Valvular Heart Disease

Flow-Gradient Patterns in Severe Aortic Stenosis With Preserved Ejection Fraction
Clinical Characteristics and Predictors of Survival

Mackram F. Eleid, MD; Paul Sorajja, MD; Hector I. Michelena, MD; Joseph F. Malouf, MD; Christopher G. Scott, MS; Patricia A. Pellikka, MD

Background—Among patients with severe aortic stenosis (AS) and preserved ejection fraction, those with low gradient (LG) and reduced stroke volume may have an adverse prognosis. We investigated the prognostic impact of stroke volume using the recently proposed flow-gradient classification.

Methods and Results—We examined 1704 consecutive patients with severe AS (aortic valve area <1.0 cm²) and preserved ejection fraction using 2-dimensional and Doppler echocardiography. Patients were stratified by stroke volume index (<35 mL/m² [low flow, LF] versus ≥35 mL/m² [normal flow, NF]) and aortic gradient (<40 mm Hg [low gradient, LG]) into 4 groups: NF/HG, NF/LG, LF/HG, and LF/LG. NF/LG (n=352, 21%), was associated with favorable survival with medical management (2-year estimate, 82% versus 67% in NF/HG; P<0.0001). LF/LG severe AS (n=53, 3%) was characterized by lower ejection fraction, more prevalent atrial fibrillation and heart failure, reduced arterial compliance, and reduced survival (2-year estimate, 60% versus 82% in NF/HG; P<0.001). In multivariable analysis, the LF/LG pattern was the strongest predictor of mortality (hazard ratio, 3.26; 95% confidence interval, 1.71–6.22; P<0.001 versus NF/LG). Aortic valve replacement was associated with a 69% mortality reduction (hazard ratio, 0.31; 95% confidence interval, 0.25–0.39; P<0.0001) in LF/LG and NF/HG, with no survival benefit associated with aortic valve replacement in NF/LG and LF/HG.

Conclusions—NF/LG severe AS with preserved ejection fraction exhibits favorable survival with medical management, and the impact of aortic valve replacement on survival was neutral. LF/LG severe AS is characterized by a high prevalence of atrial fibrillation, heart failure, and reduced survival, and aortic valve replacement was associated with improved survival. These findings have implications for the evaluation and subsequent management of AS severity. (Circulation. 2013;128:1781-1789.)

Key Words: echocardiography ■ heart valves ■ surgery ■ survival ■ valves

Aortic stenosis (AS) is a serious health problem worldwide, with a dismal prognosis ensuing after the development of symptoms if untreated. Although severe AS traditionally has been defined as an aortic valve area (AVA) <1 cm² with a mean systolic Doppler gradient ≥40 mm Hg or a peak aortic velocity ≥4 m/s, in clinical practice, it is common for a patient to present with only 1 or 2 of these criteria.1 Recently, there has been increased scrutiny of the syndrome of low-gradient (LG) severe AS and preserved ejection fraction (EF), as well as the entity called paradoxical low-flow (LF)/LG severe AS.2 These conditions have importance not only for their illustration of the discordance that exists in AS severity criteria but also because they may be associated with a poor prognosis.2 When the triad of Doppler criteria is absent, and especially when the aortic valve gradient is low, patients may not be referred for aortic valve replacement (AVR).

It is well recognized that stroke volume is an important determinant of the aortic valve gradient. In patients with LG severe AS, stroke volume may be decreased as a result of a multitude of factors, including small body habitus, concentric remodeling with decreased ventricular cavity size, and elevated arterial impedance. To further define the hemodynamic features of severe AS, a recent flow-gradient classification was proposed that incorporates both mean gradient and stroke volume.3 The utility of examining stroke volume with this classification has been demonstrated in a relatively small study of patients with asymptomatic AS.4 Whether stroke volume is predictive of outcome in large populations of patients with severe AS, including those with symptoms, remains unclear.

We hypothesized that LF/LG severe AS is associated with increased mortality compared with normal flow (NF)/LG severe AS and may benefit from AVR. Accordingly, the aim of the present investigation was to determine the clinical
characteristics and long-term outcome of patients with severe AS and preserved EF according to stroke volume and aortic valve gradient.

