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Insulin Resistance and LVH Progression in Patients With Calcific Aortic Stenosis

A Substudy of the ASTRONOMER Trial

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OBJECTIVES The objective of this substudy of the ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial was to examine the association between insulin resistance and progression of left ventricular hypertrophy (LVH) in patients with aortic stenosis (AS).

BACKGROUND In a recent cross-sectional study, the authors reported that the metabolic syndrome was associated with an increased prevalence of concentric LVH in patients with AS. As a central feature of the metabolic syndrome, insulin resistance could be an important mediator of this association.

METHODS This substudy included 250 of 269 patients enrolled in ASTRONOMER. Follow-up was 3.4 ± 1.3 years. Insulin resistance was evaluated using the homeostatic assessment model (HOMA) index, and patients were dichotomized using the median HOMA index value (1.24). The rate of LVH progression was estimated by calculating the annualized change in LV mass index (LVMi), measured on echocardiography. The presence of LVH was defined as an LVMi >47 g/m$^{2.7}$ in women and >49 g/m$^{2.7}$ in men.

RESULTS There was a significant progression of LVH among the patients without LVH at baseline (n = 134; p < 0.0001) but not in those with it (n = 116; p = NS). In those without LVH at baseline, the annualized progression rate of LVMi was significantly faster in the subset with HOMA >1.24 compared to that in the subset with HOMA <1.24 (2.49 ± 4.38 g/m$^{2.7}$/year vs. −0.03 ± 3.90 g/m$^{2.7}$/year; p = 0.001). During follow-up, LVH developed in 46% of patients with HOMA >1.24 compared to 11% of those with HOMA <1.24 (p = 0.0005). Independent predictors of faster LVH progression identified on multivariate analysis were history of hypertension (p = 0.048), degree of aortic valve calcification (p = 0.035), and HOMA index (p = 0.02).

CONCLUSIONS In this ASTRONOMER substudy, insulin resistance was a powerful independent predictor of progression to LVH in patients with AS. Visceral obesity and ensuing insulin resistance may thus present novel therapeutic targets in AS patients. (J Am Coll Cardiol Img 2013;6:165–74) © 2013 by the American College of Cardiology Foundation

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The pressure overload associated with aortic stenosis (AS) as well as with concomitant systemic arterial hypertension may lead to the development of left ventricular hypertrophy (LVH). LVH has been linked to occurrence of LV dysfunction, an increased risk for cardiac events, and a higher operative risk for aortic valve replacement in the AS population (1–5). Besides the pressure overload caused by valvular obstruction and concomitant arterial hypertension, the other factors influencing the development and progression of LVH in AS patients are unknown.

Visceral obesity is associated with a cluster of metabolic abnormalities often referred to as the *metabolic syndrome* (MetS), including insulin resistance, atherogenic dyslipidemia, and proinflammatory state (6). Although visceral fat accumulation may be causally related to the features of insulin resistance, it may also be a marker of dysfunctional adipose tissue resulting from a sedentary lifestyle and excessive calorie consumption (6). Previous studies suggest that this dysmetabolic state is associated with an increased prevalence of aortic valve calcification (7), faster progression rate of AS (8,9), and increased arterial stiffness (10). In a recent cross-sectional substudy of the ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial, which enrolled patients with mild to moderate AS, the authors reported that MetS was independently associated with a higher prevalence of concentric LVH and impairment of LV systolic function, even after adjustment for global LV pressure overload (11). In the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) trial, greater body mass index (BMI) was associated with the presence of LVH in patients with asymptomatic AS, independent of AS severity and the presence of hypertension (12). More recently, Lindman et al. (13) reported an association between type 2 diabetes and LVH and LV dysfunction in patients with severe AS referred for aortic valve replacement. These findings lend support to the hypotheses that: 1) in AS patients, the dysmetabolic state associated with visceral obesity may pre-dispose to the development of LVH independently of global (i.e., valvular and arterial) hemodynamic load; and 2) insulin resistance could be a key mediator of this association. The objective of this substudy of the ASTRONOMER trial was to test the hypothesis that insulin resistance is related to the progression of LVH and global LV hemodynamic load.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
BMI = body mass index
FFA = free fatty acid
HOMA = homeostatic assessment model
LVH = left ventricular hypertrophy
LVMi = left ventricular mass index
MetS = metabolic syndrome
SBP = systolic blood pressure
Z_{va} = valvuloarterial impedance

METHODS

The protocol and results of the ASTRONOMER trial have been extensively described elsewhere (14).

