Prognostic Value of Energy Loss Index in Asymptomatic Aortic Stenosis

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Background—Aortic valve area index adjusted for pressure recovery (energy loss index [ELI]) has been suggested as a more accurate measure of aortic stenosis (AS) severity, but its prognostic value has not been determined in a prospective study.

Methods and Results—The relation between baseline ELI and rate of aortic valve events and combined total mortality and hospitalization for heart failure resulting from the progression of AS was assessed by multivariate Cox regression and reclassification analysis in 1563 patients with initial asymptomatic AS in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. During 4.3 years follow-up, a total of 498 aortic valve events and 181 combined total mortalities and hospitalizations for heart failure caused by the progression of AS occurred. In Cox regression analyses, 1-cm²/m² lower baseline ELI predicted a 2-fold higher risk both for aortic valve events and for combined total mortality and hospitalization for heart failure independently of baseline peak aortic jet velocity or mean aortic gradient and independently of aortic root size (all P<0.05). In reclassification analysis, ELI improved the prediction of aortic valve events by 13% (95% confidence interval, 5–19), whereas the prediction of combined total mortality and hospitalization for heart failure resulting from the progression of AS did not improve significantly.

Conclusions—In asymptomatic AS patients without known atherosclerotic disease or diabetes mellitus, ELI provides independent and additional prognostic information to that derived from conventional measures of AS severity, suggesting that ELI should be measured in such patients.


Key Words: aortic valve ■ aortic valve stenosis ■ cardiovascular system ■ energy loss index

Current guidelines recommend a variety of Doppler echocardiographic measures for assessing the severity of aortic stenosis (AS), including peak aortic jet velocity, mean aortic gradient, aortic valve area (AVA), and AVA indexed for body surface area (AVAI).1–5 These measures may categorize the severity of AS differently, and inconsistently graded severe AS has been reported in up to 30% of patients.6 In particular, AS severity is frequently overestimated by AVAI in patients with milder degree of AS if pressure recovery in the aortic root is not taken into account.7 Recently, it was demonstrated that patients with inconsistently graded severe AS had a prognosis comparable to that seen in patients with moderate AS.8 Whether assessment of pressure recovery adjusted AVAI (energy loss index [ELI]) in this setting could add accuracy to risk assessment is unknown.
patients with asymptomatic AS, defined as aortic valve thickening and peak aortic jet velocity ≥2.5 m/s. Subjects were randomized to placebo-controlled combined treatment with simvastatin 40 mg and ezetimibe 10 mg daily for a median of 4.3 years. The main results of the SEAS study have been published and demonstrated that aggressive lipid-lowering treatment did not reduce AVEs or the progression of AS, whereas ischemic cardiovascular events were significantly reduced in the overall study population. The present study population comprises 1563 (83.4%) of the total 1873 SEAS patients in whom both AVal and pressure recovery at the sinotubular junction could be measured on the baseline study echocardiogram. The present study population did not differ in age, sex, or body mass index compared with the 310 excluded patients, in whom these measurements could not be determined. The SEAS study was approved by regional ethics committees in all participating countries. All patients gave written informed consent to participate in the SEAS study. All end points were adjudicated by an independent expert committee.

**Echocardiography**

Baseline echocardiograms were obtained at 173 study centers in 7 European countries (Norway, Sweden, Finland, Denmark, United Kingdom, Ireland, and Germany) following a standardized protocol. A copy of all echocardiograms was sent for expert interpretation at the SEAS echocardiography core laboratory at Haukeland University Hospital, Bergen, Norway. Management of patients in the study was based on local clinical and echocardiographic interpretation at the study centers. In contrast, the present analysis is based on echocardiography core laboratory measurements.

Quantitative echocardiography and assessment of AS were performed following the joint European Association of Echocardiography and American Society of Echocardiography guidelines. Stroke volume was calculated from Teichholz-derived left ventricular volumes and indexed to body surface area. End-diastolic inner diameter of the aortic root was measured at the sinotubular junction. Peak aortic jet velocity was measured from different windows by imaging and nonimaging transducers, and the highest velocity was used for tracing of the time-velocity integral. The effective AVal was calculated by the continuity equation using velocity-time integrals and indexed for body surface area. Pressure recovery (mm Hg) was calculated by the previously published equation. ELI was calculated by a validated equation as follows: AVal = Aa − AAVA/m², where Aa is the aortic area at the level of the sinotubular junction and m² is the body surface area. A value <0.6 cm²/m² was used as the cutoff for diagnosing severe AS by both AVal and ELI. Severely graded AS was defined as having severe AS by AVal and nonsevere AS by mean aortic gradient in an individual patient (AVal <1.0 cm²/m² and mean aortic gradient ≤40 mm Hg). Small aortic root was defined as an aortic diameter <2.60 cm at the level of the sinotubular junction corresponding to the lowest tertile of aortic sinotubular junction diameter in our study population.

