Aortic stenosis (AS) is characterized by left ventricular (LV) pressure overload leading to LV hypertrophy and concentric remodeling, and it may lead to reduced LV systolic function that is uncommonly asymptomatic. According to American College of Cardiology/American Heart Association guidelines and European Society of Cardiology guidelines, LV systolic dysfunction, defined as LV ejection fraction (LVEF) of <50%, is a class I indication for aortic valve replacement (AVR) in asymptomatic severe AS, whereas asymptomatic severe AS with preserved LVEF (≥50%) has no AVR indication unless critical (very severe) AS is present.2,3

**Methods**

**Study Patients**

This study was approved by the Mayo Clinic Institutional Review Board. This retrospective study included all patients aged >18 years who underwent surgical AVR from January 1995 to June 2009 at Mayo Clinic, Rochester, MN, for severe AS defined as a mean aortic valve gradient of ≥40 mm Hg, aortic valve area (AVA) of <1 cm², or indexed AVA of <0.6 cm²/m², as well as leaflet calcification with severe restriction of opening. Only patients who had undergone a trans-thoracic echocardiography (TTE) at Mayo Clinic within 3 months before AVR and agreed to allow access to their medical records for research were included. Patients with concomitant moderate-severe data exist to substantiate this cut point as the optimal threshold for referral to AVR. The focus of this study was to determine the effect of preoperative LVEF on postoperative outcome after AVR in patients with severe AS.

**Conclusions**

LVEF is a powerful predictor of outcome in patients with severe aortic stenosis undergoing aortic valve replacement, independent of the presence of valve-related symptoms. (Circ Cardiovasc Imaging. 2015;8:e002917. DOI: 10.1161/CIRCIMAGING.114.002917.)

**Key Words:** aortic valve ■ aortic valve stenosis ■ cardiac surgical procedures ■ echocardiography ■ ventricular remodeling
or severe valvular conditions other than AS, previous valve surgery, need for concomitant aortic root surgery, active endocarditis, complex congenital heart disease, or supravalvular or subvalvular AS were excluded. Coronary heart disease was defined as a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting surgery before AVR. Patients were considered to be symptomatic if they reported symptoms of dyspnea, chest pain, or syncope on exertion. Patients were divided into 4 groups depending on preoperative LVEF (<50%, 50%–59%, 60%–69%, and ≥70%).

### Echocardiography

Two-dimensional and Doppler TTE studies were performed on commercially available ultrasound equipment (Acuson Sequoia, Siemens Medical, Mountain View, CA; Vivid-7, GE Healthcare, Milwaukee, WI; and iE33, Philips Healthcare, Andover, MA) in accordance with the American Society of Echocardiography guidelines with interpretation performed by an experienced cardiologist with level III training in echocardiography. Doppler values were calculated as the average of 3 cardiac cycles for patients with sinus rhythm and 10 for atrial fibrillation. 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. AVA was estimated by quantitative Doppler ultrasound using the continuity equation. Peak and mean flow velocity across the valve were determined in the window where the highest velocity could be recorded using continuous wave Doppler with the cursor as parallel as possible with the flow across the valve. Peak and mean transvalvular gradients were estimated using the modified Bernoulli equation. LVEF was determined by the modified method of Quinones or Simpson biplane method; the final reported LVEF method was at the discretion of the echocardiographer. LV stroke volume was calculated using pulsed-wave Doppler as the product of the LV outflow area and LV outflow tract time velocity integral and indexed for body surface area (stroke volume index [SVi]). LV mass index was estimated using Devereux formula. In men, LV mass index >116 g/m² and in women, >104 g/m² were considered indicative of LV hypertrophy. Relative wall thickness was calculated for assessment of LV geometry using the formula 2×posterior wall thickness/LV internal diameter in diastole. Increased relative wall thickness was present when this ratio was >0.42. Valvular aortic stenosis (Zva) was calculated using the formula (systolic blood pressure+mean aortic valve pressure gradient)/SVi.