Patient population. Between 2002 and 2005, 269 patients with mild to moderate AS were enrolled into the ASTRONOMER trial at 23 Canadian sites. Patients between 18 and 82 years of age and having a peak aortic jet velocity between 2.5 and 4.0 m/s were included. Patients with severe or symptomatic AS, severe aortic regurgitation, mitral valve disease (mitral stenosis or greater than mild mitral regurgitation), symptomatic coronary artery disease, congestive heart failure, diabetes, or a need for cholesterol-lowering treatment were excluded. Patients were randomly assigned to receive rosuvastatin 20 mg or placebo. For the purpose of this prespecified substudy, clinical, laboratory, and Doppler echocardiography data were collected and analyzed in 250 of the 269 patients (93%) recruited in the ASTRONOMER trial. Nineteen patients (7%) were excluded from this substudy because Doppler echocardiography follow-up data were not available. The mean follow-up time was 3.4 ± 1.3 years.

Clinical and laboratory data. Clinical data included age, sex, weight, height, BMI, waist circumference, smoking history, documented diagnosis of hypertension (blood pressure ≥130/85 mm Hg and/or receiving antihypertensive medication), and randomization group (statin or placebo).

Fasting blood samples were collected at the baseline and last follow-up visits to determine

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glucose, insulin, and creatinine concentrations and a complete lipid profile, which included total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and apolipoprotein B, using automated techniques standardized with the Canadian reference laboratory. To assess insulin resistance, the homeostatic assessment model (HOMA) index (15) was calculated using fasting glucose and insulin levels and the following formula: insulin (in μU/ml) $\times$ (glucose [in mmol/l]/22.5).

Doppler echocardiography data. **AORTIC VALVE MORPHOLOGY AND FUNCTION.** The Doppler echocardiography indexes of AS severity included peak aortic jet velocity; peak and mean transvalvular pressure gradients, obtained with the use of the modified Bernoulli equation; and the aortic valve area, calculated by the standard continuity equation. The degree of aortic valve calcification was scored according to the criteria proposed by Rosenhek et al. (16).

LV GEOMETRY AND FUNCTION. LV minor axis internal dimension (LVID), posterior wall thickness (PWT), and interventricular septal thickness (IVST) were measured according to the recommendations of the American Society of Echocardiography (17). Relative wall thickness (RWT) was calculated as (PWT + IVST)/LVID. The corrected formula of the American Society of Echocardiography was used to calculate LV mass, which was indexed to a 2.7 power of height (LVMi) (18). LVH was defined as LVMi >49 g/m$^{2.7}$ in men and >47 g/m$^{2.7}$ in women (18).

By taking into account both LVMi and RWT, patients were classified as having 1 of 4 LV remodeling patterns, using the following criteria suggested by Cramariuc et al. (2): 1) normal pattern: absence of LVH and RWT <0.43; 2) concentric remodeling: absence of LVH and RWT ≥0.43; 3) concentric hypertrophy: presence of LVH and RWT ≥0.43; and 4) eccentric hypertrophy: presence of LVH and RWT <0.43. LV ejection fraction was measured with the use of the biplane Simpson method.

GLOBAL LV HEMODYNAMIC LOAD. As a measure of global LV hemodynamic load, valvuloarterial impedance (Z_{va}) was calculated as (SBP + ΔP_{mean})/SVi, where SBP is systolic blood pressure, ΔP_{mean} is the mean transvalvular gradient, and SVi is the stroke volume indexed to a 2.04 power of height (11).

Study outcomes. The primary outcome of this study was LVH progression, measured as the change from baseline in LVMi during follow-up. To account for varying durations of follow-up, change in LVMi was annualized by dividing the total change in LVMi by the duration of follow-up. The secondary end points were changes from baseline in severity of AS and global LV hemodynamic load, assessed by annualized changes in peak aortic jet velocity and Z_{va}, respectively. We also assessed the effect of rosuvastatin on these end points.

Statistical analysis. Continuous data are expressed as mean ± SD and were compared using the Student *t* test. Categorical data are expressed as percentages and were compared using the chi-square or Fisher exact test as appropriate. According to the prespecified analysis plan, the patients were dichotomized on the basis of the median HOMA index value (i.e., 1.24 in this series). Multivariate linear regression analysis was performed to identify independent predictors of the primary and secondary study outcomes: progression to LVH and hemodynamic load. Variables entered into the multivariate model were: 1) all variables with a p value <0.10 on individual analysis; and 2) clinically relevant variables (i.e., age, male, creatinine level, and baseline LVMi) regardless of p value. Standardized raw-score regression coefficients (i.e., β) are presented. Logistic generalized linear mixed modeling using multinomial distribution for the response variable was performed to identify predictors of worsening LV patterns. All mixed models were adjusted for duration of follow-up. A subsequent adjustment for randomization status was performed in the mixed and multivariate models. A p value <0.05 was considered statistically significant.