**Statistical Analysis**

Data management and analysis were performed primarily with SPSS 17.0 (SPSS, Chicago, IL) software. All continuous variables were normally distributed. The study population was grouped according to the presence or absence of severe AS by ELI at baseline. Continuous variables are presented as mean±SD and categorical variables as percentages. Groups were compared by the Student unpaired t test or ANOVA with the Scheffé post hoc test as appropriate. Cox regression analyses and Kaplan-Meier plots were used to test whether lower baseline ELI independently predicted higher rates of combined AVEs (combined aortic valve replacement, hospitalization for heart failure resulting from AS progression, and cardiovascular death), a prespecified secondary end point in the SEAS study; individual AVE composites; total mortality, a prespecified tertiary end point; and combined total mortality and hospitalization for heart failure caused by the progression of AS. In different Cox regression models, baseline mean aortic gradient, peak aortic jet velocity, and aortic root diameter were included as continuous variables, and study treatment allocation was included as an indicator variable. Receiver-operating characteristic curve analyses were used to assess the sensitivity and specificity of ELI in predicting these outcomes. In receiver-operating characteristic analysis, the area under the curve for different measures of AS severity were compared by use of the DeLong test. Enhanced predictive performance of multivariate Cox model with and without ELI was assessed by continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for censored survival data using classification and reclassification analysis with R-2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria), package survIDINRI, version 1.0-2. Estimates and 95% confidence intervals are reported for NRI and IDI. A value of P < 0.05 was regarded as statistically significant in all analyses.

**Results**

Severe AS by ELI was found in 374 patients (23.9%) at baseline (Table 1). These patients were older and had a higher body mass index than patients with nonsevere AS by ELI (both P < 0.05; Table 1). They also had smaller aortic root dimensions and more severe AS by the conventional measures of AVal, peak aortic jet velocity, and transaortic gradient (all P < 0.001; Table 2).

**Relation Between ELI and Outcome in the Total Study Population**

During follow-up (median, 4.3 years; range, 2 days–6.9 years), a total of 498 AVEs (31.9%) occurred, including 429 aortic valve replacements, 31 hospitalizations for congestive heart failure resulting from the progression of AS, and 81 cardiovascular deaths (some patients had >1 event). The total number of deaths was 161, including 11 patients previously hospitalized for heart failure. Thus, the combined total mortality and hospitalization for heart failure resulting from the progression of AS end point included 181 events. Both overall survival and event-free survival were significantly lower in the group of patients with severe AS by ELI at baseline (Figure 1). In Cox regression analysis, including baseline ELI as a continuous variable and active study treatment as an indicator variable, 1-cm²/m² lower baseline ELI independently predicted a 5-fold higher rate of AVEs (P < 0.001; Table 3, part A, model 1). Adding baseline peak aortic jet velocity or mean aortic gradient to this model attenuated the association, but a 1-cm²/m² lower baseline ELI still independently predicted a 2-fold higher rate of AVEs (both P < 0.001; Table 3, part A, models 2 and 3). In addition, when aortic diameter was added as a covariate, the results remained unchanged (Table 3, part A, model 4). In further Cox analysis, 1-cm²/m² lower baseline ELI predicted a 2-fold higher rate of total mortality and hospitalization for heart failure caused by progression of AS (P < 0.001; Table 3, part B, model 1) independently of baseline peak aortic jet velocity, mean aortic gradient, and aortic diameter in different models (all P < 0.05; Table 3, part B, models 2–4). In additional Cox regression models, the relations between baseline ELI and rates of the individual components of the end point of AVEs and total mortality were assessed. After adjustment for active study treatment, 1-cm²/m² lower baseline ELI predicted a 6-fold higher rate of aortic valve replacement, an 11-fold higher rate of hospitalization for congestive heart failure caused by the progression of AS, a 2-fold higher rate of cardiovascular death, and a 2-fold increased rate of total mortality (all P < 0.05; Table 4). When baseline mean aortic gradient was added to the covariates in
Table 1. Clinical Characteristics in the Total Study Population and in Groups of Patients With or Without Severe Aortic Stenosis by Energy Loss Index at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe AS by ELI (n=374)</th>
<th>Nonsevere AS by ELI (n=1189)</th>
<th>Total Study Population (n=1563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.9±9.1 *</td>
<td>67.0±9.7</td>
<td>67.4±9.6</td>
</tr>
<tr>
<td>Women, %</td>
<td>42</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.71±0.92</td>
<td>1.70±0.93</td>
<td>1.70±0.92</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±15</td>
<td>78±15</td>
<td>78±15</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.91±0.20</td>
<td>1.89±0.20</td>
<td>1.90±0.20</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3±4.3 †</td>
<td>26.8±4.3</td>
<td>27±4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65.8±10.6</td>
<td>65.8±11.8</td>
<td>65.8±11.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145±21</td>
<td>145±21</td>
<td>145±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83±11</td>
<td>82±10</td>
<td>82±10</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>89.6</td>
<td>87.6</td>
<td>86.1</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; and ELI, energy loss index.
*P<0.001, severe AS by ELI versus nonsevere AS by ELI.
†P<0.05, severe AS by ELI versus nonsevere AS by ELI.