### Outcomes

Beginning the day of AVR, follow-up was obtained from the electronic medical records and Mayo Clinic registration system. Mayo Clinic obtains follow-up from several sources, including Minnesota State Death records. Because not all subjects were followed uniformly, those who were not known to be deceased were censored at last follow-up. The primary end point of this study was all-cause mortality. The primary end point of this study was all-cause mortality. The primary end point of this study was all-cause mortality.

### Analysis

Data are presented as mean±SD or number and percentages. Differences in values between groups were tested by 1-way ANOVA; categorical variables were tested by the χ² exact test or Fisher exact test when the expected value in any of the cells of a contingency table was below 5. Creatinine and E/E′ were presented as a median and interquartile range, and differences were tested using the Kruskal–Wallis test because of a non-Gaussian distribution for these variables. In the case of significant differences between groups, paired comparisons were performed and significance was set using the Bonferroni correction (0.05/6=0.008). Correlations were obtained using Spearman rank test. For overall tests, a P value of <0.05 was considered significant and 2-sided tests were used. Mortality rates were calculated and plotted using the product limit method; rates were compared using the log-rank test. Further estimation of risk was performed using Cox proportional hazard models. All significant variables in the univariate analysis were inserted in the multivariable analysis, except Zva because of significant collinearity with SVi. Sex was not significant in the univariate analysis, but it was included as it is known to affect long-term outcome in the general population. As symptomatic status is known to be an important factor among patients with AS undergoing AVR, we also tested LVEF stratified according to the presence of symptoms. Because patients over a long-time period were included, we adjusted for the effect of time period, dividing the patients into 3 groups of similar size (1995–1999, 2000–2004, and 2005–2009). To further study the importance of LVEF, we tested the multivariable model in patients without another indication for AVR, such as very severe AS defined as AVmax≥5 m/s or aortic valve mean gradient≥260 mm Hg, symptoms or positive stress test, LVEF<50%, or concomitant coronary revascularization indicated to improve survival. The overall differences between models were tested by calculating the difference in log likelihood χ² between models that were based on the same set of patients. The assumptions (proportional hazard assumption, linearity of continuous variables, and lack of interaction) were tested and found valid. Statistical analysis was performed with STATA/SE 12.0 (StataCorp LP; TX) software.

### Results

#### Patients

From 2606 patients with severe AS undergoing AVR, excluded were 295 with no TTE <3 months before AVR, 154 with moderate-severe or severe valve condition other than AS, 52 with missing values for LVEF, 32 with concomitant aortic root replacement, 30 previous AVR, 18 previous mitral valve surgery, and 8 endocarditis leading to the final study population of 2017 patients. LVEF was <50% in 300 (15%) patients, 50% to 59% in 331 (16%), 60% to 69% in 908 (45%), and ≥70% in 478 (24%). Clinical characteristics at the time of TTE are presented in Table 1. Symptomatic status was obtainable in 1983 (98.3%) patients. Of these, 1467 (74%) were symptomatic. Patients with lower LVEF, particularly those with LVEF<50%, presented more often with symptoms and with worse New York Heart Association functional class (NYHA-FC; 2.1±0.6 versus 1.9±0.7 versus 1.9±0.7 versus 1.8±0.7 in patients with LVEF<50%, 50% to 59%, 60% to 69%, ≥70% respectively; P<0.001). Comparing patients with LVEF<50% to those with LVEF between 50% and 59%, the first group were more likely to be men, more often treated with diuretics and angiotensin-converting enzyme inhibitors, had a higher NYHA-FC, and were less likely treated with calcium-channel blockers (P<0.05 for each).

#### Echocardiographic Data

Both end-systolic and end-diastolic LV diameters correlated inversely with LVEF (r²=-0.83; P<0.0001 and r²=-0.52; P<0.0001, respectively). Clinically small, but statistically significant differences in AVA, indexed AVA, and transvalvular gradients were observed between groups (Table 2). Eccentric hypertrophy (higher LV mass index and lower relative wall thickness) was a common geometry pattern in patients with LVEF<50%.