RESULTS

Progression of LV hypertrophy. Among the 250 patients included in this substudy, 134 (54%) had no significant LVH at baseline, and 116 patients (46%) presented LVH, among whom 73 (63%) had concentric hypertrophy. The group without LVH at baseline had a significant increase in LVMi from baseline to last follow-up (37.8 ± 6.4 g/m$^{2.7}$ vs. 42.9 ± 10.2 g/m$^{2.7}$; p < 0.0001), whereas the change in LVMi from baseline to follow-up was nonsignificant in the group with LVH at baseline (61.0 ± 10.8 g/m$^{2.7}$ vs. 58.9 ± 14.4 g/m$^{2.7}$; p = NS). The prevalences of MetS (37% vs. 19%; p = 0.002) and hypertension (48% vs. 19%; p < 0.0001), as well as the HOMA index (2.2 ± 1.7 vs.

1.7 ± 1.4; p = 0.02), were significantly higher in the group with LVH at baseline compared to the group without it (Online Table). However, the severity of AS and the Z_{va} were similar in the 2 groups. The durations of follow-up were similar in the 2 groups (no LVH: 3.5 ± 1.3 years; LVH: 3.3 ± 1.3 years.

There was a significant interaction between baseline HOMA index and baseline LVMi with regard to the effect on LVH progression (i.e., annualized change in LVMi) during follow-up (p = 0.04). No significant association was found between HOMA index and LVH progression in patients with LVH at baseline (p = 0.23), whereas HOMA index was a significant predictor of progression of LVH in patients without LVH at baseline (p = 0.0003). Hence, most of the analyses presented in this paper focus on the group of patients without LVH at baseline (n = 134).

After dichotomization according to the median value of HOMA index in the group of patients without LVH at baseline, the subset with a HOMA index >1.24 was found to have a greater BMI and waist circumference; higher prevalence of smoking history; higher prevalence of MetS; lower prevalence of bicuspid aortic valve phenotype; higher plasma levels of triglycerides, fasting glucose, fasting insulin, and creatinine; and a lower plasma level of high-density lipoprotein cholesterol compared to the subset with a HOMA index <1.24 (Table 1). Numerical but statistically nonsignificant differences in the following parameters were also found in the subset with HOMA index >1.24: older age, greater baseline LVMi, higher prevalence of hypertension, higher SBP, and higher plasma level of low-density lipoprotein cholesterol. Baseline Doppler echocardiography data showed similar AS severity, Z_{va}, and LV ejection fraction values in the 2 groups. The durations of follow-up were similar in the subset with a HOMA index >1.24 and the subset with a HOMA index <1.24 (3.4 ± 1.3 years vs. 3.6 ± 1.2 years; p = NS).

During follow-up, LVH developed in 46% of patients with a HOMA index >1.24 compared to 11% in patients with a HOMA index <1.24 (p = 0.0005). On analysis of change in the LV remodeling pattern during follow-up, the group with a HOMA index >1.24 had significant worsening of LV geometry during follow-up (p = 0.003), whereas the group with a HOMA index <1.24 did not (Fig. 1).

Progression of LVH was significantly faster in the group with a HOMA index >1.24 compared to the group with a HOMA index <1.24 (annualized change in LVMi: 2.49 ± 4.38 g/$m^{2.7}$/year vs. −0.03 ± 3.90 g/$m^{2.7}$/year; p = 0.001) (Fig. 2A). Other baseline variables associated with faster LVH progression on univariate analysis were BMI (p = 0.001), history of hypertension (p = 0.008), degree of aortic valve calcification (p = 0.004), and peak aortic jet velocity (p = 0.03) (Table 2). After adjustment for these variables as well as other clinically relevant variables (i.e., age, male sex, creatinine level, and baseline LVMi), independent predictors of faster LVH progression were a history of hypertension (p = 0.048), degree of aortic valve calcification (p = 0.035), and HOMA index (p = 0.02) (Table 2, multivariate model 1). After additional adjustment for baseline SBP and global LV hemodynamic load (i.e., Z_{va}), the predictors of LVH progression were degree of aortic valve calcification (p = 0.031) and HOMA index (p = 0.015) (Table 2, multivariate model 2).