Methods

Patients

The Mayo Clinic Institutional Review Board approved this study. Consecutive patients ≥18 years of age who underwent transthoracic echocardiography between January 1, 2006, and December 31, 2011, with the following criteria were enrolled: A V A <1.0 cm2, preserved left ventricular (LV) EF (≥50%), and absence of prosthetic valves, complex congenital heart disease, supravalvular or subvalvular AS, hypertrophic cardiomyopathy, and other moderate or severe native valvular lesions. These criteria led to a final study population of 1704 patients. The medical record was reviewed for symptoms, comorbidities, and laboratory data.

2-Dimensional and Doppler Echocardiography

Comprehensive 2-dimensional and Doppler echocardiographic studies were performed on commercially available ultrasound equipment (Acuson Sequoia, Siemens Medical, Mountain View, CA; Vivid-7, GE Healthcare, Milwaukee, WI; and IE33, Phillips Healthcare, Andover, MA) in accordance with the American Society of Echocardiography guidelines.67 LV outflow tract diameter was measured in the parasternal long-axis view in early systole from the point of aortic cusp insertion into the interventricular septum to the point of aortic cusp insertion into the interventricular fibrosa. LV outflow tract time-velocity integral was measured with pulsed-wave Doppler by placing the sample volume just below the region of flow convergence at ≈5 mm apically from the aortic valve in the apical long-axis view and aligning it parallel with blood flow. LV stroke volume was calculated using pulsed-wave Doppler as follows: LV outflow tract area×LV outflow tract velocity-time integral. For each study, a nonimaging probe was routinely used in multiple transducer positions to record the peak aortic jet velocity. For patients in sinus rhythm, 3 cardiac cycles were averaged; for atrial fibrillation, 10 cardiac cycles were averaged. Relative wall thickness was measured with this formula: (2×posterior LV wall thickness)/LV dimension in end diastole. LV stroke volume was also estimated by the cube formula to examine a subgroup of patients with agreement between 2 methods of stroke volume calculation.

Afterload Assessment

Ventricular afterload was assessed by use of the methods derived from echocardiography and systolic blood pressure. Valvuloarterial impedance (Zva), a measure of global LV afterload, was calculated with the following formula:7 Zva (mm Hg·mL−1·m−2)=stroke volume index×(mean systolic aortic valve Doppler gradient+systolic blood pressure)/stroke volume index. Systemic arterial compliance (SAC), a measure of pulsatile arterial load, was measured with the following formula: SAC (mL·mm Hg−1·m−2)=stroke volume index×(systolic−diastolic blood pressure). Systemic vascular resistance (SVR), a measure of nonpulsatile vascular load, was measured with this formula: SVR (dyne·s·cm−5)=80×mean blood pressure/cardiac output.

Clinical Outcomes

Symptom onset, need for aortic valve intervention (valvuloplasty, transcatheter AVR, or surgical AVR), and vital status were determined from medical records and data obtained from the Rochester Epidemiology Project and National Death Index Data Registry. Records were reviewed manually, and patients were classified as symptomatic if they reported symptoms of angina (typical chest pain), dyspnea that was believed to be related to AS by their treating physician, or syncope. Heart failure was defined as a clinical history of congestive heart failure with evidence of pulmonary edema on chest radiograph that responded to diuretic therapy. Patients not known to be deceased were censored at the time of the last known follow-up.

Statistical Analysis

Patients were stratified according to stroke volume index (<35 mL/m2 [LF] versus ≥35 mL/m2 [NF]) and aortic gradient (40 mm Hg [HGI] into 4 groups: group 1, LF/HGI; group 2, LF/LGI; group 3, NF/LGI; or group 4, NF/HGI). Data are reported as mean±SD or number (percentage). Student t tests were used to compare continuous variables, and Pearson χ2 or Fisher exact tests were used to compare categorical variables between individual groups. ANOVA was used to compare multiple groups. Kaplan-Meier methods and log-rank tests were used for temporal analysis of outcomes in each group. The end points of interest were all-cause mortality, the combination of death and AVR, and all-cause mortality censored at AVR.