#### Operative Data

Operative data are summarized in Table 3. The overall median time from TTE to AVR was 12 days (interquartile range, 4–29
days); however, there were significant differences between groups \(P=0.0001\). Patients with LVEF<50% had a shorter time from TTE to AVR with a median of 7 days (3–18) compared with 14 days (5–31) in patients with LVEF≥50%. There was no significant difference in TTE to AVR time between the 3 groups with LVEF≥50%. Concomitant coronary

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>LVEF&lt;50%, n=300</th>
<th>LVEF 50%–59%, n=331</th>
<th>LVEF 60%–69%, n=908</th>
<th>LVEF≥70%, n=478</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.7±9.0</td>
<td>73.4±10.0</td>
<td>72.7±10.0*</td>
<td>72.4±9.8*</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex, male</td>
<td>234 (78)</td>
<td>228 (69)</td>
<td>569 (63)</td>
<td>244 (51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>58 (20)</td>
<td>50 (15)</td>
<td>117 (13)</td>
<td>40 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>159 (54)</td>
<td>197 (60)</td>
<td>581 (64)</td>
<td>316 (66)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>85 (29)</td>
<td>80 (25)</td>
<td>225 (25)</td>
<td>124 (26)</td>
<td>0.56</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>86 (29)</td>
<td>108 (33)</td>
<td>334 (37)</td>
<td>130 (28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.96±0.25</td>
<td>1.96±0.24</td>
<td>1.95±0.23</td>
<td>1.92±0.22</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Symptoms**

- Symptoms: 265 (91) vs. 247 (76) vs. 637 (71) vs. 318 (68) \(<0.001\)
- NYHA-FC, no. 1/2/3/4: 48/189/46/7 vs. 83/190/44/8 vs. 261/499/122/7 vs. 151/239/69/6 \(<0.001\)

**Treatment**

- Diuretics: 161 (56) vs. 124 (39) vs. 314 (35) vs. 171 (37) \(<0.001\)
- Beta-blockers: 111 (38) vs. 130 (41) vs. 323 (36) vs. 167 (36) 0.43
- CCB: 42 (15) vs. 73 (23) vs. 208 (23) vs. 110 (24) 0.01
- ACE inhibitors: 113 (39) vs. 95 (30) vs. 257 (29) vs. 138 (30) 0.01
- Nitrates: 66 (23) vs. 45 (14) vs. 113 (13) vs. 53 (11) \(<0.001\)
- Creatinine, mg/dL: 1.2 (1.0–1.4) vs. 1.2 (1.0–1.3) vs. 1.1 (0.9–1.3) vs. 1.1 (0.9–1.2) 0.0001

Data are represented as number and percentage or for continuous variables, as mean±SD. A total of 426 patients had missing values for COPD (83 in LVEF<50%, 73 in LVEF 50%–59%, 175 in LVEF 60%–69%, and 95 in LVEF≥70%). Forty-eight patients had missing values at NYHA-FC (10 in LVEF<50%, 6 in LVEF 50%–59%, 19 in LVEF 60%–69%, and 13 in LVEF≥70%). ACE indicates angiotensin-converting enzyme; CCB, calcium-channel blocker; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; and NYHA-FC, New York Heart Association functional class.

\*\(P<0.008\) vs. LVEF<50%.