Progression of AS and global LV hemodynamic load. Higher HOMA index was significantly associated with faster progression of AS (i.e., annualized change in peak aortic jet velocity: r = 0.17; p = 0.05). HOMA index was also associated with increased global LV hemodynamic load (i.e., annualized change in Z_{va}) in the group without LVH at baseline (r = 0.21; p = 0.045), but not in the overall cohort (p = 0.80) or in the group with pre-existing LVH (p = 0.38). Lower SBP (r = −0.25; p = 0.01) and lower Z_{va} (r = −0.38; p = 0.0001) at baseline were also associated with greater progression of Z_{va} during follow-up. On multivariate analysis that included these variables as well as age, sex, and peak aortic jet velocity, HOMA index remained an independent predictor of Z_{va} progression rate in the subset of patients without LVH (p = 0.003) (Table 3).

Given that the HOMA index was associated with faster progression of AS and Z_{va}, additional multivariate models were examined for progression of LVH, with further adjustment for the annualized changes in peak aortic jet velocity and SBP (Table 2, multivariate model 3) and for annualized change in Z_{va} (Table 2, multivariate model 4). In these models, HOMA index remained independently associated with faster progression of LVH.

Effects of statin therapy. Among the patients treated with rosuvastatin, the progression of LVH was significantly faster in the subgroup with a HOMA index >1.24 compared to that with a HOMA index <1.24 (annualized change in LVMi: 3.26 ± 5.17 g/$m^{2.7}$/year vs. 0.06 ± 2.28 g/$m^{2.7}$/year; p =

Table 1. Baseline Characteristics of the Study Patients Without LVH at Baseline

	Patients Without LVH at Baseline (n = 134)	HOMA Index <1.24 (n = 67)	HOMA Index >1.24 (n = 67)	p Value
Clinical				
Age, yrs	56 ± 13	54 ± 11	58 ± 13	0.09
Male	56	49	63	NS
Height, cm	170 ± 9	168 ± 10	171 ± 10	0.07
Weight, kg	77 ± 18	69 ± 11	84 ± 17	<0.0001
Body surface area, m^2	1.88 ± 0.23	1.78 ± 0.18	1.96 ± 0.24	<0.0001
Body mass index, kg/m^2	26.5 ± 5.5	24.3 ± 3.1	28.4 ± 4.6	<0.0001
Waist circumference, cm	91 ± 14	84 ± 11	95 ± 12	<0.0001
History of hypertension	19	13	25	0.08
Systolic blood pressure, mm Hg	124 ± 17	121 ± 15	127 ± 20	0.06
Diastolic blood pressure, mm Hg	75 ± 11	76 ± 12	74 ± 10	NS
History of smoking	44	33	52	0.04
Metabolic syndrome	19	5	33	<0.0001
Medication				
Antihypertensive treatment	15	6	20	0.02
ACE inhibitor	8	3	12	0.051
ARB	7	3	8	NS
Rosuvastatin	49	51	50	NS
Laboratory data				
LDL cholesterol, mg/dl	124 ± 29	119 ± 30	128 ± 28	0.08
ApoB, mg/dl	100 ± 20	97 ± 21	103 ± 19	NS
HDL cholesterol, mg/dl	60 ± 18	66 ± 21	53 ± 14	0.0001
Triglycerides, mg/dl	118 ± 61	104 ± 56	130 ± 63	0.01
Fasting glucose, mg/dl	94 ± 12	90 ± 7	98 ± 14	<0.0001
Fasting insulin, μU/ml	7.8 ± 5.5	3.9 ± 0.9	10.3 ± 5.8	<0.0001
HOMA index	1.7 ± 1.4	0.8 ± 0.2	2.5 ± 1.5	<0.0001
Creatinine, mg/dl	0.90 ± 0.18	0.85 ± 0.14	0.93 ± 0.21	0.03
Doppler echocardiography data				
Bicuspid aortic valve	51	70	34	<0.0001
Aortic valve calcification score	1.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.6	NS
Peak aortic jet velocity, m/s	3.14 ± 0.39	3.15 ± 0.41	3.09 ± 0.35	NS
Peak transvalvular gradient, mm Hg	40 ± 10	40 ± 11	39 ± 9	NS
Mean transvalvular gradient, mm Hg	22 ± 7	23 ± 7	21 ± 6	NS
Aortic valve area, cm^2	1.30 ± 0.40	1.27 ± 0.43	1.34 ± 0.38	NS
Indexed aortic valve area, cm^2/m^2	0.70 ± 0.20	0.72 ± 0.22	0.69 ± 0.19	NS
Valvuloarterial imped., mm $Hg/ml/m^{2.04}$	4.9 ± 1.5	4.7 ± 1.1	5.1 ± 1.8	NS
LV end-diastolic diameter, mm	47.2 ± 5.8	46.8 ± 5.9	47.4 ± 5.6	NS
Interventricular septal thickness, mm	9.8 ± 1.7	9.6 ± 1.4	10.2 ± 1.8	0.03
Posterior wall thickness, mm	9.5 ± 1.3	9.2 ± 1.2	9.9 ± 1.3	0.004
Relative wall thickness ratio	0.42 ± 0.09	0.41 ± 0.08	0.43 ± 0.09	NS
LV mass index, $g/m^{2.7}$	37.8 ± 6.4	36.8 ± 6.6	39.0 ± 6.0	0.052
Left ventricular ejection fraction	66 ± 6	65 ± 6	66 ± 6	NS

