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Effect of Overweight and Obesity on Cardiovascular Events in Asymptomatic Aortic Stenosis

A SEAS Substudy (Simvastatin Ezetimibe in Aortic Stenosis)

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Objectives This study investigated whether overweight and obesity impacted outcome in patients with aortic valve stenosis (AS).

Background Increased body mass index (BMI) is a strong predictor of higher cardiovascular (CV) morbidity and mortality in the general population but not among patients undergoing heart surgery.

Methods Cardiovascular events in 1,664 patients with initially asymptomatic AS were recorded during a mean of 4.3 years of follow-up in the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study. Patients were grouped according to baseline BMI class.

Results Overweight ($n = 737$) and obese patients ($n = 334$) had higher prevalence of hypertension, more abnormal left ventricular geometry, and lower stress-corrected midwall shortening throughout the study compared with normal weight patients (all $p < 0.01$). The AS progression rate did not differ between BMI classes. In univariate Cox regression, overweight was associated with a 17% to 22% lower rate of AS-related ($p = 0.04$) and ischemic CV events ($p = 0.05$). In multivariate analyses, adjusting for AS severity and differences in baseline characteristics, overweight had no significant influence on the rate of ischemic CV or AS-related events, whereas overweight and obesity had 46% and 67% higher rate of total mortality and 42% and 69% higher rate of combined hospital stay for heart failure and death from any cause, respectively, compared with normal weight patients (all $p < 0.05$).

Conclusions In patients with initially asymptomatic AS participating in the SEAS study, overweight and obesity did not influence AS progression or rate of AS-related or ischemic CV events but were both associated with increased mortality. (J Am Coll Cardiol 2013;62:1683–90) © 2013 by the American College of Cardiology Foundation

Obesity is often associated with clustering of other cardiovascular (CV) risk factors like hypertension, dyslipidemia, and type 2 diabetes mellitus. These factors have been associated with development of atherosclerosis and aortic valve stenosis (AS) (1,2) and demonstrated to influence the incidence of CV events both in the general population and among patients with AS (3,4). In patients with mild to moderate AS participating in the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study, increased body mass index (BMI) at baseline was associated with higher left ventricular (LV) mass, increased prevalence of LV hypertrophy, as well as lower left ventricular ejection fraction (LVEF) independently of AS severity (5), confirming findings from population studies and in patients with essential hypertension (6–8). Similarly, the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin) study showed that presence of clustering of metabolic factors, often referred to as the metabolic syndrome (MetS), was associated with increased progression rate in AS as well

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Abbreviations and Acronyms

ANOVA = analysis of variance
AS = aortic valve stenosis
BMI = body mass index
CABG = coronary-artery bypass grafting
CV = cardiovascular
LV = left ventricular
LVEF = left ventricular ejection fraction
MetS = metabolic syndrome
PCI = percutaneous coronary intervention

as more abnormal LV geometry and presence of LV myocardial dysfunction (9,10).

Epidemiologic data have demonstrated that obesity is associated with increased CV morbidity and total mortality both in men and women (3,11). In contrast, among patients with coronary artery disease, several studies have reported that overweight and obesity are associated with better outcome after coronary revascularization therapy (12,13). This phenomenon has been called the obesity paradox. Recently, Roberts et al. (14) reported better survival in mildly obese patients also after surgical aortic valve replacement for AS on the basis of registry data. However, whether increased BMI independently influences CV morbidity and mortality in AS has not been reported from a prospective, longitudinal study. Thus, the aim of the present study was to determine the impact of increased BMI on rate of major CV events in initially asymptomatic, mild to moderate AS patients participating in the SEAS study.