**Table 2. Echocardiographic Data**

<table>
<thead>
<tr>
<th></th>
<th>LVEF&lt;50%, n=300</th>
<th>LVEF 50%–59%, n=331</th>
<th>LVEF 60%–69%, n=908</th>
<th>LVEF≥70%, n=478</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>35±9</td>
<td>54±3</td>
<td>64±3</td>
<td>73±3</td>
<td>...</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.75±0.16</td>
<td>0.78±0.18</td>
<td>0.81±0.18*</td>
<td>0.81±0.16*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AVAi, cm²/m²</td>
<td>0.38±0.09</td>
<td>0.40±0.08</td>
<td>0.42±0.09*</td>
<td>0.43±0.08*†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AV maximum velocity, m/s</td>
<td>4.5±0.5</td>
<td>4.8±0.6*</td>
<td>4.8±0.6*</td>
<td>4.9±0.6†‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AV mean gradient, mmHg</td>
<td>51±12</td>
<td>56±15*</td>
<td>56±14*</td>
<td>58±16†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Zva, mmHg mL⁻¹ m⁻²</td>
<td>4.7±1.2</td>
<td>4.4±1.1</td>
<td>4.1±2.1*</td>
<td>4.0±0.9*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV EDD, mm</td>
<td>57±7</td>
<td>51±7*</td>
<td>49±6†</td>
<td>46±5†‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ESD, mm</td>
<td>45±8</td>
<td>36±5*</td>
<td>30±4†</td>
<td>25±4†‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>153±36</td>
<td>138±39*</td>
<td>123±32†</td>
<td>115±31†‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.42±0.09</td>
<td>0.49±0.12*</td>
<td>0.50±0.10*</td>
<td>0.53±0.12‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV geometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Normal</td>
<td>11 (5)</td>
<td>27 (10)</td>
<td>87 (12)</td>
<td>47 (12)</td>
<td>...</td>
</tr>
<tr>
<td>Concentric remodeling</td>
<td>4 (7)</td>
<td>35 (14)</td>
<td>181 (24)</td>
<td>145 (36)</td>
<td>...</td>
</tr>
<tr>
<td>Eccentric hypertrophy</td>
<td>93 (45)</td>
<td>52 (20)</td>
<td>75 (10)</td>
<td>17 (4)</td>
<td>...</td>
</tr>
<tr>
<td>Concentric hypertrophy</td>
<td>101 (48)</td>
<td>145 (56)</td>
<td>409 (54)</td>
<td>191 (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>39±9</td>
<td>45±9*</td>
<td>48±9†</td>
<td>49±9†‡</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AV indicates aortic valve; AVAi, aortic valve area index; EDD, end-diastolic diameter; ESD, end-systolic diameter; LVEF, left ventricular ejection fraction; and Zva, valvuloarterial impedance.

\*\(P<0.008\) vs. LVEF<50%.

†\(P<0.008\) vs. LVEF 50%–59%.

‡\(P<0.008\) vs. LVEF 60%–69%.
revascularization surgery was performed in 42% of patients (n=850) with no differences between groups. Larger prostheses were used in patients with LVEF<60% (23.6±2.2 versus 23.3±2.1, 22.9±2.0, and 22.6±1.9 mm in the LVEF<50%, LVEF 50% to 59%, LVEF 60% to 69%, and LVEF ≥70% groups, respectively; P=0.0004). However, when indexed for body surface area, only patients with LVEF<50% had larger prostheses.

**Clinical Outcomes**

During follow-up of 5.3±4.4 years, 1056 (52%) patients died. A significant decrease in all-cause mortality during follow-up was observed with increasing LVEF, P<0.0001. Five-year all-cause mortality estimates (95% confidence interval) were 0.41 (0.35–0.47), LVEF<50%; 0.35 (0.29–0.41), LVEF 50% to 59%; LVEF 60% to 69%; and LVEF≥70% (Figure 1).

In the subset of patients with LVEF≥50%, mortality was increased among those with LVEF<60% (hazard ratio [HR], 1.58; P<0.001), with a similar risk increase in both symptomatic (HR, 1.56; P<0.001) and asymptomatic patients (HR, 1.58; P=0.006). Finally, the 5-year event rates increased with decreasing LVEF in a linear relationship.