Values are mean ± SD or %.
ACE = angiotensin-converting enzyme; apoB = apolipoprotein B; ARB = angiotensin receptor blocker; HOMA = homeostatic assessment model; LDL = low-density lipoprotein; LV = left ventricle; LVH = left ventricular hypertrophy.

0.003), whereas the difference between these 2 subgroups did not reach statistical significance in the patients receiving placebo (1.74 ± 3.36 $g/m^{2.7}$/year vs. −0.12 ± 5.03 $g/m^{2.7}$/year; p = 0.09). However, there was no significant difference between the statin and placebo arms in the overall study group or within each HOMA index subgroup with respect to the progression of LVH (<1.24: p = 0.86; >1.24: p = 0.18) (Fig. 2B). When status of randomization was added into the multivariate

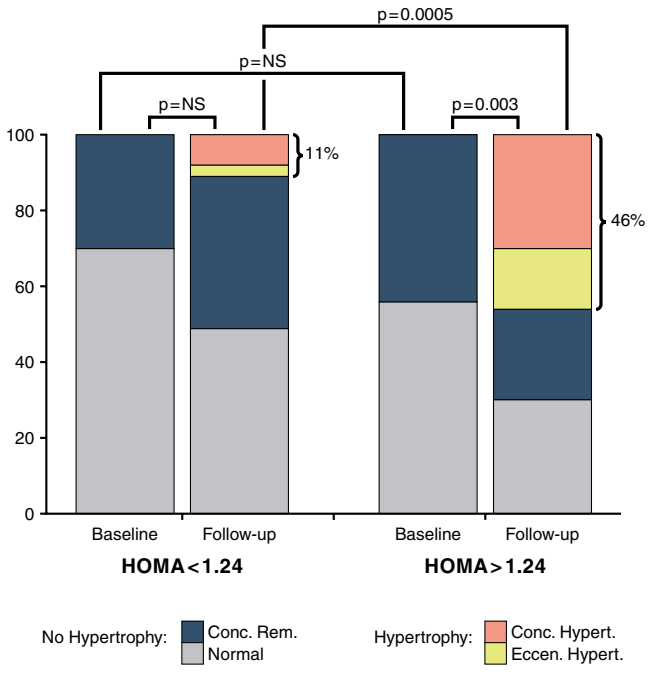

Figure 1. Prevalence of LV Remodeling Patterns in Patients Without LVH at Baseline (N = 134)

Comparison of left ventricular (LV) remodeling patterns at baseline and last follow-up visits in patients with a homeostatic assessment model (HOMA) index <1.24 versus those with a HOMA index >1.24. Conc. Hypert. = concentric hypertrophy; Conc. Rem. = concentric remodeling; Eccen. Hypert. = eccentric hypertrophy; LVH = left ventricular hypertrophy.

models, HOMA index remained significantly associated with faster progression of LVH ($p = 0.018$) and worsening LV geometry ($p = 0.008$), whereas statin therapy was not a significant predictor.

DISCUSSION

This is the first prospective study, to our knowledge, to report that insulin resistance is a powerful independent predictor of faster progression of LVH in patients with AS. This detrimental contribution of insulin resistance to changes in LV mass and geometry persisted even after the adjustment for the baseline AS severity and global LV hemodynamic load, their progression over time, and the status of randomization.

In patients with AS, LVH compensates for pressure overload. However, the presence and magnitude of LVH is highly variable from one patient to another. Excessive LV concentric remodeling or hypertrophy has been linked to poorer myocardial function, faster progression to symptoms, and increased operative and late mortality rates after aortic valve replacement (1–5).

