

# ApoB/ApoA-I Ratio is Associated With Faster Hemodynamic Progression of Aortic Stenosis: Results From the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis) Study

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**Background**—Previous studies reported that middle-aged patients with atherogenic lipoprotein-lipid profile exhibit faster progression of aortic valve stenosis (AS). The ratio of apolipoprotein B/apolipoprotein A-I (apoB/apoA-I) reflects the balance between atherogenic and anti-atherogenic lipoproteins. The aim of this study was to examine the association between apoB/apoA-I ratio and AS hemodynamic progression and to determine whether this association varies according to age.

**Methods and Results**—A total of 159 patients ( $66 \pm 13$  years, 73% men) with AS were prospectively recruited in the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis) study. Hemodynamic progression of AS was determined by the change in peak aortic jet velocity ( $V_{\text{peak}}$ ) measured by Doppler-echocardiography between baseline and 2-year follow-up. Patients in the top tertile of apoB/apoA-I ratio ( $\geq 0.62$ ) had a faster progression rate of AS compared with those in the bottom/mid tertiles ( $V_{\text{peak}}$  progression: 0.30 [0.09–0.49] versus 0.16 [0.01–0.36] m/s,  $P=0.02$ ). There was a significant interaction ( $P=0.007$ ) between apoB/apoA-I ratio and age. Among younger patients (ie, aged  $<70$  years; median value of the cohort), those in the top tertile of apoB/apoA-I ratio had a 3.4-fold faster AS progression compared with those in the bottom/mid tertiles ( $V_{\text{peak}}$  progression: 0.34 [0.13–0.69] versus 0.10 [–0.03–0.31] m/s,  $P=0.002$ ), whereas there was no significant difference between tertiles in the subgroup of older patients ( $P=0.83$ ). After comprehensive adjustment, higher apoB/apoA-I ratio was significantly associated with faster AS progression in the subset of younger patients (all, standardized  $\beta \geq 0.36$ ;  $P \leq 0.01$ ).

**Conclusions**—Higher apoB/apoA-I ratio is significantly associated with faster hemodynamic progression of AS in the younger patients. These findings suggest that atherogenic lipid factors may play a crucial role in the pathogenesis of AS in younger patients, but may be less important in older patients.

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**Key Words:** aging • aortic valve stenosis • apolipoprotein • echocardiography

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Accompanying Tables S1 through S4 and Figures S1 through S4 are available at <http://jaha.ahajournals.org/content/7/4/e007980/DC1/embed/inline-supplementary-material-1.pdf>

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Calcific aortic valve stenosis (AS) is the most common valvular disease in Western countries<sup>1</sup> and is characterized by progressive fibro-calcific remodeling of the aortic valve leaflets. Until recently, AS was considered as a purely passive degenerative process because of time-dependent wear and tear of the valve leaflets leading to passive calcium deposition. However, there is now compelling evidence suggesting that AS is an active and multifactorial disease involving numerous pathophysiological processes, such as atherosclerotic-like processes.<sup>1–5</sup> In this regard, well-known atherosclerotic risk factors, including age, male sex, smoking, hypertension, hypercholesterolemia, obesity, metabolic syndrome, diabetes mellitus, as well as elevated plasma level of lipoprotein(a) (Lp[a]) have been associated with the

## Clinical Perspective

### What Is New?

- This prospective study is the first to report a significant association between higher apoB/apoA-I ratio and faster hemodynamic progression of calcific AS in younger/middle-aged patients (ie, aged <70 years).
- Within a time frame of 2 years, at least two-thirds of younger/middle-age patients with mild AS and higher apoB/apoA-I ratio progressed to moderate or severe AS.
- The association of higher apoB/apoA-I ratio with faster AS progression was independent of other traditional cardiovascular risk factors.