**Predictors of Outcome**

In a univariable Cox regression analysis, age, NYHA-FC, concomitant concomitant coronary revascularization surgery, a history of hypertension, atrial fibrillation, diabetes mellitus, coronary heart disease, chronic obstructive pulmonary disease, AVA, Zva, SVi, LV mass index, time period 1995 to 1999, and LVEF were univariate predictors of mortality (Table 4). When adjusting for the aforementioned variables except Zva (because of significant colinearity with SVi), LVEF, age, sex, history of atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, SVi, and NYHA-FC remained associated with mortality. These findings were comparable when Zva was substituted for SVi.

Comparing the overall log likelihood χ² of the predictive power of the multivariable models, the model including clinical variables (age, sex, concomitant concomitant coronary revascularization surgery, history of hypertension, chronic obstructive pulmonary disease, diabetes mellitus, coronary heart disease, atrial fibrillation, and NYHA-FC) was significantly improved by addition of TTE data (LV mass index, AVA, and stroke volume index), P=0.005. Further improvement was achieved by addition of LVEF<60% to the combined clinical and TTE model, P<0.0001.

The relationship between mortality and LVEF adjusted for the presence of symptoms is shown in Figure 2; in this model, the coexistence of symptoms and LVEF<60% was associated with the highest mortality rate (5 year-mortality of 0.39; n=172). The isolated presence of LVEF<60% was associated with a 5-year survival rate of 0.27 (n=214) and the isolated presence of symptoms with a 5-year survival rate of 0.34 (n=29). Patients with LVEF≥60% and no symptoms had the lowest mortality rate (0.19; n=66). Interaction terms were

### Table 3. Operative Data

<table>
<thead>
<tr>
<th></th>
<th>LVEF&lt;50%, n=300</th>
<th>LVEF 50%–59%, n=331</th>
<th>LVEF 60%–69%, n=908</th>
<th>LVEF≥70%, n=478</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>141 (47)</td>
<td>150 (45)</td>
<td>367 (41)</td>
<td>192 (40)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>6 (2)</td>
<td>11 (3)</td>
<td>24 (3)</td>
<td>23 (5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Tricuspid surgery</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>7 (1)</td>
<td>5 (1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Septal myectomy</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>22 (2)</td>
<td>32 (6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Prosthesis type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Biological</td>
<td>236</td>
<td>251</td>
<td>687</td>
<td>359</td>
<td>...</td>
</tr>
<tr>
<td>Mechanical</td>
<td>64</td>
<td>80</td>
<td>219</td>
<td>118</td>
<td>...</td>
</tr>
<tr>
<td>Ross procedure</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Prosthesis size, mm</td>
<td>23.6±2.2</td>
<td>23.3±2.1</td>
<td>22.9±2.0*</td>
<td>22.6±1.9†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prosthesis size/BSA, mm/m²</td>
<td>12.2±1.7</td>
<td>12.0±1.4</td>
<td>11.8±1.2*</td>
<td>11.9±1.2†</td>
<td>0.0004</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>8 (2.7)</td>
<td>7 (2.1)</td>
<td>4 (0.4)</td>
<td>4 (0.8)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; CABG, coronary artery bypass graft; and LVEF, left ventricular ejection fraction.

*P<0.008 vs. LVEF<50%.

†P<0.008 vs. LVEF 50%–59%.

Figure 1. Overall survival as a function of left ventricular ejection fraction (LVEF). The expected survival is based on mortality rates of the Minnesota white population with a similar age and sex.
analyzed for interdependence between LVEF and date of AVR and were nonsignificant.

Testing the multivariable models in 1333 patients without history of coronary heart disease, LVEF remained associated with mortality (HR, 0.90 per 10%; $P=0.008$, for the model including age, sex, LV mass index, SVi, AVA, NYHA-FC, history of hypertension, atrial fibrillation, chronic obstructive pulmonary disease, and diabetes mellitus, and HR=0.89 per 10%; $P=0.002$, when Zva was substituted for SVi).