In a recent cross-sectional substudy of the ASTRONOMER trial, the authors reported that, notwithstanding AS severity and magnitude of global LV hemodynamic load (i.e., Z_{va}), MetS was independently associated with more pronounced concentric LVH in patients with mild to moderate AS. In the present longitudinal study, insulin resistance, which is a central feature of visceral obesity, MetS, and diabetes, predicted faster progression of LVH and global LV hemodynamic load. Insulin resistance may worsen LV remodeling and function by several mechanisms. First, it may promote myocardial hypertrophy and fibrosis through several signaling pathways, including Akt, transforming growth factor β, and peroxisome proliferator-activated receptor (19). Second, insulin resistance is associated with several alterations in plasma substrates of myocardial metabolism, mainly increased free fatty acid (FFA) and glucose levels (20). In the myocardium exposed to pressure overload related to AS and/or concomitant systemic hypertension, FFA oxidation is reduced, and insulin resistance may further enhance FFA supply and thereby worsen the accumulation of triglycerides within the myocytes (21,22). The resulting lipotoxicity may predispose to hypertrophy, dysfunction, and apoptosis of myocytes. In this regard, studies in animals (21,23) have reported that the dysregulation of FFA metabolism induced by a high-carbohydrate, high-

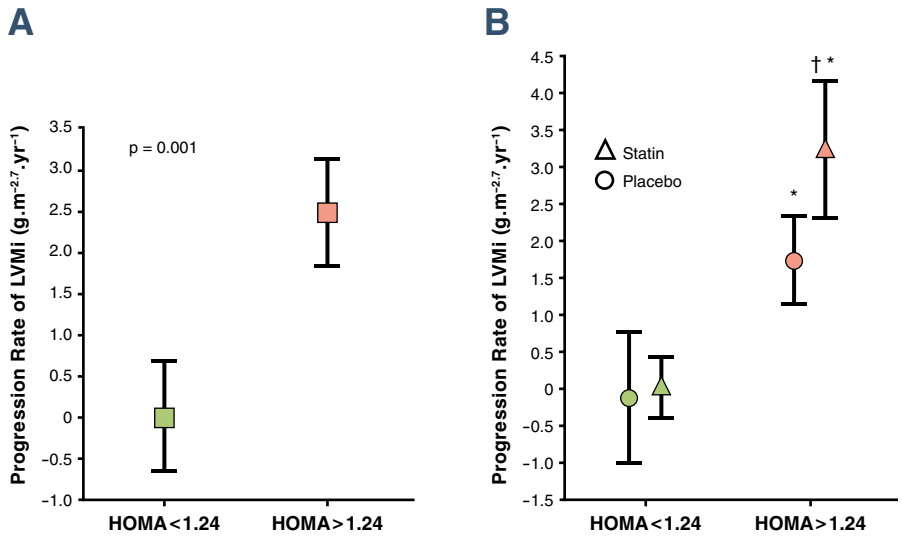

Figure 2. Annualized Progression Rate of Indexed LV Mass in Patients Without LVH at Baseline (N = 134)

Comparison of patients with a HOMA index <1.24 versus those with a HOMA index >1.24 in the overall group **(A),** and after dichotomization according to randomization status (statin **[triangles]** vs. placebo **[circles]**) **(B).** Error bars represent SEM. *p < 0.05 versus statin–HOMA <1.24; †p < 0.05 versus placebo–HOMA <1.24. HOMA = homeostatic assessment model; LVH = left ventricular hypertrophy; LVMi = left ventricular mass index.

fat diet worsens LVH induced by aorta constriction. In these models, there was a synergistic interaction between the hemodynamic load and the metabolic condition (i.e., LV mass was increased to a greater extent in the animals fed the high-carbohydrate, high-fat diet compared to those fed a normal diet). In the present study, the association between insulin resistance and faster progression of LVH persisted even after adjustment for the global (i.e., valvular and arterial) LV hemodynamic load and its progression over time. These findings suggest that, in AS patients, the contribution of insulin resistance to the progression of LVH is, at least in part, independent of pressure overload. However, further studies are needed to determine whether this metabolic-hemodynamic stress interaction is simply additive or synergistic.

Insulin resistance was associated with a more pronounced increase in the prevalence of LV concentric remodeling and hypertrophy. This may, in turn, increase the risk for paradoxical low-flow AS, a clinical entity recently described by Hachicha et al. (24). Paradoxical low-flow AS is characterized by exaggerated LV concentric remodeling, small LV cavity size with impaired filling, increased myocardial fibrosis, and reduced stroke volume despite preserved LV ejection fraction (25).

