Relation of Left Ventricular Mass to Prognosis in Initially Asymptomatic Mild to Moderate Aortic Valve Stenosis

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Background—The prognostic importance of left ventricular (LV) mass in nonsevere asymptomatic aortic stenosis has not been documented in a large prospective study.

Methods and Results—Cox regression analysis was used to assess the impact of echocardiographic LV mass on rate of major cardiovascular events in 1656 patients (mean age, 67 years; 39.6% women) with mild-to-moderate asymptomatic aortic stenosis participating in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study. Patients were followed during 4.3 years of randomized treatment with combined simvastatin 40 mg and ezetimibe 10 mg daily or placebo. At baseline, LV mass index was 45.9±14.9 g/m², and peak aortic jet velocity was 3.09±0.54 m/s. During follow-up, 558 major cardiovascular events occurred. In Cox regression analyses, 1 SD (15 g/m²) higher baseline LV mass index predicted increases in hazards of 12% for major cardiovascular events, 28% for ischemic cardiovascular events, 34% for cardiovascular mortality, and 23% for combined total mortality and hospitalization for heart failure (all P<0.01), independent of confounders. In time-varying models, taking the progressive increase in LV mass index during follow-up into account, 1 SD higher in-study LV mass index was consistently associated with 13% to 61% higher hazard for cardiovascular events (all P<0.01), independent of age, sex, body mass index, valvuloarterial impedance, LV ejection fraction and concentricity, and the presence of concomitant hypertension.

Conclusions—Higher LV mass index is independently associated with increased cardiovascular morbidity and mortality during progression of aortic stenosis.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00092677.

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Key Words: aortic valve stenosis ■ echocardiography ■ hypertrophy, left ventricular ■ mortality ■ prognosis

It is well known that the presence of left ventricular (LV) hypertrophy by echocardiography predicts increased cardiovascular morbidity and mortality both in general and in hypertensive populations.1-3 In patients with aortic valve stenosis (AS), LV hypertrophy is mainly considered an adaptive response that keeps LV wall stress close to normal, offsetting the hemodynamic load.4 However, as recently demonstrated, the presence of concomitant hypertension, obesity, and metabolic syndrome significantly modulates LV mass and geometry in patients with asymptomatic AS independent of AS severity.5-7 Few studies in AS have focused on the prognostic impact of LV mass. In patients with severe symptomatic AS, concentric LV geometry and severe LV hypertrophy by echocardiography have been associated with increased mortality after aortic valve replacement.8,9 Increased cardiovascular morbidity and mortality has also been demonstrated for asymptomatic patients with severe AS and excessive LV hypertrophy.10 Recently, higher LV mass was associated with worse outcome after transcatheter aortic valve replacement for severe symptomatic AS.11 However, the independent prognostic impact of LV mass by echocardiography in asymptomatic mild-to-moderate AS patients has not been reported from a large prospective study. Thus, the aim of this study was to test the...
hypothesis that higher LV mass is independently associated with higher rate of cardiovascular events in these patients.

**Methods**

**Patient Population**

The present analysis was prespecified within the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study analysis plan. Study design, baseline characteristics, and main outcome results of the SEAS study have previously been published. In short, 1873 men and women aged 45 to 85 years with asymptomatic mild-to-moderate AS having a peak aortic jet velocity between 2.5 and 4.0 m/s by echocardiography were randomized to placebo or to combination treatment with simvastatin 40 mg and ezetimibe 10 mg daily. Patients with known coronary heart disease, heart failure, diabetes mellitus, history of stroke or peripheral vascular disease, clinically significant mitral valve disease, severe or predominant aortic regurgitation, rheumatic valvular disease, aortic valve prosthesis, or renal insufficiency and patients already on lipid-lowering therapy or with a guideline indication for lipid-lowering therapy were not included in the SEAS study. Core laboratory readings of peak aortic jet velocity and LV mass were available from baseline and at least 1 follow-up echocardiogram in 1656 patients (88% of the study population), who comprise the present study population. Hypertension was defined as history of hypertension, use of antihypertensive drug treatment, or elevated blood pressure at the baseline clinic visits. All patients gave written informed consent and the study was approved by ethics committees in all participating countries.