In the subset of patients with very severe AS (n=756), LVEF of 60% to 69% and LVEF $\geq 70$% but not LVEF 50% to 59% were associated with lower mortality compared with LVEF <50% (LVEF 50%–59%; HR=0.87, $P=0.42$; LVEF 60%–69%; HR=0.62, $P=0.003$; and LVEF $\geq 70$%, HR=0.54, $P<0.001$).

Finally, we tested the effect of LVEF in 255 patients without any other indication for AVR; LVEF $\geq 60$% was associated with reduced mortality compared with patients with LVEF of 50% to 59% (LVEF 60%–69%; HR, 0.48; $P=0.003$ and LVEF $\geq 70$%; HR, 0.52; $P=0.02$). This association persisted when adjusting for the same variables in the aforementioned models (LVEF 60%–69%; HR, 0.28; $P<0.001$ and LVEF $\geq 70$%; HR, 0.45; $P=0.03$ for both models).

**Discussion**

The primary finding of this study in a large population of patients with severe AS was that preoperative LVEF was a strong predictor of survival during long-term follow-up after AVR. This was true in both symptomatic and asymptomatic patients, in patients with very severe AS, and in patients without a history of coronary heart disease.

Although there is evidence that LVEF is an indicator of the outcome of patients undergoing cardiac surgery, the definition of reduced LVEF is less clear. In one of the first articles...
Tribouilloy et al., the outcome after AVR in 81 patients with symptoms and LVEF occurred in most patients. In the article by $\leq$40 mm Hg, and no contractile reserve. Although not significant, there was a trend toward increased mortality in the subset of patients with AS and LVEF<$\leq$50%, and the authors concluded that depressed LVEF might cause a moderate increase in postoperative mortality. Current guidelines propose that AVR should be recommended in patients with LVEF<$\leq$50% and provide 2 supporting references. In the first article, Connolly et al. studied the prognosis of 154 patients with severe AS and reduced LVEF. To our knowledge, no clinical studies have demonstrated that these patients indeed have reduced longitudinal LV function, re-emphasizing the need to choose a different LVEF cutoff.20 Further supporting this, LV end-diastolic diameter increased across groups as LVEF decreased. Despite larger LV size, SVi was lower in patients with LVEF $\geq$50% to $\leq$59% compared with those with LVEF<$\leq$50%, it was lower than in the LVEF$\geq$60% group, suggesting adaption with eccentric remodeling to preserve stroke volume in this subgroup. A recent study in hypertensive patients has shown that nondilated eccentric LV remodeling is associated with better outcome compared with other types of remodeling.23 Further supporting this, LV end-diastolic diameter increased across groups as LVEF decreased. Despite larger LV size, SVi was lower in patients with LVEF $\geq$50% to $\leq$59% compared with patients with LVEF$\geq$60%, suggesting that LV systolic function is impaired in this subgroup of patients.

The triad of severe AS, reduced stroke volume, and preserved LVEF has lately received great attention, and several studies have demonstrated that a reduced stroke volume in this setting is associated with a poor outcome.21 Compared with patients with normal stroke volume, this paradoxical low-flow condition is associated with concentric remodeling, smaller LV chamber size, and, although within the normal range, lower LVEF.22 The increased mortality in patients with paradoxical low-flow AS could thus be attributed to reduced LV function not detected when defining this as LVEF<$\leq$50%. This finding is supported by several studies demonstrating that these patients indeed have reduced longitudinal LV function, re-emphasizing the need to choose a different LVEF cutoff.24,25

This study has several limitations. It was a retrospective review of prospectively gathered data, and its accuracy depended on the availability of information within the medical records. LVEF was prospectively measured using multiple echocardiographic methods. Strain rate information was not available. Most of the patients had indications for AVR other than LV systolic dysfunction at LVEF<$\leq$50% was associated with the highest 5-year mortality rate, LVEF $\geq$50% to $\leq$59% was also associated with increased mortality at 5 years compared with the higher LVEF groups. In a recent publication, we demonstrated that reduced longitudinal LV function was associated with a poor postoperative outcome in patients with AS and LVEF$\geq$40% undergoing AVR. Similar findings have since been demonstrated in asymptomatic patients with AS$^{16}$ and AS patients with LVEF$\geq$50%.17 The findings from these small cohort studies have been attributed to the improved ability of global longitudinal strain in detecting early stages of LV systolic impairment, as reduced longitudinal function is known to precede reduced circumferential function. However, it is also possible that these findings reflect that the threshold for preserved LVEF was set too low, as our findings suggest.