Effects of statins. In a recent substudy of the ASTRONOMER trial (9), statin therapy was associated with a deterioration of patients' insulin resistance, and this effect was more pronounced in those patients with MetS. In this latter subset, statin therapy was also associated with faster progression of AS severity; however, on multivariate analysis, there was no significant independent contribution of statin therapy and no significant association between MetS and statin use. In the present study, patients with evidence of insulin resistance as reflected by a high HOMA index and treated with a statin had the fastest progression of LVH. However, there was no significant difference between the statin and placebo arms in the overall group or in either of the 2 HOMA index groups. The apparent faster progression of stenosis and LVH in the subset of normocholesterolemic patients with MetS who received the statin thus needs to be confirmed in future studies.

Clinical implications. In light of the previous studies (8,9,11,13) and of the present work, the metabolic abnormalities linked to visceral obesity, and in particular insulin resistance, may accelerate the deterioration of the structure and function, not only of the aortic valve and arteries, but also of the left ventricle, which may, in turn, yield to an increased risk for cardiac events. These findings thus underline the importance of identifying viscerally obese patients and assessing the degree of insulin resistance in the AS population. Aggressive lifestyle changes such as increased physical activity and

Table 2. Predictors of LV Mass Progression in Patients Without LVH at Baseline (N = 134)

	Univariate Model		Multivariate Models*							
			1		2		3		4	
	β	p Value	β	p Value	β	p Value	β	p Value	β	p Value
Baseline variables										
Age, yrs	0.12 ± 0.003	0.17	−0.06 ± 0.003	0.59	−0.03 ± 0.003	0.57	0.03 ± 0.003	0.69	−0.03 ± 0.003	0.88
Male	0.02 ± 0.03	0.60	0.03 ± 0.04	0.57	0.03 ± 0.04	0.55	0.04 ± 0.05	0.45	0.07 ± 0.04	0.24
Body mass index, kg/m^2	0.28 ± 0.006	0.001	0.14 ± 0.009	0.23	0.13 ± 0.01	0.29	0.14 ± 0.009	0.25	0.16 ± 0.01	0.20
History of hypertension	0.12 ± 0.03	0.008	0.09 ± 0.04	0.048	0.07 ± 0.05	0.15	0.04 ± 0.05	0.44	0.08 ± 0.05	0.16
Systolic blood pressure, mm Hg	0.16 ± 0.002	0.11	—	—	0.08 ± 0.003	0.38	0.12 ± 0.003	0.25	0.04 ± 0.003	0.64
History of smoking	0.12 ± 0.03	0.09	0.04 ± 0.03	0.58	0.03 ± 0.03	0.64	0.002 ± 0.03	0.98	0.01 ± 0.04	0.83
Creatinine, μmol/l	−0.04 ± 0.003	0.69	−0.18 ± 0.003	0.09	−0.22 ± 0.003	0.10	−0.22 ± 0.003	0.06	−0.29 ± 0.003	0.034
HOMA index	0.32 ± 0.02	0.0003	0.25 ± 0.03	0.02	0.27 ± 0.03	0.015	0.24 ± 0.03	0.02	0.24 ± 0.03	0.040
Aortic valve calcification score ≥3	0.13 ± 0.03	0.004	0.10 ± 0.04	0.035	0.10 ± 0.04	0.031	0.08 ± 0.04	0.09	0.05 ± 0.04	0.35
Peak aortic jet velocity, m/s	0.19 ± 0.09	0.03	0.10 ± 0.09	0.23	0.08 ± 0.09	0.36	0.02 ± 0.09	0.87	0.04 ± 0.10	0.72
Valvuloarterial impedance, mm Hg/ml/m$^{2.04}$	−0.03 ± 0.02	0.74	—	—	−0.06 ± 0.03	0.52	−0.07 ± 0.02	0.44	−0.03 ± 0.03	0.83
LV mass index, g/m$^{2.7}$	−0.04 ± 0.005	0.65	−0.11 ± 0.004	0.18	−0.16 ± 0.006	0.10	−0.17 ± 0.006	0.07	−0.14 ± 0.006	0.15
Follow-up variables										
Annualized peak aortic jet velocity, m/s/yr	0.15 ± 0.12	0.10	—	—	—	—	−0.4 ± 0.19	0.37	—	—
Annualized systolic blood pressure, mm Hg/yr	0.19 ± 0.003	0.03	—	—	—	—	0.23 ± 0.004	0.043	—	—
Annualized valvuloarterial impedance, mm Hg/ml/m$^{2.04}$/yr	0.11 ± 0.08	0.28	—	—	—	—	—	—	0.11 ± 0.09	0.32