To account for differences in likelihood of treatment with AVR, a propensity score was created by using a logistic regression model for AVR based on the following variables: age, sex, obesity, flow-gradient pattern, EF, A V A, mean gradient, peak velocity, Zva, SAC, hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, history of heart failure, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, previous coronary artery bypass grafting surgery, and symptomatic status. The probabilities from this model were then used as inverse probability weights in Cox proportional hazards regression to test for associations with outcomes of interest. To adjust for differences in baseline variables between groups, a multivariable model was constructed using stepwise selection for the outcome of mortality. Candidate variables incorporated into the multivariable model included the same variables that were used to determine the propensity to receive AVR. Within the weighted proportional hazards framework, AVR and concomitant coronary artery bypass grafting were analyzed as time-dependent variables to determine the effect of AVR on all-cause mortality. To test whether the effect of AVR differed between flow groups, an interaction between the AVR effect and group was fitted and tested. Statistical analysis was performed with JMP version 9.0 and SAS version 9.3 (SAS Institute Inc, Cary, NC). An a priori level of significance was determined at P<0.05.

Results

Clinical and Hemodynamic Characteristics

A total of 14656 patients with AS underwent transthoracic echocardiography during the study period. There were 9558 patients excluded for A V A >1 cm2, 2231 patients excluded for EF <50%, and 1156 patients excluded for ≥1 concomitant moderate valvular heart lesions. Two patients had supra-valvular AS and 5 had subaortic stenosis resulting from tunnel/ridge and were excluded, leaving 1704 included in the analysis.

LF/HG was present in 3% (n=50), LF/LG in 3% (n=53), NF/LG in 21% (n=352), and NF/HG in 73% (n=1249). In a subgroup of patients who had stroke volume by the Doppler method within 15% of stroke volume estimated with the LV end-diastolic and end-systolic dimension cube formula (n=675), there was a similar distribution of flow-gradient patterns: 3% with LF/HG, 3% with LF/LG, 22% with NF/LG, and 72% with NF/HG. Characteristics of each group at the time of the echocardiogram are shown in Tables 1 and 2. The majority of patients were symptomatic; however, NF/LG patients were less symptomatic at study entry (53% versus 74%–80% in other groups; P<0.001). Events occurring during the follow-up period are listed in Table 3.
The NF/LG group was characterized by a higher prevalence of women (58% versus 27%–42%; \(P<0.0001\)) and smaller body size (\(P<0.0001\) for each group comparison), smaller LV outflow tract diameter (\(P<0.0001\) versus LF/HG and NF/HG), lower Zva (\(P<0.001\) versus NF/HG), and lower left atrial volume index (\(P=0.03\) versus NF/HG).

The LF/LG group had a lower EF compared with the NF groups (\(P<0.0001\) for both). On further stratification, 37% of patients in the LF/LG group had an EF in the 50% to 59% range, with 24% having an EF of 50% to 54%. In contrast, only 16% and 5% had an EF in the 50% to 59% and 50% to 54% range, respectively, in the NF/HG group (\(P<0.0001\) for all). The LF/LG group was characterized by smaller LV mass index (\(P<0.0001\) versus NF/HG and LF/HG), smaller LV chamber size (\(P<0.001\) versus NF/HG group), higher Zva (\(P<0.001\) versus NF/LG and NF/HG), lower SAC (\(P<0.001\) for each group comparison), and a higher prevalence of atrial fibrillation compared with the NF groups (26% versus 7% and 5%, \(P<0.0001\)).

### Atrial Fibrillation
Patients with atrial fibrillation were older, had higher resting heart rate and a higher prevalence of symptoms, and more commonly had a history of previous heart failure episodes compared with patients without atrial fibrillation (Table 4). Additionally, patients with atrial fibrillation...
had a slightly lower ejection fraction, lower SAC, higher E/e’ ratio, higher right ventricular systolic pressure, and larger left atrial volume compared with those without atrial fibrillation.