**Echocardiography**

Echocardiograms were performed at baseline, annually and before planned aortic valve surgery following a standardized protocol at 173 study centers in 7 European countries. Echocardiographic images were stored on videotapes, compact discs, or magnetic optical discs and forwarded for blinded interpretation at the SEAS echocardiography core laboratory at Haukeland University Hospital, Bergen, Norway, as previously published. Severity of AS and LV structure and function were measured following current guidelines, and LV mass was measured by an autopsy-validated method and indexed to height in allometric power of 2.7. LV hypertrophy was defined using the prognostically validated cutoff values LV mass in grams >46.7 g/m^2.7 in women and >49.2 g/m^2.7 in men. Relative wall thickness was assessed from 2×LV posterior wall thickness/LV end-diastolic diameter ratio and considered increased if >0.43 (concentric LV geometry). Valvuloarterial impedance was calculated using a previously validated method. Pressure recovery was assessed at the aortic sinotubular junction and used for calculation of energy loss index as prognostically validated.

**End Points**

The prespecified primary end point of SEAS was major cardiovascular events, a composite end point, including aortic valve–related events (combined aortic valve replacement, hospitalization for heart failure because of aortic stenosis, and death from cardiovascular causes) and ischemic cardiovascular events (combined death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, coronary revascularization, and nonhemorrhagic stroke). The secondary end points were aortic valve events and ischemic cardiovascular events analyzed separately. Total mortality was a tertiary end point. All end points were classified by an independent end point classification committee whose members were unaware of study group assignments. We also assessed the post hoc defined composite end point of total mortality and hospitalization for heart failure because of aortic stenosis.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY). Values are given as mean±SD for continuous variables and as percentages for categorical variables. Comparison between groups was performed by paired and unpaired t test, χ^2 test, and general linear model with post hoc test and Bonferroni adjustment as appropriate. Cumulative incidences of cardiovascular events during follow-up were estimated by Kaplan–Meier. Kaplan–Meier plots were used to compare event-free survival in groups of patients with and without LV hypertrophy at baseline. Correlates of the prespecified primary and secondary composite end points were identified by Cox regression analysis in univariable and multivariable models and presented as hazard ratio and 95% confidence intervals. In the primary analyses, LV mass index was used as the continuous variable. In secondary models, LV hypertrophy as a dichotomous variable was used. Age, sex, body mass index, peak aortic jet velocity, LV ejection fraction, concentric LV geometry, hypertension, and valvuloarterial impedance were included as covariates in all multivariable models. Aortic valve replacement was included as a time-varying covariate in models assessing cardiovascular death and total mortality. In subsequent models, concentric LV geometry was replaced by stress-corrected midwall shortening, and the presence of aortic regurgitation was added. To take the progressive increase in LV mass during progression of AS into account, time-varying Cox regression analysis was used. Two-tailed P<0.05 was regarded as statistically significant both in univariable and multivariable analyses.

**Results**

Compared with patients with normal LV mass index at baseline, the group with LV hypertrophy was older, had higher body mass index, lower LV midwall function, and included more patients with hypertension (all P<0.01; Tables 1 and 2). During a median of 4.3-year follow-up, LV mass indexed to height^2.7 (LV mass index) and concentricity increased, whereas LV endocardial and myocardial function declined (all P<0.001). The prevalence of LV hypertrophy increased from 36% at baseline to 60% at the last study visit (P<0.01). The annual AS progression rate did not differ between groups of patients with and without LV hypertrophy at baseline, whether calculated based on change in peak aortic jet velocity (0.21±0.39 versus 0.20±0.27 m/s per year), mean gradient (4±7 versus 4±5 mm Hg/m), or aortic valve area (−0.03±0.25 versus −0.03±0.29 cm^2/y, all P=0.3). The average time between the baseline and the last follow-up study was 3.6±1.2 years. The average time between the follow-up study and an aortic valve event, an ischemic cardiovascular event, and death from any cause was on average 0.59±0.03, 0.94±0.06, and 0.80±0.55 years, respectively.