β Values are standardized raw-score regression coefficients ± SE. *Model 1 was adjusted for variables that were significantly associated with the progression of LVH on univariate analysis and other clinically relevant variables (i.e., age, sex, creatinine level, and baseline LVMi), regardless of their statistical significance; model 2 was model 1 + adjustment for systolic blood pressure and valvuloarterial impedance; model 3 was model 2 + adjustment for annualized changes in peak aortic jet velocity and systolic blood pressure; model 4 was model 2 + adjustment for annualized progression of valvuloarterial impedance.
LVH = left ventricular hypertrophy; LVMi = indexed left ventricular mass; other abbreviations as in Table 1.

Table 3. Predictors of Valvuloarterial Impedance Progression in Patients Without LVH at Baseline (N = 134)

Variable	Univariate Model		Multivariate Model*	
	β	p Value	β	p Value
Age, yrs	0.02 ± 0.00009	0.96	0.02 ± 0.0003	0.80
Male	−0.03 ± 0.004	0.33	−0.04 ± 0.003	0.12
Systolic blood pressure, mm Hg	−0.15 ± 0.0003	0.01	−0.04 ± 0.0003	0.41
HOMA index	0.13 ± 0.003	0.045	0.18 ± 0.003	0.003
Aortic valve calcification score ≥3	0.05 ± 0.004	0.09	0.03 ± 0.004	0.21
Peak aortic jet velocity, m/s	0.02 ± 0.01	0.71	0.06 ± 0.01	0.30
Valvuloarterial impedance, mm Hg/ml/m$^{2.04}$	−0.22 ± 0.003	0.0001	−0.26 ± 0.003	0.0003

β Values are standardized raw-score regression coefficients ± SE. *Adjusted for variables that were significantly associated with annualized change in valvuloarterial impedance on univariate analysis as well as other clinically relevant variables (i.e., age, sex, and peak aortic jet velocity).
Abbreviations as in Table 1.

dietary changes aimed at weight loss should be implemented in patients with a higher HOMA index and/or with a diagnosis of MetS or type 2 diabetes (6). Unfortunately, long-term compliance with lifestyle changes is difficult to achieve, and specific pharmacologic therapies directed toward an improvement in insulin sensitivity will have to be assessed in future studies. Furthermore, patients with a high HOMA index, MetS, and/or diabetes should receive close clinical and echocardiographic follow-up, given that they are at a higher risk for fast progression of valve stenosis, increased global LV hemodynamic load, and LVH.

Study limitations. Although patients with pre-existing LVH had poorer metabolic profiles and a higher prevalence of hypertension at baseline compared to those with no LVH, they nonetheless had no significant progression of LVH during follow-up and no significant association was found with HOMA index. These findings may be related to the following factors: 1) patients with a normal LV mass at baseline likely have a greater potential for LVH progression than do those with pre-existing LVH; and 2) the inability to detect statistically significant progression of LVH as well as a significant association with HOMA index in the subset of patients with pre-existing LVH may have been due to the interobserver/intraobserver variability in the measurement of LVMi, which has been reported to be higher in patients with greater LV mass (26).

In view of the relatively small number of patients included in this study, some subanalyses have limited statistical power. In particular, the lack of a statistically significant difference in LVMi between patients treated with statin versus those with placebo in the subgroup with HOMA >1.24 ($p = 0.18$) may have been due to a type II error.

Given that the need for statin therapy was a prespecified exclusion criterion in the ASTRONOMER trial, the results and conclusions of this substudy can be applied only to patients with no clinical indication for lipid-lowering therapy with a statin.

Myocardial strain was not measured in the ASTRONOMER study. Follow-up data of systolic and diastolic mitral annulus velocities by Doppler tissue imaging were available only in a small proportion of patients included in this study. Hence, the impact of insulin resistance on the progression of LV dysfunction could not be assessed.

CONCLUSIONS

Insulin resistance was a powerful and independent predictor of progression of LVH and global hemodynamic burden in these patients with AS. The effect of insulin resistance on LVH progression persisted after adjustment for AS severity, global LV hemodynamic load, and their progression during follow-up. The metabolic abnormalities linked to visceral obesity and, in particular, insulin resistance may thus present novel therapeutic targets in AS.

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Key Words: aortic stenosis ■ Doppler echocardiography ■ insulin resistance ■ obesity ■ statins.

▶APPENDIX

For the full list of ASTONOMER investigators, please see the online version of this article.