Methods

Study population. The present analysis was a prospectively planned explorative substudy performed within the 1,873 women and men 45 to 85 years of age with asymptomatic, mild-to-moderate AS with peak aortic jet velocity between 2.5 and 4.0 m/s, randomized in the SEAS study to >4 years of lipid-lowering treatment with simvastatin 40 mg and ezetimibe 10 mg daily in combination (15). Exclusion criteria in the SEAS study were known CV disease, diabetes mellitus, or any condition requiring lipid-lowering therapy. For the present analysis, 1,664 patients with registered body stature and complete study echocardiogram at baseline and at least 1 follow-up study visit before occurrence of any CV endpoint were included. The last study echocardiogram was defined as the final study echocardiogram in patients who did not experience CV events and the last echocardiogram taken before a CV event in those who did. We used the modified American Heart Association/National Heart, Lung, and Blood Institute criteria to identify presence of MetS (16). Because waist circumference was not measured in the SEAS study, BMI was used as a substitute for the definition of obesity (17,18). The MetS was considered present if at least 3 of the following 5 criteria at baseline were fulfilled: 1) BMI $\geq$30 kg/m^2; 2) blood pressure $\geq$130/85 mm Hg; 3) fasting serum glucose $\geq$100 mg/dl 4) serum triglycerides $\geq$1.7 mmol/l; and 5) serum high-density lipoprotein cholesterol <1.3 mmol/l in women and <1.03 mmol/l in men.

Endpoints. The pre-specified primary endpoint in the SEAS study was major CV events, a composite endpoint including AS-related events (combined aortic valve replacement, congestive heart failure due to progression of AS, and CV death) and ischemic CV events (combined nonfatal myocardial infarction, hospital stay for unstable angina, coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], CV death, and non-hemorrhagic stroke) (19). This analysis focused on the pre-specified secondary outcomes AS-related events and ischemic CV events analyzed separately and on total mortality, a predefined tertiary study endpoint. This analysis also assessed the post hoc defined endpoint of combined hospital stay for heart failure and death from any cause. All outcomes were classified by an independent endpoint classification committee whose members did not have access to the study-group assignments (19).

Echocardiography. Echocardiography was performed in 173 study centers in Europe at baseline, annually during follow-up, and before planned aortic valve replacement, according to a standardized echocardiographic protocol and sent for blinded interpretation at the Echocardiography Core Laboratory at Haukeland University Hospital in Bergen, Norway (15,20). All echocardiograms were initially read by a junior and finally by a senior investigator (93% of baseline and 100% of follow-up echocardiograms were finally read by the same senior investigator) at off-line digital workstations with Image Arena (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) software (21). Quantitative echocardiography was performed following the joint European Association of Echocardiography and the American Society of Echocardiography guidelines (22). The LV mass was indexed for height in the allometric power of 2.7 (23). Abnormal LV geometry was considered present when relative wall thickness $\geq$0.43 or if LV mass/height$^{2.7}$ exceeded the prognostically validated cutoff values 46.7 g/m$^{2.7}$ in women and 49.2 g/m$^{2.7}$ in men (24). The LV systolic function was assessed by Teichholz' ejection fraction and stress-corrected midwall shortening calculated as the ratio of actual to predicted midwall shortening for the actual circumferential end-systolic stress, taking mean aortic gradient into account (25–27). Evaluation of AS severity was performed according to the joint European Association of Echocardiography and American Society of Echocardiography guidelines (28). Aortic and mitral valve regurgitation were graded by color Doppler (29,30).

Statistical analysis. The IBM SPSS 20.0 software (IBM Corporation, Armonk, New York) was used for data management and analysis. Data are presented as mean $\pm$ SD for continuous variables and as percentages for categorical variables. The number of antihypertensive drugs was not normally distributed and therefore reported as median and range. The study population was divided into 3 BMI classes according to clinical guidelines: normal weight, overweight, and obese (BMI 18.5 to 24.9 kg/m^2, 25.0 to 29.9 kg/m^2, and $\geq$30 kg/m^2, respectively) (31). Nineteen patients with BMI <18.5 kg/m^2 were excluded from the study population for statistical reasons due to the small subgroup size. Comparisons between groups