**Survival by Flow-Gradient Pattern**

Mean follow-up duration was 2.3±1.9 years (limits, 0–6.9 years). Overall, 1057 patients (62%) had surgical AVR and 64 patients (4%) had transcatheter AVR. NF/LG patients had the lowest rate of AVR with a 2-year survival free of AVR of 59% (95% confidence interval, 53–65).

Patients with LF/LG had the highest all-cause mortality of all groups (Figure 1). Overall 2-year survival in the LF/LG group was 60% versus 85% in the NF/LG group, 82% in the NF/HG group, and 78% in the LF/HG group (P=0.0004). The combined outcome of death or AVR was highest in the HG groups, followed by the LF/LG group (P<0.0001; Figure 2). NF/LG had the best survival to AVR (P<0.0001). Figure 3 shows survival with medical management (outcome of all-cause mortality censored at AVR). NF/LG patients had the best survival with medical management alone (2-year estimate, 82%), followed by 81% in the LF/HG group, 67% in the NF/HG group, and 44% in LF/LG group (P<0.0001).

### Predictors of Mortality

Multivariable Cox proportional hazards regression analysis using inverse probability weights identified age, male sex, obesity, hypertension, history of heart failure, AVA, EF, and flow-gradient pattern to be associated with all-cause mortality (Table 5). The presence of symptoms at baseline was not associated with mortality in any of the 4 groups (Figure 4).

Overall, AVR was associated with a 69% reduction in the risk of death (hazard ratio, 0.31; 95% confidence interval, 0.25–0.39; P<0.0001). Concomitant coronary artery bypass grafting was not associated with mortality (P=0.66). There was evidence of a difference in the effect of AVR between flow-gradient pattern groups (P<0.0001). AVR conferred a strong survival benefit in LF/LG and NF/HG patients, whereas there was no survival benefit from AVR in the NF/LG and LF/HG groups. There was a trend toward NF/HG patients deriving more survival benefit from AVR than LF/LG patients (P=0.08).

**Discussion**

This study represents the largest analysis to date of characteristics and outcomes according to flow-gradient patterns in patients with AVA <1 cm² and preserved EF, providing new insights into the pathophysiology, prevalence, and clinical implications of this condition.
outcomes in AS. LG was present in 24% of patients with AVA <1 cm² and preserved EF; these included only 3% with LF/LG and 21% with NF/LG. LF/LG was associated with reduced survival compared with all other groups. In contrast, patients with NF/LG had better survival with medical management compared with NF/HG. In fact, the NF/LG pattern was an independent predictor of survival after multivariable analysis, demonstrating that NF/LG is a marker of lower risk. AVR was associated with excellent survival across all flow-gradient patterns, and in multivariable analysis, there was evidence of a difference in the effect of AVR among groups. Both the LF/LG and NF/HG groups had a survival benefit from AVR, whereas NF/LG had no observed survival advantage from AVR. These data have important implications for the assessment and management of patients with AS and underscore the need to revise current definitions of AS severity.

Clinical Implications

NF/LG AS patients tended to be female (58%) with a smaller body size and smaller LV outflow tract diameter. Recent studies have demonstrated that patients with small body size have smaller LV outflow tract diameters with inherently smaller AVA. A study by Michelena et al showed that in patients with LV outflow tract diameters ≤2.2 mm, the majority of patients with valve area <1 cm² have a mean gradient <40 mm Hg. Additionally, NF/LG patients in the present study had a larger AVA and indexed AVA compared with the other groups. These data, coupled with lower prevalence of symptoms and mortality shown in our analysis, suggest that to improve classification of severity, patients with NF/LG should have a lower AVA cut point to define severe AS. This is further supported by the independent association between AVA and survival in our analysis. Some patients with NF/LG severe AS may have only moderate AS; thus, special care should be taken with this group to ensure that AS severity is adequately characterized.