these models, the relation with cardiovascular death became statistically insignificant, whereas the relation with total mortality remained unchanged (Table 4).

In univariate receiver-operating characteristic analysis, baseline peak aortic jet velocity and mean aortic gradient were both superior predictors of AVEs compared with ELI, AVA, and AVA1 (area under the curve, 0.73, 0.75, and 0.68 for ELI, AVAI, and AVA; all P<0.001; Figure 2A). In addition, receiver-operating characteristic analysis, baseline ELI, AVAI, AVA, peak aortic jet velocity, and mean aortic gradient all predicted the rate of combined total mortality and hospitalization for heart failure resulting from the progression of AS (all P<0.001; Figure 2B). In this analysis, the area under the curve did not differ significantly between different measures of AS severity (all pairwise comparisons, P>0.41). Finally, reclassification analysis for survival data was performed to assess the predictive differences between the final Cox models in Table 3, parts A and B. For AVEs, using ELI improved reclassification for those with events by 62% and for those without events by 49%, resulting in a significantly improved NRI of 13% (95% confidence interval, 5–19) and IDI of 1.5% (95% confidence interval, 0.4–3). For combined total mortality and hospitalization for heart failure resulting from the progression of AS, ELI did not improve event prediction (NRI, 9%; 95% confidence interval, −0.2 to 16).

The baseline cutoff values for AVA and AVAI providing the best balance between sensitivity and specificity in prediction of AVEs and combined total mortality and hospitalization for heart failure resulting from the progression of AS were close to the current guideline recommended cutoff values for severe AS. In contrast, the best cutoff value for ELI was higher and the best cutoff values for peak aortic jet velocity and mean aortic gradient were lower than current guideline definitions (Table 5).