were done with analysis of variance (ANOVA), general linear models, ANOVA for repeated measures with post hoc tests, and Bonferroni adjustment for multiple comparisons and Kruskal-Wallis ANOVA as appropriate. Univariate correlations were tested with Pearson's correlation coefficient. Kaplan-Meier curves were used to calculate the cumulative proportions of CV events over 4.3 years and reported as percentage ± SEM. The impact of BMI on different types of events was assessed with multiple Cox regression analyses adjusting for sex, mean aortic gradient, smoking, hypertension, abnormal LV geometry, LVEF, and randomized study treatment in the first model and adding age to the covariates in the second model. The models assessing total mortality and combined hospital stay for heart failure and death from any cause were also adjusted for any intervening nonfatal events included in the primary study endpoint. Two-tailed $p < 0.05$ was considered significant both in univariate and multivariate analyses.

Results

Patients. Cardiometabolic risk factors including sex, age, smoking, hypertension, fasting serum glucose, and lipids differed significantly between BMI classes (Table 1). The prevalence of hypertension increased in parallel with BMI class, as did fasting serum glucose and serum triglycerides, whereas total serum cholesterol and high-density lipoprotein cholesterol fell progressively. The MetS was identified in 421 (27.3%) patients; the incidence increased exponentially with BMI class ($p < 0.001$) (Table 1).

Change in left ventricular structure during follow-up. The time span between the baseline and the last study echocardiogram did not differ between normal weight (3.4 ± 1.4 years), overweight (3.4 ± 1.4 years), and obese groups of patients (3.4 ± 1.3 years, $p = 0.706$). The LV mass and prevalence of abnormal LV geometry increased in parallel with BMI class (Fig. 1, Table 2). Obesity was associated with higher prevalence of abnormal LV geometry throughout the study (Fig. 1). The LVEF remained normal (above 50%) in 97.2% of patients during progression of AS. Stress-corrected midwall fractional shortening was progressively reduced during follow-up in all BMI classes and was significantly lower in obese patients compared with the normal weight group throughout the study (Fig. 2).

Outcome. The progression of AS did not differ between BMI groups (0.19 ± 0.24 m/s/year in the normal weight group vs. 0.21 ± 0.34 m/s/year in the overweight group vs. 0.19 ± 0.30 m/s/year in obese patients, $p = 0.547$) or in relation to presence of MetS (0.19 ± 0.23 m/s/year in patients without MetS vs. 0.22 ± 0.43 m/s/year in patients with MetS, $p = 0.211$).

Within the 459 patients who underwent aortic valve replacement, the AS severity assessed from peak aortic jet velocity, mean aortic gradient, and aortic valve area did not

Table 1 Baseline Clinical Characteristics of Normal Weight, Overweight, and Obese Groups of Patients

	Normal Weight (n = 593)	Overweight (n = 737)	Obese (n = 334)
Women (%)	44.2	29.2*	48.5*
Age (yrs)	69 ± 9.7	66 ± 9.9*	67 ± 8.8
BMI (kg/m^2)	23 ± 1.5	27 ± 1.4	33 ± 3.4
Height (m)	1.7 ± 0.1	1.7 ± 0.1†	1.7 ± 0.1†
Weight (kg)	66.5 ± 8.5	80.4 ± 9.3*	94.6 ± 12.7*
Hypertension (%)	82.8	85.2*	95.2*
Systolic blood pressure (mm Hg)	144 ± 21	144 ± 20	147 ± 18†
Diastolic blood pressure (mm Hg)	80 ± 10	82 ± 10*	84 ± 10*
Smoking (%)	22.8	18.5*	12.3*
Number of antihypertensive agents	1.7 ± 1.0	1.8 ± 1.0	2.0 ± 1.1*
Glucose (mg/dl)	92.2 ± 11.0	95.2 ± 14.4*	101.4 ± 18.9*
Total cholesterol (mmol/l)	5.8 ± 1.0	5.7 ± 1.0	5.6 ± 1.0†
HDL cholesterol (mmol/l)	1.7 ± 0.4	1.4 ± 0.4*	1.3 ± 0.4*
LDL cholesterol (mmol/l)	3.6 ± 0.9	3.6 ± 0.9	3.5 ± 0.9
LDL/HDL cholesterol ratio	2.4 ± 0.9	2.7 ± 1.0*	2.7 ± 0.9*
Triglycerides (mmol/l)	1.2 ± 0.5	1.5 ± 0.7*	1.7 ± 0.8*
Metabolic syndrome (%)	9.9	20.7*	71.2*