LF/LG severe AS with preserved EF was an uncommon hemodynamic pattern in our study. LF/LG patients had reduced SAC and smaller LV cavity dimensions compared with patients with NF/HG. Despite increased relative wall thickness, LV mass was lower, consistent with more concentric LV remodeling compared with NF/HG patients. These data are in accordance with previous studies highlighting the unique features of this syndrome. Despite a higher Zva, a marker of increased risk, the reduced LV mass suggests altered adaptive responses to pressure overload in patients with LF/LG. New findings from our study include a higher prevalence of atrial fibrillation and history of heart failure in LF/LG patients. Patients with heart failure and preserved EF are at increased risk for atrial fibrillation, which may also contribute to an LF state as seen in the LF/LG pattern. Additionally, the higher mortality in the LF/LG group even with AVR indicates that this group of patients has a continuum of disease involving increased arterial afterload and abnormal ventricular properties that is not limited to the calcific aortic valve stenosis and does not resolve entirely with surgical correction. Nevertheless, there was a significant survival benefit from AVR in patients with LF/LG, supporting the recommendation that this group should not be denied AVR when symptomatic.

Interestingly, the LF/LG group had a lower EF compared with the NF/HG group (61±7% versus 65±6%; P<0.0001). Studies evaluating LV long-axis function with 2-dimensional speckle tracking measurement of longitudinal strain have demonstrated reduced global longitudinal strain in patients with LF/LG compared with NF/HG AS. Given the adverse prognosis associated with the LF/LG phenotype shown

### Table 3. Characteristics Associated With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atrial Fibrillation</th>
<th>No Atrial Fibrillation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>82±8</td>
<td>77±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>157 (55)</td>
<td>794 (56)</td>
<td>0.79</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±14</td>
<td>68±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms, n (%)</td>
<td>219 (77)</td>
<td>974 (69)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>218 (76)</td>
<td>1032 (73)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous heart failure event, n (%)</td>
<td>80 (28)</td>
<td>108 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>47±5</td>
<td>48±5</td>
<td>0.21</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>30±5</td>
<td>29±5</td>
<td>0.74</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.50±0.09</td>
<td>0.49±0.09</td>
<td>0.10</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64±6</td>
<td>65±6</td>
<td>0.01</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>116±32</td>
<td>114±28</td>
<td>0.45</td>
</tr>
<tr>
<td>Systemic arterial compliance, mL·mm⁻¹·m⁻²</td>
<td>0.83±0.35</td>
<td>0.89±0.32</td>
<td>0.004</td>
</tr>
<tr>
<td>Mitral annulus E/e’</td>
<td>21±11</td>
<td>17±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right ventricular systolic pressure, mmHg</td>
<td>43±13</td>
<td>37±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial volume index, mL/m²</td>
<td>51±15</td>
<td>39±11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate. LV indicates left ventricular.

### Table 4. Events During Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Group 1, LF/HG (n=50, 3%)</th>
<th>Group 2, LF/LG (n=53, 3%)</th>
<th>Group 3, NF/LG (n=352, 21%)</th>
<th>Group 4, NF/HG (n=1249, 73%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical AVR</td>
<td>29 (58)</td>
<td>26 (49)</td>
<td>141 (40)</td>
<td>861 (69)</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>9 (18)</td>
<td>12 (23)</td>
<td>63 (18)</td>
<td>289 (23)</td>
</tr>
<tr>
<td>Transcatheter AVR</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>7 (2)</td>
<td>51 (4)</td>
</tr>
<tr>
<td>Balloon valvuloplasty</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>7 (2)</td>
<td>36 (3)</td>
</tr>
<tr>
<td>Death</td>
<td>14 (28)</td>
<td>24 (45)</td>
<td>80 (23)</td>
<td>262 (21)</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate. AVR indicates aortic valve replacement, and CABG, coronary artery bypass grafting.
previously and in the present study, using a higher threshold of EF in patients with severe AS (eg, from 50% to 60%) might be useful for identifying subnormal functional reserve. Patients identified to have reduced intrinsic systolic function may potentially benefit from a hemodynamic evaluation to augment stroke volume with dobutamine to differentiate true severe AS from pseudosevere AS to determine whether patients would benefit from AVR.

