.43-3.49) | 1.88 (1.10-3.21)<br>2.06 (1.03-4.10)<br>1.15 (0.59-2.26) | Reference |

**Echo Examples**

$SVi = \frac{\text{Stroke Volume}}{\text{Body Surface Area}}$

$FR = \frac{\text{Stroke Volume}}{\text{Ejection Time}}$




**Sen, J. et al. J Am Coll Cardiol Img. 2021;■(■):■-■.**

In the example Doppler traces of flow in the left ventricular outflow tract, stroke volume was calculated from the velocity time integral and indexed to body surface area to calculate stroke volume index. Stroke volume and ejection time were used to calculate aortic transvalvular flow rate. FR = flow rate; SVi = stroke volume index; VTI = velocity-time integral.

Reduced stroke volume in paradoxical LFLG is characterized by left ventricular concentric remodeling, with small left ventricular size and impaired diastolic function and systolic longitudinal function, analogous to HF with preserved ejection fraction (9,14,23). Other studies report a greater proportion of AS with paradoxical rather than classical LFLG, similar to our study (22,24,25). We also found that paradoxical LFLG had a lower mean left ventricular mass index and fewer patients with left ventricular hypertrophy compared with classical LFLG. The low-flow state may also be associated with significant mitral regurgitation, mitral stenosis, tricuspid regurgitation, and atrial fibrillation (26). Our findings revealed a higher frequency of moderate or severe mitral regurgitation and tricuspid regurgitation in classical LFLG compared to paradoxical and non-LFLG subtypes. The frequency of atrial fibrillation was also higher in patients with LFLG than in non-LFLG subtypes.

**OUTCOMES.** Compared with other forms of severe AS based on classification by LVEF, FR, SVi, and MPG, patients with classical LFLG-AS with low SVi and FR had the highest mortality risk and HF readmission rate, followed by paradoxical LFLG-AS with low SVi and FR. The effects of LVEF (reduced vs. preserved), FR, and SVi on mortality and HF readmission were significant even after adjustment for multiple demographic and clinical baseline characteristics. In patients with a low gradient, low SVi and FR was predictive of a 2.3-fold increase in composite outcome compared with normal SVi and normal FR after adjustments. This contrasts with a previous study that showed all-cause mortality to be independently associated with low FR (HR: 2.89; 95% CI: 1.25 to 6.69; p = 0.013) but not with low SVi (HR: 0.79; 95% CI: 0.33 to 1.90; p = 0.59) over a median follow-up of 46.8 months (11). However, that study included only patients undergoing aortic valvular intervention and therefore had a lower prevalence of patients with low LVEF. Nevertheless, other studies have demonstrated that low flow stratified by SVi was independently associated with all-cause mortality (10,20,27,28) (Supplemental Table 3).

Our study is the first to include reclassification analyses and found incremental value of SVi but not FR. The prediction of outcomes in patients with low SVi does not improve significantly when FR is added, even though the combination of low SVi and low FR leads to significantly higher risk of the composite endpoint of all-cause mortality and HF readmission.

Our study found discordant findings from the C-statistic and NRI, which was likely due to different aspects of the predictive performance that the 2 metrics assess. Although the C-statistic assesses the gain in discrimination, NRI assesses changes in risk classification. In our study, although adding either SVi or FR to the echocardiographic prediction model (incorporating clinical and echocardiographic predictors) produced modest improvements in the C-statistic with borderline statistical significance, the addition of SVi

produced a significant improvement in reclassification. The echocardiographic prediction model in our study already had good discriminative ability. Previous studies have pointed out that, in such a scenario, very large "independent" associations of the new predictors with the outcome are required to result in a meaningfully larger area under the curve (29-31). Furthermore, a number of previous studies have also suggested that sole reliance on the C-statistic to evaluate a new predictor is inappropriate because it often fails to detect improvements in prediction that result from adding clinically relevant risk factors (31-35). Therefore, our findings from both the C-statistic and NRI demonstrated that SVi significantly increases the prediction of HF readmission or death.