Values are % or mean ± SD. *$p < 0.001$ vs. normal group. †$p < 0.05$ vs. normal group.
BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

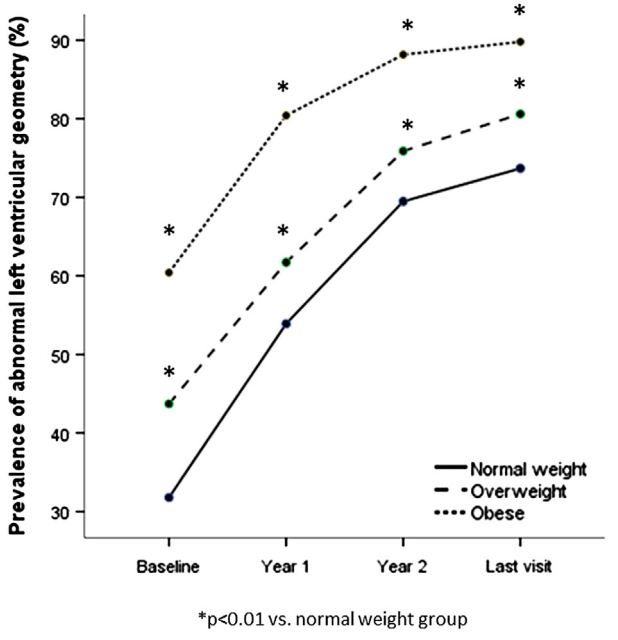

Figure 1 Prevalence of Abnormal Left Ventricular Geometry in Groups of Patients

Compared with normal weight patients, overweight and obese patients had significantly higher prevalence of abnormal left ventricular geometry during follow-up.

Table 2 Echocardiographic Characteristics of Patients at Baseline and at Last Visit

	Baseline			Last Visit		
	Normal Weight (n = 593)	Overweight (n = 737)	Obese (n = 334)	Normal Weight (n = 593)	Overweight (n = 737)	Obese (n = 334)
Left atrial diameter (cm)	3.5 ± 0.6	3.8 ± 0.6*	4.1 ± 0.6*	3.6 ± 0.6	3.8 ± 0.7*	4.0 ± 0.7*
LV end-diastolic diameter (cm)	4.9 ± 0.6	5.1 ± 0.6*	5.2 ± 0.6*	4.6 ± 0.6	4.8 ± 0.7*	4.9 ± 0.7*
Septum end-diastolic diameter (cm)	1.1 ± 0.3	1.2 ± 0.3*	1.2 ± 0.3*	1.3 ± 0.3	1.4 ± 0.3*	1.5 ± 0.3*
Posterior wall end-diastolic diameter (cm)	0.8 ± 0.2	0.9 ± 0.2*	0.9 ± 0.2*	1.0 ± 0.2	1.1 ± 0.2*	1.1 ± 0.2*
LV mass (g)	171 ± 55	202 ± 66*	220 ± 79*	205 ± 63	233 ± 72*	254 ± 91*
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	40.6 ± 12.0	46.7 ± 14.0*	53.6 ± 17.2*	48.8 ± 13.8	53.8 ± 15.4*	61.8 ± 18.7*
Relative wall thickness	0.35 ± 0.09	0.36 ± 0.09	0.37 ± 0.09	0.47 ± 0.11	0.47 ± 0.12	0.47 ± 0.11
Stress-corrected midwall shortening (%)	102 ± 20	99 ± 20*	97 ± 19*	78 ± 17	79 ± 17	77 ± 15†
Ejection fraction (%)	67 ± 8.0	65 ± 8.3*	65 ± 8.1*	65 ± 8.7	65 ± 8.4	64 ± 8.4
Aortic valve area (cm^2)	1.2 ± 0.4	1.3 ± 0.5*	1.3 ± 0.5†	1.1 ± 0.4	1.2 ± 0.5*	1.2 ± 0.5*
Aortic valve area/body surface area (cm^2/m^2)	0.67 ± 0.22	0.69 ± 0.24	0.64 ± 0.22	0.60 ± 0.23	0.62 ± 0.23	0.59 ± 0.22
Peak aortic jet velocity (m/s)	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.6	3.7 ± 0.8	3.7 ± 0.8	3.6 ± 0.8
Mean aortic gradient (mm Hg)	23 ± 9	22 ± 9	23 ± 9	35 ± 15	33 ± 15	33 ± 14