Table 2. Echocardiographic Characteristics in the Total Study Population and in Groups of Patients With or Without Severe Aortic Stenosis by Energy Loss Index at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe AS by ELI (n=374)</th>
<th>Nonsevere AS by ELI (n=1189)</th>
<th>Total Study Population (n=1563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic annulus diameter, cm</td>
<td>2.05±0.24*</td>
<td>2.23±0.26</td>
<td>2.19±0.26</td>
</tr>
<tr>
<td>Aortic sinotubular junction diameter, cm</td>
<td>2.83±0.43</td>
<td>2.82±0.43</td>
<td>2.82±0.43</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter, cm</td>
<td>5.03±0.63</td>
<td>5.05±0.63</td>
<td>5.04±0.63</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter, cm</td>
<td>3.23±0.58</td>
<td>3.19±0.56</td>
<td>3.20±0.56</td>
</tr>
<tr>
<td>Septal wall thickness, cm</td>
<td>1.19±0.29†</td>
<td>1.15±0.27</td>
<td>1.16±0.28</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.90±0.20</td>
<td>0.90±0.20</td>
<td>0.89±0.19</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>65±7*</td>
<td>67±7</td>
<td>66±7</td>
</tr>
<tr>
<td>Stroke volume, mL/BSA</td>
<td>41±11†</td>
<td>43±11</td>
<td>43±11</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>3.43±0.48*</td>
<td>2.98±0.51</td>
<td>3.08±0.54</td>
</tr>
<tr>
<td>Peak aortic gradient, mm Hg</td>
<td>48±13*</td>
<td>37±13</td>
<td>39±14</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>28±8*</td>
<td>21±8</td>
<td>23±9</td>
</tr>
<tr>
<td>Pressure recovery, mm Hg</td>
<td>5.58±2.13*</td>
<td>5.99±2.32</td>
<td>5.89±2.28</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>0.81±0.15*</td>
<td>1.42±0.42</td>
<td>1.27±0.45</td>
</tr>
<tr>
<td>AVAI, cm²/m²</td>
<td>0.42±0.07*</td>
<td>0.75±0.20</td>
<td>0.67±0.23</td>
</tr>
<tr>
<td>ELI, cm²/m²</td>
<td>0.49±0.08*</td>
<td>1.02±0.44</td>
<td>0.90±0.45</td>
</tr>
<tr>
<td>Aortic regurgitation, %</td>
<td>61.1</td>
<td>61.0</td>
<td>61.0</td>
</tr>
<tr>
<td>Mitral regurgitation, %</td>
<td>51.5</td>
<td>48.0</td>
<td>50.8</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; AVA, aortic valve area; AVAI, aortic valve area indexed for body surface area; BSA, body surface area; and ELI, energy loss index.
*P<0.001, severe AS by ELI versus nonsevere AS by ELI.
†P<0.05, severe AS by ELI versus nonsevere AS by ELI.

215 (48.6%) AVEs and 75 (15.1%) combined total mortality and hospitalizations for heart failure resulting from the progression of AS occurred during follow-up. In a multivariate Cox regression including baseline ELI as a continuous variable and active study treatment as an indicator variables, 1- cm²/m² lower ELI predicted a 9-fold higher rate of AVEs (hazard ratio, 8.93; 95% confidence interval, 2.77–28.57; P<0.001). This association was attenuated but remained statistically significant when peak aortic jet velocity or mean aortic gradient was included in the model (Table 6). ELI did not predict combined total mortality and hospitalization for heart failure in univariate analysis within this subgroup. Using the same approach for reclassification analysis as for the total study population, we found that ELI did not improve prediction of either AVEs or combined total mortality and hospitalization for heart failure resulting from the progression of AS in this subgroup.

ELI in the Prediction of Outcome in Patients With Small Aortic Roots

A small aortic root (corresponding to the lowest tertile of aortic diameter at the sinotubular junction, <2.60 cm) was found in 509 of the study patients (32.6%) at baseline. In this patient subgroup, a total of 178 (35.0%) AVEs and 71 (14.0%) combined total mortality and hospitalizations for heart failure resulting from the progression of AS occurred during follow-up. Using the same set of multivariate Cox regression models, we found
that 1-cm²/m² lower baseline ELI predicted a 3-fold higher rate of AVEs (P<0.001) and a 4- to 4.5-fold higher rate of combined total mortality and hospitalization for heart failure resulting from the progression of AS (both P<0.05) independently of peak aortic jet velocity or mean aortic gradient in different models (Table 7). When the same approach was used for reclassification analysis as for the total study population, for AVEs, ELI improved reclassification by 58% for those with events and by 47% for those without events, resulting in a significantly improved event prediction (NRI, 11% [95% confidence interval, 0.3–21]; IDI, 4% [95% confidence interval, 0.9–7]). For combined total mortality and hospitalization for heart failure resulting from the progression of AS, the improvement in reclassification by adding ELI to the model for those with events was 61% and for those without events was 49%, yielding an NRI of 12% (95% confidence interval, 0.2–26) and an IDI of 1% (95% confidence interval, 0–4).

**Discussion**

Several Doppler echocardiographic measures are recommended for routine assessment of AS in current guidelines, including peak aortic jet velocity, mean aortic gradient, AOA, and AVA. Grading of AS severity was originally derived from cardiac catheterization data, which take pressure recovery into account, and then extrapolated to Doppler echocardiography. Because Doppler echocardiography has become the standard method for evaluating AS severity in current practice, adjustment for pressure recovery in the aortic root has been suggested for milder degrees of AS to prevent overestimation of AS severity.