Only 1 other study assessed discrimination from the addition of SVi categories to a multivariable model with clinical factors such as age, sex, body mass index, hypertension, coronary artery disease, Charlson comorbidity index, atrial fibrillation, and systolic blood pressure (27). These authors reported that an SVi of $<35$ ml/m$^2$ had incremental value, with a C-statistic of 0.806 (95% CI: 0.770 to 0.835; $p = 0.026$). Although this model was more predictive than that described in our study (0.71; 95% CI: 0.67 to 0.76), this previous work included nonsevere AS and preserved LVEF and assessed a longer time period (5-year) for all-cause mortality.

Outcomes of AS subtypes have been previously studied with inconsistent findings. In a study of 809 patients, when low flow was classified by an SVi of $<35$ ml/m$^2$, the adjusted mortality risk of paradoxical LFLG-AS was similar to patients with mild to moderate AS (36). Another study of 391 patients with severe AS undergoing transcatheter aortic valve replacement found no difference in all-cause mortality among classical LFLG-AS; paradoxical LFLG-AS; and normal-flow, low-gradient AS ($p = 0.154$), even after adjustments for age, sex, coronary artery disease, Society of Thoracic Surgeons risk score, and HF (37). Recently, the prediction of mortality in 218 patients undergoing aortic valve interventions with low flow defined by an SVi of $<35$ ml/m$^2$ was significantly improved by the use of FR (11). Discrepancies in some previous published reports could be explained by the low numbers of LFLG-AS cases with inadequate statistical power, inaccuracies in classification of flow and gradient, selection bias (e.g., exclusion of patients who did not have aortic valve intervention), and inconsistent inclusion and AS classification criteria. Our study in a large cohort of patients with severe AS suggests that low FR is not superior to low SVi in identifying patients at risk of adverse outcomes. We further demonstrated that low SVi and FR were independent risk factors for composite outcomes regardless of low or high gradient.

**STUDY STRENGTHS AND LIMITATIONS.** Through analysis of individual echocardiographic parameters rather than descriptive reports, we ensured that the diagnosis of severe AS was consistent over time and not affected by changing definitions or misclassification of paradoxical and classical LFLG subtypes due to assessor variability. A unique strength of our analysis is that we examined all quantitative echocardiographic data to minimize missing data (reduced to 3%) and validated parameters extracted from picture archiving and communication system. Limitations of this study include the retrospective nature of this observational population-based cohort study, lack of data on frailty in relation to decisions regarding aortic valve replacement and outcomes, echocardiographic measurement errors, and missing echocardiographic parameters required to screen for severe AS cases. In our study, LVOT was done based on ASE guidelines at the time of the echocardiographic studies within 0.5-1 cm of the valve orifice (5), yet more recent studies suggested that measuring LVOT diameter at the annulus improves the accuracy of SVi estimation (38,39).

We were also limited by the small number of patients with certain AS subtypes (e.g., classical normal SVi, low FR, and low gradient). Only a small proportion of this study cohort had aortic valvular intervention, and the high prevalence of patients with LFLG may limit the generalizability of our findings.

## CONCLUSIONS

A substantial proportion of patients with severe AS have a LFLG phenotype. Classical LFLG with low SVi and FR has the poorest prognosis compared to other combinations of SVi, FR, LVEF, and gradient parameters. The discrimination of AS phenotypes with FR is comparable to SVi, but FR did not significantly improve risk reclassification compared with conventional clinical and echocardiographic predictors. These results suggest that SVi is superior to FR for the identification of patients at risk of an adverse outcome.

**ACKNOWLEDGMENTS** The authors acknowledge the contribution of Paul Canham and Brendan Hooper of Western Health for their assistance in preparing data from clinical databases.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work has been supported in part by a partnership grant (1149692) from the National Health and Medical Research Council, Canberra. Dr. Sen was supported by scholarships from the National Heart Foundation of Australia (identification: 102578), National Health and Medical Research Council of Australia (identification: 1191044), Baker Heart and Diabetes Institute (Bright Sparks), and the Australian Government Research Training Program. Dr. Stub is supported by a fellowship from the National Heart Foundation, Canberra. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** The proportion of patients classified as having LFLG-AS is reduced if the flow state is assessed by using FR rather than SVi (39% vs. 50%). Although patients with either low SVi and FR are likely to readmitted with HF, die, or have AV intervention, FR does not enhance risk prediction in patients with AS compared with SVi.

**TRANSLATIONAL OUTLOOK:** The current approach for the evaluation of AS phenotypes based on SVi appears justified.

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**KEY WORDS** aging, aortic stenosis, low-flow

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