During follow-up, each SD higher unindexed LV mass, LV mass/height^2.7, and LV mass/body surface area was associated with comparable 21%, 23%, and 25% higher rates of the primary study end point, respectively, in univariable analyses (all P<0.001). The rates of aortic valve events, ischemic cardiovascular events, cardiovascular death, and combined death from any cause and hospitalization for heart failure because of progression of AS all increased progressively with increasing quartile of baseline LV mass index and were 1.5, 1.8, 3.2, and 2.5 times higher in the upper LV mass index quartile than in the lowest quartile (Figure 1). In multivariable Cox regression, higher LV mass index was associated with higher rates of aortic valve events, ischemic cardiovascular events, cardiovascular death, and combined death from any cause and hospitalization for heart failure when adjusted for known prognosticators in AS patients like age, sex, body mass index, AS severity, LV ejection fraction,
concentric LV geometry, and concomitant hypertension (Table 3). Similar results were found in a second model, replacing concentric geometry by stress-corrected midwall shortening (hazard ratio, 1.13 for primary end point per 1 SD higher LV mass index [95% confidence interval, 1.02–1.24]; \( P=0.017 \)). Adding the presence of aortic regurgitation or type of antihypertensive drug among the covariates did not influence results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population, n=1616</th>
<th>LV Hypertrophy, n=592</th>
<th>No LV Hypertrophy, n=1064</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.4±9.6</td>
<td>68.2±9.2*</td>
<td>66.9±9.8</td>
</tr>
<tr>
<td>Women, %</td>
<td>39.4</td>
<td>38.3</td>
<td>40.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>146±20</td>
<td>149±20*</td>
<td>145±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82±10</td>
<td>83±10†</td>
<td>81±10</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±11</td>
<td>66±11</td>
<td>66±12</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.89±0.20</td>
<td>1.92±0.20*</td>
<td>1.88±0.20</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±4.3</td>
<td>28.5±4.6*</td>
<td>25.9±3.9</td>
</tr>
<tr>
<td>Baseline hypertension, %</td>
<td>83.0</td>
<td>88.2*</td>
<td>80.2</td>
</tr>
<tr>
<td>Baseline current smoker, %</td>
<td>19.0</td>
<td>15.4*</td>
<td>21.1</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.06±0.18</td>
<td>1.06±0.18</td>
<td>1.06±0.17</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.  
*\( P<0.01 \) vs no LV hypertrophy group.  
†\( P<0.05 \) vs no LV hypertrophy group.
In a secondary set of models, having LV hypertrophy on the baseline echocardiogram was associated with higher rates of the primary and secondary composite study end points and combined all-cause death and hospitalization for heart failure, consistent with the outcome association demonstrated for LV mass index (Table 4; Figure 2).

In multivariable linear regression higher LV mass/height$^{2.7}$ at the last study echocardiogram was associated with male sex ($\beta=0.06$), and higher mean aortic gradient ($\beta=0.15$), systolic blood pressure ($\beta=0.04$), body mass index ($\beta=0.14$), initial LV mass/height$^{2.7}$ ($\beta=0.54$), and presence of normal midwall shortening ($\beta=0.05$, all $P<0.05$) at the baseline echocardiogram. To take into account the progressive increase in LV mass during progression of AS, a set of time-varying Cox regression models were used. Higher LV mass index during follow-up was associated with a 16% higher rate of the primary study end point, 13% higher rate of aortic valve events, 25% higher rate of ischemic cardiovascular events, 63% higher cardiovascular mortality, and 44% higher combined death from any cause and hospitalization.

![Figure 1. Cumulative incidences of aortic valve events (AVE), ischemic cardiovascular (CV) events (ICE), CV death (CVD), and combined death from any cause and hospitalization for heart failure because of progression of aortic stenosis (DEATH&CHF) during >4.3 years of follow-up in relation to quartile of baseline left ventricular (LV) mass index in mild-to-moderate asymptomatic aortic stenosis.](http://circimaging.ahajournals.org/)

**Table 3. Impact of Baseline Left Ventricular Mass Index (Per 1 SD [15 g/m$^{2.7}$] Higher) on the Rates of the Primary and Secondary Study End Points, Hospitalization for Heart Failure, Cardiovascular Death, All-Cause Death, and Combined All-Cause Death and Hospitalization for Heart Failure During >4.3 Years of Follow-Up in Patients With Initially Asymptomatic AS**