To the best of our knowledge, this is the first study to assess the prognostic value of ELI in a large prospective study of initially asymptomatic AS patients. The present finding adds to previous knowledge by demonstrating that lower baseline ELI predicted higher total mortality and higher rates of AVEs in asymptomatic AS patients without known coronary artery disease participating in the SEAS study for a mean of 4.3 years. Of note, lower ELI predicted higher event risk independently of peak aortic jet velocity or mean aortic gradient, both commonly used measures of AS severity. Furthermore, the relations between lower ELI and higher event rate were also independent of aortic root size.

**Table 3.** Baseline Energy Loss Index as a Predictor of Aortic Valve Events and Combined Total Mortality and Hospitalization for Heart Failure Resulting From the Progression of Aortic Stenosis in Multivariate Cox Regression Analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1 (HR [95% CI])</th>
<th>Model 2 (HR [95% CI])</th>
<th>Model 3 (HR [95% CI])</th>
<th>Model 4 (HR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Aortic valve events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower ELI, cm²/m²</td>
<td>5.32 (3.85–7.30)*</td>
<td>2.22 (1.60–3.10)*</td>
<td>2.05 (1.48–2.85)*</td>
<td>2.05 (1.48–2.85)*</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>NA</td>
<td>3.22 (2.67–3.88)*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>NA</td>
<td>NA</td>
<td>1.08 (1.06–1.09)*</td>
<td>1.08 (1.06–1.09)*</td>
</tr>
<tr>
<td>Aortic sinotubular junction diameter, cm</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.02 (0.84 1.25)</td>
</tr>
<tr>
<td><strong>B. Combined total mortality and hospitalization for heart failure due to progression of AS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower ELI, cm²/m²</td>
<td>2.28 (1.45–3.57)*</td>
<td>2.08 (1.27–3.40)†</td>
<td>1.86 (1.14–3.03)†</td>
<td>1.88 (1.15–3.05)†</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>NA</td>
<td>1.14 (0.84–1.54)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>NA</td>
<td>NA</td>
<td>1.02 (0.99–1.04)</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>Aortic sinotubular junction diameter, cm</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.34 (0.95–1.89)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ELI, energy loss index; HR, hazard ratio; and NA, not included in model. Variable included in all models: study treatment.

*P<0.001.
†P<0.05.
of follow-up. In the SEAS study, aortic valve replacement was combined death and aortic valve replacement during 8 months of moderate or severe AS, ELI was superior to AVAI in predicting heart failure resulting from the progression of AS independently of stenosis severity used, particularly valve velocity and gradient, as demonstrated in the Euro Heart Survey on valvular heart disease. Interestingly, baseline cutoff values for AVAI and AVAI providing the best balance between sensitivity and specificity to predict AVEs and combined total mortality and hospitalization for heart failure in our study were close to current guideline-recommended cutoff values for severe AS. The ~30% difference in cutoff values between AVAI and ELI is in line with the previously demonstrated overestimation of AS severity by AVAI at baseline in this study.7 The demonstrated moderate sensitivity and specificity for predicting events by baseline measures of AS severity may reflect individual AS progression rates and differences in comorbidity that affect outcome.

The present results confirm and extend a previous observation by Garcia et al. In their retrospective study of 138 patients with moderate or severe AS, ELI was superior to AVAI in predicting combined death and aortic valve replacement during 8 months of follow-up. In the SEAS study, aortic valve replacement was the main component, accounting for 86% of the prespecified secondary composite AVE end point. As demonstrated, 1-cm²/m² lower ELI predicted 2- to 6-fold increased incidence of aortic valve replacement in different models and a nearly 2-fold higher total mortality. Our findings also add to a previous report by Bermejo et al in which peak aortic jet velocity and mean aortic gradient were both superior to AVA in predicting risk for all-cause mortality in 307 symptomatic patients with moderate to severe AS. Univariate analysis yielded similar results for combined AVEs in the present study, whereas in multivariate Cox analyses, ELI predicted higher mortality and combined total mortality and hospitalization for heart failure resulting from the progression of AS independently of the mean aortic gradient. Furthermore, as demonstrated by reclassification analysis, ELI significantly improved the prediction of AVEs but not of combined total mortality and hospitalization for heart failure in the total study population. It should be mentioned, however, that unlike the SEAS investigators, Bermejo et al did not exclude patients with coronary artery disease, and patients in their study were on average somewhat older (mean, 71 years of age). Furthermore, Bermejo et al calculated stroke volume by Doppler, whereas in this large multicenter study including 173 study centers and even more operators, we found during core laboratory reading that pulsed-wave velocity in some patients was recorded too low in the left ventricular outflow tract, leading to underestimation of stroke volume by this method. For this reason, we calculated stroke volume by the Teichholz-corrected cube formula in the present study.