Afterload measures \(Zva, SAC, \) and \(SVR\) were uniformly abnormal in LF compared with NF. \(Zva,\) an indirect measure of global LV afterload, was lower in LF/LG compared with the LF/HG group, a result of higher mean aortic valve gradient in the LF/HG group in the setting of similar blood pressure and stroke volume. The LF/LG group had the lowest SAC and highest SVR, indicating increased vascular stiffness and peripheral resistance. Reduced SAC is common in AS and is associated with LV systolic and diastolic dysfunction. Additionally, after multivariable analysis, systemic hypertension, a disease associated with abnormal arterial properties, was independently associated with mortality.

Atrial fibrillation was more common in the LF groups compared with the NF groups, with 22% and 26% prevalence in the LF/HG and LF/LG groups, respectively, compared with...
7% in the NF/LG and 6% in the NF/HG groups at the time of echocardiographic assessment ($P<0.0001$). For patients in atrial fibrillation, 10 cardiac cycles were averaged to obtain stroke volume and mean transvalvular aortic pressure gradient; it is unlikely that differences in flow and gradient were a result of error caused by variable cycle lengths in atrial fibrillation. In atrial fibrillation, atrial contribution to LV filling in late diastole diminishes and diastolic filling time is shortened by increased heart rate, resulting in reduced stroke volume. Additionally, the presence of atrial fibrillation may serve as a marker of more advanced diastolic dysfunction and left atrial hypertension resulting from comorbidities such as coronary artery disease, obesity, and diabetes mellitus, which were more common in the LF groups. These mechanisms are supported by the higher resting heart rate, LV filling pressures, left atrial volume, and right ventricular systolic pressure observed in patients with atrial fibrillation.

The prevalence of flow-gradient patterns found in this study is similar to that in a recent study by Lancellotti et al. (7% had LF/LG pattern), who described the clinical outcomes of asymptomatic AS patients with AVA $<1$ cm$^2$ and EF $\geq55\%$ according to flow-gradient pattern over a median follow-up of 26 months. Although the numbers of patients with LF/LG and LF/HG were small (n=11 and n=15, respectively), these groups had the highest risk of cardiac death or need for AVR (2-year cardiac event-free survival: 83±6%, 44±6%, 30±12%, and 27±13% in the NF/LG, NF/HG, LF/HG, and LF/LG groups, respectively; $P<0.0001$). In a study of 333 patients undergoing both echocardiography and cardiac catheterization, Minners and colleagues reported that 34% to 43% of severe AS patients with AVA $<1$ cm$^2$ have inconsistent grading, with 15% having paradoxical LF/LG severe AS. Adda et al. found the LF/LG pattern in 9% of 340 severe AS patients with normal EF. Our study shows a smaller prevalence of both LG severe AS (24%) and paradoxical LF/LG severe AS (3%) with preserved EF but similarly shows both poor overall survival and a lower referral rate for AVR in the LF/LG group. A recent analysis from the Placement of Aortic Transcatheter Valves (PARTNER) trial showed that one third of patients with preserved EF had LF at baseline, which may be related to the higher prevalence of advanced cardiovascular and pulmonary disease in the highly selected group of patients entered in the trial.

Our data also provide new insights into the pathophysiology of LF/HG AS. The LF in the LF/HG group is affected by increased body surface area and is driven primarily by excess weight and body mass index (nearly 80% were obese). The average absolute stroke volume of this group was 70 mL, which would not be considered LF in a patient with normal body surface area. The higher prevalence of diabetes mellitus, atrial fibrillation, and previous heart failure episodes in LF/HG compared with NF/HG may also be associated with obesity. Additionally, the LF/HG hemodynamic pattern was associated with increased mortality compared with NF/LG, and the majority of these patients underwent AVR.