<table>
<thead>
<tr>
<th>Study End Point</th>
<th>No. of Events</th>
<th>Unadjusted HR (95% CI)</th>
<th>$P$ Value</th>
<th>Adjusted HR (95% CI)*</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary study end point</td>
<td>498</td>
<td>1.23 (1.14–1.37)</td>
<td>&lt;0.001</td>
<td>1.12 (1.02–1.23)</td>
<td>0.020</td>
</tr>
<tr>
<td>Aortic valve events</td>
<td>468</td>
<td>1.19 (1.11–1.29)</td>
<td>&lt;0.001</td>
<td>1.09 (0.99–1.19)</td>
<td>0.083</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>411</td>
<td>1.17 (1.07–1.27)</td>
<td>&lt;0.001</td>
<td>1.03 (0.93–1.14)</td>
<td>0.562</td>
</tr>
<tr>
<td>Heart failure due to progression of AS</td>
<td>36</td>
<td>1.47 (1.16–1.61)</td>
<td>0.001</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>66</td>
<td>1.34 (1.12–1.70)</td>
<td>&lt;0.001</td>
<td>1.34 (1.07–1.67)</td>
<td>0.011</td>
</tr>
<tr>
<td>Ischemic cardiovascular events</td>
<td>232</td>
<td>1.28 (1.15–1.43)</td>
<td>&lt;0.001</td>
<td>1.28 (1.13–1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total mortality</td>
<td>129</td>
<td>1.27 (1.11–1.46)</td>
<td>&lt;0.001</td>
<td>1.19 (1.01–1.42)</td>
<td>0.048</td>
</tr>
<tr>
<td>Total mortality and hospitalization for heart failure</td>
<td>149</td>
<td>1.30 (1.15–1.47)</td>
<td>&lt;0.001</td>
<td>1.23 (1.05–1.44)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Univariable and multivariable Cox regression analyses. AS indicates aortic stenosis; CI, confidence interval; HR, hazard ratio; and na, multivariable analysis not performed because of low number of events.

*Adjusted for aortic jet velocity, sex, age, left ventricular ejection fraction, body mass index, randomized study treatment, hypertension, concentric left ventricular geometry, and valvuloarterial impedance.
for heart failure (all *P*<0.01; Table 5). In subsequent models replacing energy loss index by peak aortic jet velocity, mean aortic valve gradient, or aortic valve area as measure of AS severity, or LV ejection fraction by midwall shortening or stress-corrected midwall shortening, the results did not change (data not shown).

### Discussion

This is the first large prospective study to assess the prognostic impact of LV mass and hypertrophy assessed by echocardiography in patients with asymptomatic mild-to-moderate AS without known coronary heart disease or diabetes mellitus. As demonstrated by our results, higher LV mass at baseline or during follow-up was associated with higher rates of both the primary and secondary prespecified composite study end points in the SEAS study, resulting in a considerably increased overall cardiovascular morbidity and mortality. These findings were also independent of documented prognosticators such as AS severity, hypertension, and valvuloarterial impedance.

Population-based studies have demonstrated that increased LV mass was associated with incident heart failure independent of the presence of concomitant hypertension unless because of hypertension among indications for aortic valve replacement in AS, as this has been associated with increased perioperative morbidity and mortality and may be less reversible after delayed surgery, precluding an optimal long-term prognosis.

Experimental simulation models by Garcia et al. However, having increased LV mass on the baseline echocardiogram was associated with increased event rates in the present study independent of the prognostic impact of concomitant hypertension and increased body mass index previously demonstrated in asymptomatic mild-to-severe AS.21,23 Risk prediction in asymptomatic AS remains a challenge, including identification of AS patient with high risk for development of congestive heart failure, the most prognostically severe complication of AS.20 Both American and European guidelines recommend aortic valve replacement in patients with severe AS irrespective of symptoms if LV dysfunction defined as LV ejection fraction <50% is present.27,28 Population-based studies have demonstrated that increased LV mass was associated with incident heart failure independent of LV ejection fraction and independent of incident myocardial infarction.29-31 The present findings expands this knowledge by demonstrating that also in patients with mild-to-moderate AS, increased LV mass index is associated with higher rate of combined death and heart failure independent of LV systolic function.

Current European guidelines suggest excessive LV hypertrophy unless because of hypertension among indications for aortic valve replacement in AS, as this has been associated with increased perioperative morbidity and mortality and may be less reversible after delayed surgery, precluding an optimal long-term prognosis. The present results from the large SEAS study document the association of increased LV mass with increased cardiovascular morbidity and mortality also in patients with asymptomatic mild-to-moderate AS independent of the presence of concomitant hypertension. Our findings contrast with previous reports from smaller studies in patients with moderate-to-severe AS. Stewart et al following 183 patients with initially asymptomatic moderate or severe AS for a median of 31 months found that neither LV mass nor tissue Doppler measures of LV systolic and diastolic function predicted outcome independent of AS severity. Similar findings were reported by Monin et al in a study of 107 patients.
with moderate-to-severe AS, who therefore did not include LV mass in the suggested risk assessment score for asymptomatic patients with moderate-to-severe AS based on their findings. Electrocardiographic LV strain pattern was recently suggested as a strong correlate of mortality and hospitalization for heart failure by Greve et al in a SEAS substudy. Of note, electrocardiographic strain pattern was not significantly associated with either cardiovascular death or all-cause mortality when mean aortic gradient was included as covariate in their multivariable models, in contrast to the strong independent association with echocardiographic LV mass and hypertrophy reported in the present article. However, Shah et al documented that electrocardiographic strain pattern as a highly specific marker of midwall myocardial fibrosis, reflecting more advanced myocardial injury, LV decompensation, and impaired prognosis. 