Referral for aortic valve replacement in the SEAS study was based on clinical and echocardiographic evaluation by the local study center physician, who was unaware of core laboratory echocardiographic results. The finding that peak aortic jet velocity and mean aortic gradient were more closely related to AVEs in univariate receiver-operating characteristic curve analysis probably reflects that, in contrast to more objective end points like hospitalization for heart failure and mortality, referral for aortic valve replacement is determined mainly by the attending cardiologist’s perception of AS severity, which in turn is largely influenced by the echocardiographic indexes of stenosis severity used, particularly valve velocity and gradient, as demonstrated in the Euro Heart Survey on valvular heart disease. Interestingly, baseline cutoff values for AVA and AVAI providing the best balance between sensitivity and specificity to predict AVEs and combined total mortality and hospitalization for heart failure in our study were close to current guideline-recommended cutoff values for severe AS. The ~30% difference in cutoff values between AVAI and ELI is in line with the previously demonstrated overestimation of AS severity by AVAI at baseline in this study. The demonstrated moderate sensitivity and specificity for predicting events by baseline measures of AS severity may reflect individual AS progression rates and differences in comorbidity that affect outcome.
Inconsistent grading of AS severity from conventional assessment with AVAI and mean aortic gradient is common in clinical practice. In the present study, we hypothesized that ELI may be particularly helpful in assessing true AS severity in such patients. Confirming previous observations, patients with inconsistently graded AS severity made up ≈30% of our study population.7,8,21 Although lower ELI predicted higher risk for AVEs also within this subpopulation independently of peak aortic jet velocity or mean aortic gradient, superiority in the prediction of combined mortality and hospitalization for heart failure resulting from AS progression was not demonstrated.

A clinically significant pressure recovery is found in AS patients with small aortic roots.7,9,19 Thus, a superior prediction of cardiovascular events by ELI could be anticipated in this subgroup. As demonstrated by our results, lower ELI, independently of mean aortic gradient or peak aortic jet velocity, predicted higher risk for AVEs and combined total mortality and hospitalization from heart failure resulting from the progression of AS in Cox regression analyses also within this subpopulation. Furthermore, ELI improved the prediction of AVEs and total mortality and hospitalization for heart failure resulting from progression of AS in this subgroup. As demonstrated by our results, lower ELI, independently of mean aortic gradient or peak aortic jet velocity, predicted higher risk for AVEs and combined total mortality and hospitalization from heart failure resulting from the progression of AS in Cox regression analyses also within this subpopulation. Furthermore, ELI improved the prediction of AVEs and total mortality and hospitalization for heart failure resulting from progression of AS in this subgroup, suggesting ELI to be particularly useful in the clinical setting of a small aortic diameter. In the present study, this was defined as an aortic diameter <2.6 cm at the sinotubular junction.

Study Limitations

The SEAS study included otherwise healthy patients with mild to moderate AS. Patients with established coronary, cerebral or peripheral vascular disease, diabetes mellitus, other significant valvular disease, systolic heart failure, or renal insufficiency and patients with other indications or contraindications to lipid-lowering therapy were excluded from participation in the SEAS study.12 Projection of the present results to groups of AS patients with symptomatic AS or those with atherosclerotic artery disease should be done with caution. The value of exercise testing in risk assessment in physical active patients with asymptomatic severe AS is well demonstrated.37 However, exercise testing was not included in the large SEAS study, which began in 2002;12 neither was routine measurement of brain natriuretic peptides as a predictor of symptom-free survival.38

Table 5. Baseline Cutoff Values Providing the Best Balance Between Sensitivity and Specificity to Predict Incident Aortic Valve Events and Combined Total Mortality and Hospitalization for Heart Failure Resulting From the Progression of Aortic Stenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aortic Valve Events</th>
<th>Combined Total Mortality and Hospitalization for Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff Value</td>
<td>Sensitivity, %</td>
</tr>
<tr>
<td>ELI, cm²/m²</td>
<td>0.76</td>
<td>64</td>
</tr>
<tr>
<td>AVAI, cm²/m²</td>
<td>0.60</td>
<td>64</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>1.03</td>
<td>53</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>3.2</td>
<td>65</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>24.2</td>
<td>61</td>
</tr>
</tbody>
</table>

AVA indicates aortic valve area; AVAI, aortic valve area indexed to body surface area; and ELI, energy loss index.