Our study suggests that not only patients with LVEF$\geq$50% but also those with LVEF<$\leq$50% to $\leq$59% had a less favorable postoperative outcome. This supranormal threshold probably reflects that patients with severe AS have smaller cavities as a consequence of LV remodeling, requiring higher LVEF to preserve stroke volume. Indeed, Dumesnil et al. demonstrated an independent relationship between LVEF and relative wall thickness; thus, for a similar extent of intrinsic myocardial shortening, the LVEF will tend to increase in relation to the extent of LV concentric remodeling. In addition, impaired LV systolic deformation has been demonstrated to be present despite preserved LVEF, as a consequence of concentric remodeling.

In our study, the higher LVEF threshold is further supported by the findings that 69% of patients had LVEF$\geq$60% and that most of these patients had concentric geometry (either concentric remodeling or concentric hypertrophy). Although relative wall thickness was markedly higher in patients with LVEF $\geq$50% to $\leq$59% compared with those with LVEF<$\leq$50%, it was lower than in the LVEF$\geq$60% group, suggesting adaption with eccentric remodeling to preserve stroke volume in this subgroup.

The paucity of available data on the effect of LVEF on outcome of AVR in patients with severe AS and preserved LVEF led us to examine a large cohort of patients undergoing AVR for AS in an attempt to determine the effect of LVEF on survival after AVR. We found that although the traditionally accepted cutoff for LV systolic dysfunction at LVEF$\leq$50% was associated with the highest 5-year mortality rate, LVEF $\geq$50% to $\leq$59% was also associated with increased mortality at 5 years compared with the higher LVEF groups. In a recent publication, we demonstrated that reduced longitudinal LV function was associated with a poor postoperative outcome in patients with AS and LVEF$\geq$40% undergoing AVR. Similar findings have since been demonstrated in asymptomatic patients with AS$^{16}$ and AS patients with LVEF$\geq$50%.17 The findings from these small cohort studies have been attributed to the improved ability of global longitudinal strain in detecting early stages of LV systolic impairment, as reduced longitudinal function is known to precede reduced circumferential function. However, it is also possible that these findings describe the effect of LVEF after AVR, O’Toole et al. gathered a cohort of 93 patients with AS, aortic regurgitation, and mixed aortic regurgitation who had LVEF estimated by ventriculography. Although not significant, there was a trend toward increased mortality in the subset of patients with AS and LVEF<$\leq$50%, and the authors concluded that depressed LVEF might cause a moderate increase in postoperative mortality. Current guidelines propose that AVR should be recommended in patients with LVEF<$\leq$50% and provide 2 supporting references. In the first article, Connolly et al. studied the prognosis of 154 patients with severe AS and reduced LVEF. To our knowledge, no clinical studies have demonstrated that these patients indeed have reduced longitudinal LV function, re-emphasizing the need to choose a different LVEF cutoff.20 Further supporting this, LV end-diastolic diameter increased across groups as LVEF decreased. Despite larger LV size, SVi was lower in patients with LVEF $\geq$50% to $\leq$59% compared with patients with LVEF$\geq$60%, suggesting that LV systolic function is impaired in this subgroup of patients.