Values are mean ± SD. *p < 0.01 vs. normal weight group. †p < 0.05 vs. normal weight group.
LV= left ventricular.

differ between normal weight, overweight, and obese groups of patients at the pre-operative echocardiogram. Compared with the normal weight group, overweight patients had lower cumulative proportions of ischemic CV events and AS-related events, whereas the cumulative proportions of these events did not differ between obese and normal weight groups (Table 3). In univariate Cox regression, overweight was associated with a 17% to 22% lower rate of AS-related (p = 0.04) and ischemic CV events (p = 0.05) (Table 4).

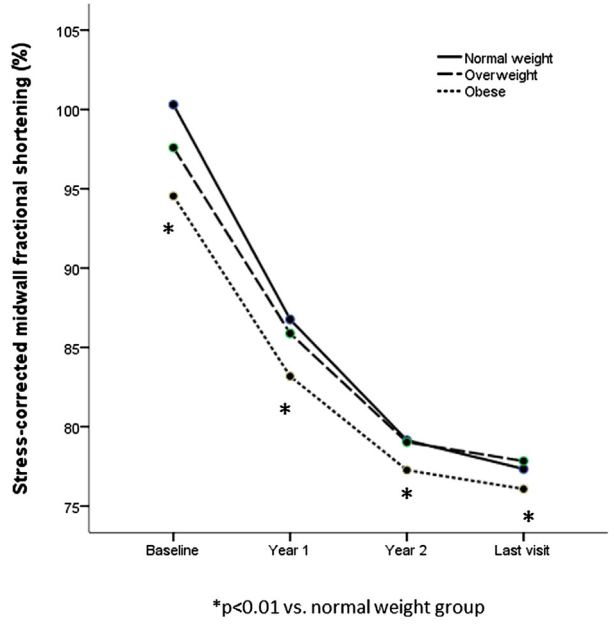

Figure 2 Stress-Corrected Midwall Shortening in Groups of Patients

Compared with normal weight patients, stress-corrected midwall shortening was significantly lower in obese patients throughout the study.

In the first multiple Cox regression model, adjusting for sex, smoking, hypertension, LV geometry, LVEF, mean aortic gradient, and randomized study drug treatment, overweight was associated with lower rates of ischemic CV events (hazard ratio: 0.69, 95% confidence interval: 0.53 to 0.90, p = 0.007) and AS-related events (hazard ratio: 0.82, 95% confidence interval: 0.68 to 0.99, p = 0.04), compared with the normal weight group, whereas obesity did not significantly influence rates of these events. Higher BMI class was not associated with statistically significant increased CV or total mortality or combined hospital stay for heart failure and death from any cause in this model.

However, overweight patients were on average 2 years younger than normal weight patients at the time of an ischemic CV event (71 ± 10 years vs. 73 ± 10 years, p < 0.01). When age was added to the covariates in a second Cox regression model, the association between overweight and lower rates of AS-related and ischemic CV events became statistically nonsignificant (Table 5). Furthermore, in this second model, overweight and obesity was associated with a 46% to 67% higher rate of death from any cause and a 42% to 69% higher rate of combined hospital stay for heart failure and death from any cause (Table 5). When BMI class was replaced by an indicator variable for presence of MetS in this model, baseline MetS did not significantly influence rates of these CV events (data not showed).