Both LV mass and concentricity increased considerably during follow-up. Concentric LV geometric patterns have been demonstrated to carry individual risk of cardiovascular morbidity and mortality in hypertension. Furthermore, an association with reduced coronary flow reserve as a substrate for reduced myocardial function in hypertensive subjects with LV concentric geometry free from coronary artery disease has been reported by Galderisi et al. In patients operated for AS, both concentric LV geometry and excessive LV hypertrophy have been associated with higher postoperative mortality. Cioffi et al previously demonstrated that excessive LV hypertrophy was the strongest correlate of combined death, congestive heart failure, and nonfatal myocardial infarction in 218 patients with asymptomatic severe AS. Of note, these findings were independent of patient age, extent of aortic valve calcification, renal dysfunction, or the presence of concomitant diabetes mellitus, all factors that have been associated with worsened prognosis in previous studies in asymptomatic severe AS. The present results expand this knowledge by demonstrating the independent prognostic importance of higher LV mass in a large prospective study of patients with initially asymptomatic mild-to-moderate AS.
Table 5. Impact of In-Study Left Ventricular Mass Index (Per 1 SD [15 g/m²] Higher) on the Rates of Study End Points During >4.3 Years of Follow-Up in Patients With Initial Asymptomatic Aortic Stenosis

<table>
<thead>
<tr>
<th>Study End Point</th>
<th>No. of Events</th>
<th>HR (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary study end point</td>
<td>466</td>
<td>1.16 (1.05–1.28)</td>
<td>0.004</td>
</tr>
<tr>
<td>Aortic valve events</td>
<td>435</td>
<td>1.13 (1.01–1.25)</td>
<td>0.027</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>381</td>
<td>1.05 (0.93–1.17)</td>
<td>0.455</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>62</td>
<td>1.61 (1.29–2.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic cardiovascular events</td>
<td>220</td>
<td>1.25 (1.08–1.43)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total mortality</td>
<td>125</td>
<td>1.42 (1.20–1.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total mortality and hospitalization</td>
<td>141</td>
<td>1.42 (1.21–1.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for time-varying aortic jet velocity, left ventricular ejection fraction, body mass index, concentric LV geometry and valvuloarterial impedance, baseline age, sex, hypertension, and randomized study treatment.

Conclusions

In patients with asymptomatic AS, higher LV mass index is independently associated with increased cardiovascular morbidity and mortality during progression of valve stenosis.

Sources of Funding

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Disclosures

Dr. Pedersen, Rossebø, and Gerds were members of the Scientific Steering Committee for the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study in the years 2002 to 2008 and received honoraria for this work. The other authors have no conflicts.

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It is well known that the presence of left ventricular (LV) hypertrophy by echocardiography predicts increased cardiovascular morbidity and mortality both in general and hypertensive populations. In patients with aortic valve stenosis (AS), LV hypertrophy has traditionally been considered as an adaptive response that keeps LV wall stress close to normal, offsetting the hemodynamic load. Recent publications have demonstrated that the presence of concomitant hypertension, obesity, and metabolic syndrome significantly modulates LV mass and geometry in patients with asymptomatic AS independent of AS severity. Furthermore, excessive LV hypertrophy in severe AS has been associated with incident heart failure and increased mortality. The present study is the first to demonstrate the prognostic impact of LV mass and hypertrophy in a large, prospective study in asymptomatic mild-to-moderate AS. Higher LV mass at baseline or during follow-up was associated with considerable increased overall cardiovascular morbidity and mortality. The findings were independent of other documented prognosticators in asymptomatic AS. Patients in the highest versus the lowest quartile of baseline LV mass index had 2.6% higher incidence per year of death and hospitalization for heart failure. Emerging data suggest that speckle strain echocardiography may be used for further identification of AS patients with more advanced LV injury. Whether asymptomatic AS patients with LV hypertrophy should undergo valve replacement at an earlier stage of disease remains unknown. However, LV hypertrophy in asymptomatic AS should not be regarded as purely compensatory, and referral to a heart valve center for further evaluation may be indicated.
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