The triad of severe AS, reduced stroke volume, and preserved LVEF has lately received great attention, and several studies have demonstrated that a reduced stroke volume in this setting is associated with a poor outcome.21 Compared with patients with normal stroke volume, this paradoxical low-flow condition is associated with concentric remodeling, smaller LV chamber size, and, although within the normal range, lower LVEF.22 The increased mortality in patients with paradoxical low-flow AS could thus be attributed to reduced LV function not detected when defining this as LVEF<$\leq$50%. This finding is supported by several studies demonstrating that these patients indeed have reduced longitudinal LV function, re-emphasizing the need to choose a different LVEF cutoff.24,25

This study has several limitations. It was a retrospective review of prospectively gathered data, and its accuracy depended on the availability of information within the medical records. LVEF was prospectively measured using multiple echocardiographic methods. Strain rate information was not available. Most of the patients had indications for AVR other than LV systolic dysfunction at LVEF<$\leq$50% was associated with the highest 5-year mortality rate, LVEF $\geq$50% to $\leq$59% was also associated with increased mortality at 5 years compared with the higher LVEF groups. In a recent publication, we demonstrated that reduced longitudinal LV function was associated with a poor postoperative outcome in patients with AS and LVEF$\geq$40% undergoing AVR. Similar findings have since been demonstrated in asymptomatic patients with AS$^{16}$ and AS patients with LVEF$\geq$50%.17 The findings from these small cohort studies have been attributed to the improved ability of global longitudinal strain in detecting early stages of LV systolic impairment, as reduced longitudinal function is known to precede reduced circumferential function. However, it is also possible that these findings...
parameter than cause-specific death. Our study concerned patients undergoing surgical AVR; patients undergoing transcatheter AVR were not included.

In summary, in patients with severe AS undergoing AVR, LVEF provides important prognostic information beyond standard risk factors. Although the traditionally accepted cutoff or LV systolic dysfunction at LVEF<50% is associated with the highest mortality, patients with LVEF 50% to 59% also have increased mortality compared with patients with LVEF≥60%, regardless of symptomatic status.

Sources of Funding

Dr Dahl was supported by a grant from Odense University Hospital. The study was supported by a grant from the Mayo Clinic Division of Cardiovascular Diseases.

Disclosures

None.

References


5. Lang RM, Bieriu M, Devereux RB, Flachkampf FA, Foster E, Pelikka PA, Picard MH, Roman MJ, Seward JB, Shah, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group, developed in conjunction with the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463. doi: 10.1016/j.echo.2005.10.005.


CLINICAL PERSPECTIVE

Although the management of symptomatic patients with severe aortic stenosis (AS) may seem straightforward, asymptomatic patients with severe AS present important challenges. In the latter group, current guidelines specify that aortic valve replacement is recommended when left ventricular ejection fraction (LVEF) is <50%. The optimal cutoff to define normal systolic function is unknown in the setting of AS-associated remodeling. We examined 2017 consecutive patients with severe AS (aortic valve area < 1 cm², indexed valve area < 0.6 cm²/m², or aortic valve mean gradient ≥ 40 mm Hg) undergoing aortic valve replacement and followed them for a median of 5 years. Preoperative LVEF was a strong predictor of survival during long-term follow-up after aortic valve replacement. This was true in both symptomatic and asymptomatic patients, in patients with very severe AS, and in patients without a history of coronary heart disease. Preoperative LVEF provided important prognostic information beyond standard risk factors and echocardiographic variables. Patients with LVEF < 50% had the highest all-cause mortality rate; in addition, compared with those with LVEF ≥ 60%, patients with LVEF 50% to 59% also experienced increased mortality. These findings should be corroborated in prospective studies, as they may indicate that the LVEF cut point recommended in the current guidelines is too low.
Effect of Left Ventricular Ejection Fraction on Postoperative Outcome in Patients With Severe Aortic Stenosis Undergoing Aortic Valve Replacement
Jordi S. Dahl, Mackram F. Eleid, Hector I. Michanela, Christopher G. Scott, Rakesh M. Suri, Hartzell V. Schaff and Patricia A. Pellikka

Circ Cardiovasc Imaging. 2015;8:
doi: 10.1161/CIRCIMAGING.114.002917

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/4/e002917

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/