Discussion

BMI and progression of AS. To our knowledge, this is the first large prospective study in patients with initially asymptomatic, mild to moderate AS reporting the effect of elevated BMI on outcome.

Although having elevated BMI was associated with clustering of cardiometabolic risk factors also in the SEAS population, the progression rate of AS did not differ between BMI classes or in relation to presence of MetS.

Table 3 Cumulative Proportions of CV Events Over 4.3 Years in Groups of Patients With Normal Weight, Overweight, and Obesity

	Normal Weight (n = 593)	Overweight (n = 737)	Obese (n = 334)
Ischemic CV events (%)	19 ± 2	15 ± 1*	18 ± 2
AS-related events (%)	34 ± 2	29 ± 2†	33 ± 3
Coronary artery bypass grafting (%)	11 ± 1	8 ± 1	8 ± 2
Myocardial infarction (%)	2 ± 1	2 ± 1	3 ± 1
CV deaths (%)	6 ± 1	4 ± 1	6 ± 1
Total mortality (%)	9 ± 1	10 ± 1	12 ± 2
Combined hospital stay for heart failure and death from any cause (%)	10 ± 1	11 ± 1	13 ± 2

Values are cumulative percentage ± SEM. *p = 0.05. †p < 0.05, vs. normal weight group.
AS = aortic valve stenosis, CV = cardiovascular.

This was a surprising finding, contrasting previous reports (18). Ngo et al. (32) reported obesity and smoking as independent predictors of a more rapid progression of AS from a small study in 87 elderly patients with mild asymptomatic AS who underwent 2 serial echocardiograms during a 2.5-year period. Similarly Briand et al. (18) reported a 2-fold increased progression rate of AS as well as a 36% lower event-free survival rate over 3 years in 105 patients with the MetS and at least moderate AS. From the ASTRONOMER study, Capoulade et al. (9) reported that MetS in asymptomatic AS predicted more rapid progression of AS. The different findings in the SEAS study compared with the ASTRONOMER study might be related to the less sensitive measure of MetS used in the SEAS study but also to important differences in CV risk profile between these 2 study populations, in particular the younger age, higher prevalence of smoking, as well as the much lower prevalence of concomitant hypertension in the ASTRONOMER study. Indeed a significant age-MetS interaction was also reported in that study, and more rapid AS progression was particularly found in MetS patients <57 years of age. Compared with the study by Briand et al., the SEAS study excluded patients with diabetes and hypercholesterolemia and had lower prevalence of smokers. However, our findings are in line with a report from the Multi-Ethnic Study of Atherosclerosis, which demonstrated an association between presence of the MetS and diabetes and increased aortic valve calcium but not between MetS and the rate of progression of AS as validated by CT (33).

BMI and outcome. Overweight and obesity were not associated with increased rate of ischemic CV or AS-related events when adjusted for confounders including age in multivariate analyses, regardless of the clustering of cardiometabolic risk factors with higher weight. However, increased BMI retained the association with a higher rate of mortality and combined hospital stay for heart failure and death from any cause compared with those with normal weight. In contrast, the obesity paradox has been described

Table 4 Impact of Overweight and Obesity on Outcome in Univariate Analyses

	ICE (n = 291)		ASE (n = 547)		CV Death (n = 86)		Total Mortality (n = 173)		Combined Hospital Stay for Heart Failure and Death From Any Cause (n = 217)	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Overweight (n = 737)	0.78 (0.60–1.00)	0.054	0.83 (0.69–1.00)	0.047	0.76 (0.47–1.23)	0.256	1.22 (0.86–1.73)	0.261	1.26 (0.92–1.72)	0.146
Obese (n = 334)	0.89 (0.65–1.22)	0.468	0.95 (0.76–1.20)	0.659	1.08 (0.62–1.88)	0.780	1.40 (0.93–2.11)	0.108	1.51 (1.05–2.16)	0.026

ASE = aortic stenosis related events; CV = cardiovascular; ICE = ischemic cardiovascular events.

