Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Data Collection

Clinical data

Clinical data included age, gender, height, weight, waist circumference, body surface area (BSA), body mass index (BMI), systolic and diastolic blood pressures, hypertension (patients receiving antihypertensive medications or having known but untreated hypertension [blood pressure ≥ 140/90 mm Hg]), history of smoking and randomization status (i.e. statin vs placebo). The clinical identification of patients with the features of the metabolic syndrome (MetS) was based on the modified criteria proposed by the National Cholesterol Education Program – Adult Treatment Panel III (1).

Doppler echocardiographic data

Randomly selected studies that contributed 10% of the total number of echocardiograms were reviewed to ensure that the studies and measurements were performed in accordance with the protocol.

Aortic valve morphology and function: The aortic valve (AV) phenotype (i.e. bicuspid vs. tricuspid) was recorded. The Doppler echocardiographic indices of CAVS severity included peak aortic jet velocity (V_{peak}), peak and mean transvalvular pressure gradients, and the aortic valve area (AVA) calculated by the standard continuity equation. The degree of AV calcification was scored according to the criteria proposed by Rosenhek et al (2).

Left ventricular geometry and function: LV ejection fraction (LVEF) was measured with the use of biplane Simpson method. As a measure of global LV hemodynamic load,

we calculated the valvulo-arterial impedance (5): $Z_{va}=(SBP+\Delta P_{mean})/SVi$ where SBP is the systolic blood pressure, ΔP_{mean} the mean transvalvular gradient, and SVi is the stroke volume indexed to a 2.04 power of height (4).

Laboratory data

The plasma levels of glucose, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and apolipoprotein B (apoB) were measured in fasting plasma samples using standardized techniques. LDL-C was corrected for the cholesterol content in Lp(a) using the following formula: corrected LDL-C = LDL-C – Lp(a) mass in mg/dl × 0.3.[1,2]

Using frozen plasma sample stored at -80°C, levels of OxPL-apoB-100, OxPL-apo(a) were measured with chemiluminescent ELISAs, as previously described in a subset of 220 patients from the ASTRONOMER trial (82% of the cohort).[3] Lp(a) was measured with a validated ELISA as previously described.[4,5]

eTable. Linear Association of Logarithmic-Transformed Lp(a), OxPL-apoB and OxPL-apo(a) Plasma Levels With CAVS Progression Rate

		Overall Group (n=220)			Patients ≤ 57 years (n=108)		
PROGRESSION RATE OF AS (I.E. ANNUALIZED V_{PEAK})							
	Univariable		Multivariable[#]		Univariable		Multivariable[§]	
	β Coefficient ±SE	*P* Value	β Coefficient ±SE	*P* Value	β Coefficient ±SE	*P* Value	β Coefficient ±SE	*P* Value
Log Lp(a)	0.12 ±0.02	.07	0.20 ±0.02	02	0.25 ±0.02	.008	0.31 ±0.03	.01
Log OxPL-apoB	0.15 ±0.02	.03	0.18 ±0.02	.03	0.27 ±0.03	.005	0.38 ±0.04	.002
Log OxPL-apo(a)	0.11 ±0.01	.09	0.17 ±0.01	.04	0.24 ±0.02	.01	0.31 ±0.02	.01
RISK OF RAPID AS PROGRESSION (I.E. ANNUALIZED VPEAK >0.20 M/S/YR)							
	Univariable		Multivariable[¶]		Univariable		Multivariable[‡]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Log Lp(a)	1.31 (1.00-1.72)	.047	1.39 (1.02-1.88)	.04	1.97 (1.27-3.08)	.003	2.53 (1.39-4.61)	.002
Log OxPL-apoB	1.35 (0.97-1.88)	.08	1.54 (1.06-2.24)	.03	1.98 (1.18-3.32)	.009	2.80 (1.39-5.65)	.004
Log OxPL-apo(a)	1.21 (0.99-1.49)	.06	1.26 (1.00-1.59)	.046	1.67 (1.20-2.34)	.003	2.05 (1.29-3.25)	.002

CAVS: calcific aortic valve stenosis; Log: logarithmic transformation; Lp(a): lipoprotein(a); OxPL: oxidized phospholipids; apoB: apolipoprotein B; apo(a): apolipoprotein (a); CAVS progression rate is defined by the annualized progression of peak aortic jet velocity; βeta coeff. is the standardized raw-score regression coefficient ±SE from the linear regression

analysis of the progression rate of AS (i.e. annualized Vpeak); OR is odds ratio with 95% confidence interval from the logistic regression analysis of the rapid progression rate of AS (i.e. annualized Vpeak >0.20 m/s/yr). Each multivariable model includes one metabolic variable and is adjusted for confounding variables as previously published. #: model adjusted for age, gender, hypertension, smoking history, metabolic syndrome, systolic blood pressure, statin use, corrected LDL-C, apoB, creatinine, bicuspid aortic valve phenotype, aortic valve calcification score, baseline peak aortic jet velocity, and valvulo-arterial impedance. **§:** model adjusted for the same variables as model #, except that age and smoking history were not included.¶: model adjusted for age, gender, hypertension, metabolic syndrome, statin use, corrected LDL-C, creatinine, bicuspid aortic valve phenotype, aortic valve calcification score, and baseline peak aortic jet velocity. ‡: model adjusted for the same variables as model ¶, except for age.

eAppendix. Investigators and Sites of the ASTRONOMER Trial

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