Table 6. Baseline Energy Loss Index as a Predictor of Aortic Valve Events in Patients With Inconsistently Graded Severe Aortic Stenosis: Multivariate Cox Regression Analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Aortic Valve Events</th>
<th>Combined Total Mortality and Hospitalization for Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Model 1</td>
</tr>
<tr>
<td>Lower ELI, cm²/m²</td>
<td>8.93</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td>(2.77–28.57)*</td>
<td>(1.16–13.16)†</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>NA</td>
<td>2.41</td>
</tr>
<tr>
<td></td>
<td>(1.75–3.31)*</td>
<td>(1.04–1.08)*</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ELI, energy loss index; HR, hazard ratio; and NA, not included in model. Variable included in all models: study treatment.

Table 7. Baseline Energy Loss Index as a Predictor of Aortic Valve Events and Combined Total Mortality and Hospitalization For Heart Failure Resulting From the Progression of Aortic Stenosis in Multivariate Cox Regression Analyses in the Lowest Tertile of Aortic Junctional Diameter (<2.60 cm)

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Aortic valve events</td>
<td></td>
</tr>
<tr>
<td>Lower ELI, cm²/m²</td>
<td>6.85</td>
</tr>
<tr>
<td></td>
<td>(3.95–11.90)*</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(2.07–3.93)*</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(1.04–1.08)*</td>
</tr>
<tr>
<td>B. Combined total mortality and hospitalization for heart failure resulting from the progression of AS</td>
<td></td>
</tr>
<tr>
<td>Lower ELI, cm²/m²</td>
<td>4.88</td>
</tr>
<tr>
<td></td>
<td>(2.12–11.24)*</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(0.66–1.80)</td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(0.99–1.04)</td>
</tr>
</tbody>
</table>

ELI indicates energy loss index; CI, confidence interval; HR, hazard ratio; and NA, not included in model. Variable included in all models: study treatment.
Conclusions
In asymptomatic AS patients without known atherosclerotic disease or diabetes mellitus, ELI provides independent and additional prognostic information to that derived from conventional measures of AS severity, including peak aortic jet velocity and mean aortic gradient. The results of the present study support systematic calculation of ELI in asymptomatic AS patients.

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Disclosures
Drs Gerds, Gohike-Baervlof, Nienaber, Wachtell, and Ray were investigators and members of the steering committees of the SEAS study and have received honoraria from Merck & Co, Inc, the sponsor of the SEAS study. Dr Chambers was an investigator and member of the steering committees of the SEAS study but has not received honoraria or other payments. Drs Gerds, Bahlmann, Wachtell, and Ray have received grant support from Merck & Co, Inc, the sponsor of the SEAS study. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Aortic stenosis (AS) severity is frequently overestimated by aortic valve area based on the continuity equation in patients with milder degree of AS or smaller aortic root dimensions. Conventional measures of AS severity such as peak jet velocity, mean aortic gradient, and aortic valve area may also grade AS inconsistently. From this, we hypothesized that adjusting aortic valve area for the pressure recovery occurring in the aortic root by calculating the energy loss index (ELI) would improve risk assessment in patients with asymptomatic mild to moderate AS. This was tested in a prospective study of 1563 patients with initially asymptomatic AS and without known atherosclerotic disease or diabetes mellitus. In Cox regression analysis, lower ELI predicted higher risk for aortic valve events, including aortic valve replacement, cardiovascular death, and heart failure resulting from progression of AS, and higher mortality and combined total mortality and hospitalization for heart failure caused by progression of AS independently of peak aortic jet velocity and mean aortic gradient. To test whether ELI was superior to mean aortic gradient in event prediction, reclassification analysis was performed. As demonstrated, ELI improved aortic valve event prediction in the total study population, whereas prediction of total mortality and hospitalization for heart failure caused by progression of AS was improved only in the subgroup of patients with an aortic diameter <2.6 cm at the sinotubular junction. The results of the present study support systematic calculation of ELI in asymptomatic AS patients. ELI may be particularly useful in AS patients with a small aortic root.

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