Table 5 Impact of Overweight and Obesity on Outcome in Multivariate Analyses

Variable	Outcome									
	ICE (n = 291)		ASE (n = 547)		CV Death (n = 86)		Total Mortality (n = 173)*		Hospital Stay for Heart Failure and Death From Any Cause (n = 217)*	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Overweight	0.78 (0.60–1.02)	0.073	0.84 (0.69–1.02)	0.072	0.78 (0.47–1.30)	0.341	1.46 (1.02–2.10)	0.041	1.42 (1.03–1.97)	0.033
Obese	0.86 (0.61–1.20)	0.360	0.86 (0.68–1.10)	0.230	1.02 (0.56–1.87)	0.953	1.67 (1.07–2.63)	0.026	1.69 (1.14–2.50)	0.009
Smoking	1.67 (1.26–2.22)	<0.001	1.12 (0.90–1.38)	0.320	1.67 (0.96–2.90)	0.069	1.87 (1.28–2.71)	<0.001	1.66 (1.19–2.33)	0.003
Age	1.05 (1.04–1.07)	<0.001	1.00 (1.00–1.02)	0.206	1.10 (1.06–1.13)	<0.001	1.10 (1.07–1.12)	<0.001	1.08 (1.07–1.10)	<0.001
Hypertension	1.90 (1.19–3.02)	0.007	1.05 (0.81–1.37)	0.703	1.74 (0.69–4.36)	0.241	1.37 (0.77–2.45)	0.282	0.88 (0.56–1.38)	0.585
Study treatment	0.79 (0.63–1.00)	0.052	0.98 (0.83–1.16)	0.818	0.89 (0.58–1.37)	0.606	1.02 (0.76–1.39)	0.878	1.07 (0.82–1.40)	0.610
Female	0.64 (0.50–0.82)	0.001	0.93 (0.78–1.11)	0.431	0.78 (0.50–1.24)	0.292	0.65 (0.47–0.91)	0.011	0.78 (0.59–1.05)	0.099
Abnormal LV geometry	1.31 (1.03–1.68)	0.029	1.29 (1.08–1.54)	0.004	1.21 (0.76–1.91)	0.418	0.98 (0.71–1.35)	0.890	1.07 (0.81–1.43)	0.625
Ejection fraction	0.99 (0.98–1.00)	0.137	0.98 (0.97–0.99)	0.001	0.96 (0.93–0.98)	0.001	0.97 (0.95–0.99)	0.003	0.95 (0.94–0.97)	<0.001
Mean aortic gradient	1.04 (1.03–1.05)	<0.001	1.08 (1.07–1.09)	<0.001	1.02 (0.99–1.04)	0.155	0.99 (0.98–1.01)	0.509	1.00 (0.98–1.01)	0.731

*Models also adjusted for intervening nonfatal major cardiovascular (CV) events.
ASE = aortic stenosis related events; BMI = body mass index; CI = confidence interval; HR = hazard ratio; ICE = ischemic cardiovascular events; LV = left ventricular.

in several publications from outcome studies in patients undergoing coronary revascularization with PCI or CABG (12,13,34). Oreopoulos et al. (12) found no evidence of reduced event-free survival in patients with BMI >25 kg/m^2 on short-term (within 30 days) and long-term (up to 5 years) mortality after PCI and CABG. The Scottish Coronary Revascularisation register, including 4,880 patients who underwent elective first time PCI, reported significantly lower risk of death during 5-year follow-up for overweight compared with normal weight patients (13). Similar results were found in a prospective Australian multicenter study of 4,762 patients undergoing PCI, reporting higher burden of CV risk factors yet lower mortality and rate of major adverse CV events among obese patients compared with their normal weight counterparts (34). In contrast, Azimi et al. (35) from the Western Denmark Heart Registry reported a 35% increased risk for death in patients with BMI >40 kg/m^2 and established CV disease but superior survival in overweight patients compared with their normal weight counterparts.