### Exclusion of Concomitant Valvular Lesions

Concomitant valvular heart disease can cause reduced forward LV stroke volume, resulting in a state of LF. For this reason, patients with moderate or greater valvular stenosis or regurgitation were excluded, similar to other previous investigations. In contrast, some studies did not exclude these patients, raising the possibility that the cause of the reduced flow in these reports may be different from that of paradoxical LF/LG severe AS described as a combination of small LV cavity, intrinsic myocardial dysfunction, and increased arterial afterload. Without correction for valvular causes of reduced stroke volume, the relative prevalences of LF would be much higher (41% of patients who initially met inclusion criteria in our study were excluded for moderate or greater concomitant valvular lesions), which may in part explain the lower prevalence of LF in our study.
Stroke Volume Assessment
The lower observed prevalence of LF/LG severe AS in the present study compared with previous studies may also be explained in part by differing methodologies. First, the present study represents a large group of consecutive AS patients regardless of symptom status and subsequent management. Second, the method of LV outflow tract diameter measurement at our institution differs from the European Society of Echocardiography/American Society Echocardiography guidelines in that we measure the LV outflow tract diameter at the level of aortic cusp insertion18 rather than “5 to 10 mm below the aortic valve orifice.” We believe this method may have greater reproducibility, although this has not been proven. A study by Poh and colleagues19 using 3-dimensional echocardiography has illustrated why measuring LV outflow tract diameter at a variable distance below the annulus can lead to wide variation in measurements. Additionally, our laboratory systematically measures peak aortic valve velocity in multiple imaging windows to obtain the peak signal, which may yield a higher prevalence of HG AS and reduce the prevalence of LG AS as a result of measurement error from an inability to detect the peak velocity.

Limitations
This investigation represents the largest consecutive population of AS patients characterized by flow-gradient patterns using comprehensive echocardiography evaluation studied to date, although its retrospective nature is an inherent limitation. There may be features of the patient groups, not accounted for in our study, that contributed to differences in outcomes. Although biplane LV volume data were not available, a subgroup analysis of patients with similar stroke volume measurements using LV dimensions showed close agreement in flow-gradient pattern prevalences with the overall group. Nevertheless, it is possible that the prevalence of LF and LF/LG was underestimated in the study. Our study is unique in that it provides insight into the prevalence, demographics, characteristics, and clinical outcomes of the various flow-gradient patterns using a systematic AS measurement methodology that is consistently performed at our institution. Finally, unindexed as opposed to indexed AVA was used to define AS severity; this may have resulted in larger differences in body mass index between groups, potentially contributing to differences in outcomes.

Conclusions
Patients with NF/LG severe AS with preserved EF exhibit favorable survival with medical management, and the impact of AVR on survival is neutral. LF/LG severe AS is characterized by a high prevalence of atrial fibrillation and heart failure events and reduced survival, with a strong association of improved survival with AVR. These findings have implications for the evaluation of AS severity and subsequent management.

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Disclosures
None.

References
Among patients with severe aortic stenosis (AS) and preserved ejection fraction, those with low gradient (LG) and reduced stroke volume may have an adverse prognosis. Whether stroke volume is predictive of outcome in large populations of patients with severe AS, including those with symptoms, has been an area of uncertainty. In the present investigation, we studied the long-term outcome of patients with severe AS (aortic valve area <1.0 cm²) and preserved ejection fraction (≥50%) using 2-dimensional and Doppler echocardiography. Patients were stratified by stroke volume index (<35 mL/m² [low flow, LF] versus ≥35 mL/m² [normal flow, NF]) and aortic gradient (<40 mm Hg [LG] versus ≥40 mm Hg [high gradient, HG]) into 4 groups: NF/HG, NF/LG, LF/HG, and LF/LG. NF/LG (n=352, 21%) was associated with better survival with medical management (2-year estimate, 82% versus 67% in NF/HG; P<0.0001). LF/LG severe AS (n=53, 3%) was characterized by lower ejection fraction, higher prevalence of atrial fibrillation and heart failure, reduced arterial compliance, and reduced survival (2-year estimate, 60% versus 82% in NF/HG; P<0.001). In adjusted multivariable analysis, the LF/LG pattern was the strongest predictor of mortality (hazard ratio, 3.26; 95% confidence interval, 1.71–6.22; P<0.001 versus NF/LG). Aortic valve replacement was associated with a 69% mortality reduction (hazard ratio, 0.31; 95% confidence interval, 0.25–0.39; P<0.0001) in LF/LG and NF/HG; there was no survival benefit associated with aortic valve replacement in NF/LG and LF/HG. These findings have implications for the evaluation and subsequent management of AS severity.
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