Recently, Roberts et al. (14) reported a strong association between BMI and post-operative survival in AS patients undergoing surgical aortic valve replacement from registry data. In particular, mildly obese patients (BMI in the low 30s) had superior survival rate compared with normal weight and morbidly obese groups of patients. These findings are not confirmed by the results from our large prospective study. Patients with increased BMI experienced ischemic CV events at a younger age than normal weight patients, as also reported from Madala et al. (36). We cannot exclude selection bias on the part of the physicians in the sense that the most fit of the patients among the overweight and obese patients were referred for operation, but the same principle can equally be expected to be applied in the group of the normal weight patients. However, as demonstrated, AS severity did not differ between normal weight, overweight, and obese patient groups at the pre-operative echocardiogram. Age was a strong predictor of adverse events in our population, and the significant association between overweight and lower rate of ischemic CV and AS-related events disappeared when age was taken into account in multivariate analysis. However, increased BMI remained associated with increased mortality and combined hospital stay for heart failure and death from any cause in both univariate and multivariate analysis.

BMI and LV geometry and function. Increased BMI significantly influenced LV mass and was associated with more abnormal LV geometry throughout the study duration, in line with previous findings in general and hypertensive population (7–9). Obesity was associated with excessive LV mass and reduced LV myocardial function, confirming results from studies in the general population and in AS patients (37,38). Of note, in the present study, LVEF remained normal in the vast majority of patients independent of BMI class, whereas stress-corrected midwall shortening was persistently lower in obese patients.

Clinical implications. The findings of the present prospective analysis suggest that closer follow-up is not indicated in overweight patients with mild-to-moderate AS. In particular, overweight AS patients without hypercholesterolemia, diabetes mellitus, a history of CV disease, or renal impairment have AS progression comparable to their normal weight counterparts and are not in need of special strategies or earlier valve intervention. Management of cardiometabolic risk factors associated with higher BMI should follow general recommendations for AS patients. Increased BMI predisposes to heart failure and increased mortality in AS, as in the general population. Weight normalization is likely to improve prognosis in AS patients, but this effect was not tested in the present study.

Study limitations. The SEAS study did not include patients with CV disease, diabetes mellitus, known reduced LVEF, renal impairment, or other major valvular heart disease. Therefore the present results are not applicable to these subpopulations. However, the elimination of important confounders also allowed a more targeted analysis of the prognostic effect of increased BMI in AS.

It is well known that BMI is a crude measurement of obesity, inferior to waist circumference. Waist circumference was not recorded in the SEAS study. We chose, to facilitate comparison with previous publications in AS, a similar approach as Briand et al. (18) for identification of MetS by substituting waist circumference with BMI $\geq$30 kg/m^2. Thus, the difference between the modified National Cholesterol Education Program—Adult Treatment Panel III criteria used by Briand et al. and the definition of MetS used in the present study was merely the cutoff value for elevated fasting glucose, which is $\geq$110 mg/dl in National Cholesterol Education Program–Adult Treatment Panel III and $\geq$100 mg/dl in the updated American Heart Association/National Heart, Lung, and Blood Institute Scientific statement (16,39). In general, comparison between studies using different criteria for MetS should be done with caution.

This study does not address the prognostic implication of underweight in AS, due to the exclusion of the very limited number of patients that fell into that category.

Conclusions

In patients with initially asymptomatic AS, without known CV disease or diabetes mellitus, participating in the SEAS study, overweight and obesity were not associated with increased AS progression rate or rates of AS-related or ischemic CV events. However, both overweight and obesity were associated with increased total mortality as well as combined hospital stay for heart failure and death from any cause.

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Key Words: aortic valve stenosis ■ body mass index ■ cardiovascular disease ■ obesity ■ outcomes.