### What Are the Clinical Implications?

- The ratio of apoB/apoA-I ratio is a good surrogate marker of the balance between pro-atherogenic and anti-atherogenic lipoproteins.
- The measurement of apoB/apoA-I ratio in clinical practice may be useful to enhance risk stratification in patients with AS, especially in younger/middle-aged patients.
- Further research is needed to determine whether apoB/apoA-I ratio is a marker of- or a contributor to- aortic valve disease progression and whether modifying this ratio would alter the disease progression rate.

development and/or progression of AS.<sup>6–14</sup> A recent Mendelian randomization study also suggests a causal association between elevated LDL-C and incidence of AS.<sup>15</sup> However, three randomized clinical trials failed to demonstrate any significant effect of statins to reduce the progression rate of AS or the occurrence of valve-related events, despite important reduction in LDL-C level.<sup>16–18</sup> Hence, it has been hypothesized that LDL-C could be involved mainly in the initiation and early stages of the disease but has less influence in the more advanced stages. Conversely, it is possible that genetically-determined elevated LDL-C level, which accelerates lifelong exposure, may lead to earlier and exacerbated phenotype. Therefore, in younger patients the measurement of lipid-derived factors would provide a better assessment of the AS risk and its progression.

A small retrospective study previously reported an association between faster hemodynamic progression of AS and higher total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio, an index of the overall balance between atherogenic and anti-atherogenic lipoproteins.<sup>19</sup> The ratio between apolipoprotein B (apoB) and apolipoprotein A-I (apoA-I) may provide a more accurate way to assess the balance of the pro-atherogenic properties of LDL particles and the anti-atherogenic properties of HDL particles. Previous studies, reported that younger patients with visceral obesity and

metabolic syndrome are at risk of faster AS progression.<sup>9,14</sup> These patients, typically have an increased apoB/apoA-I ratio.<sup>20</sup>

The aim of this prospective study was to examine the association between apoB/apoA-I ratio and hemodynamic progression rate of AS and to determine whether this association is influenced by age.

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Patient Population

The purpose and design of the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis) study were previously described.<sup>13,21</sup> Briefly, patients with at least mild AS are prospectively recruited and underwent a comprehensive Doppler echocardiography annually. Inclusion criteria were aged  $\geq 18$  years and peak aortic jet velocity ( $V_{\text{peak}}$ )  $> 2.0$  m/s. Patients were excluded if they had symptomatic AS, moderate or greater aortic regurgitation, significant mitral valve disease (ie, mitral stenosis or regurgitation), LV ejection fraction (LVEF)  $< 50\%$ , and if they were pregnant or lactating. The study was approved by the Ethics Committee at the Quebec Heart and Lung Institute and all patients signed a written informed consent. Among the 315 patients recruited until August 2016, 159 patients had reached 2-year follow-up and were included in the present analysis (Figure S1). The baseline characteristics of patients included versus excluded are presented in Table S1.

## Clinical Data

Clinical data included age, sex, height, weight, body surface area (BSA), body mass index, documented diagnoses of hypertension (patients on antihypertensive medications or with known but untreated hypertension [blood pressure  $\geq 140/90$  mm Hg]), dyslipidemia (patients receiving cholesterol-lowering medication, or in the absence of such medication, having a total plasma cholesterol level  $> 240$  mg/dL), smoking status, diabetes mellitus (patients receiving anti-diabetic medication, or in the absence of such medication, having a fasting glucose  $\geq 126$  mg/dL), and coronary artery disease (defined by history of myocardial infarction or coronary artery stenosis on coronary angiography). The clinical identification of patients with the features of the metabolic syndrome was based on the modified criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).<sup>22</sup>

## Laboratory Data

From fasting blood samples, plasma levels of glucose, creatinine, standard lipid profile, apoA-I and apoB were measured using automated techniques standardized with the Canadian reference laboratory. Plasma samples were also stored at  $-80^{\circ}\text{C}$  for future measurements, including the plasma level of Lp(a). LDL-C was corrected for the cholesterol content in Lp(a) using the formula:  $\text{LDL-corrected} = \text{LDL-C} - \text{Lp(a) mass in mg/dL} \times 0.3$ .<sup>14</sup>

## Doppler Echocardiographic Data

### *Aortic valve morphology and function*

The aortic valve phenotype (ie, bicuspid versus tricuspid aortic valve) was recorded. The Doppler-echocardiographic indices of AS severity included  $V_{\text{peak}}$ , mean transvalvular pressure gradient (MG), and aortic valve area calculated by the standard continuity equation and indexed to body surface area (AVAi).

### *Global LV hemodynamic load and LV function*

As a measure of global LV hemodynamic load, we calculated the valvulo-arterial impedance:  $Z_{\text{va}} = (\text{SBP} + \Delta P_{\text{mean}}) / \text{SVi}$ , where SBP is the systolic blood pressure,  $\Delta P_{\text{mean}}$  the mean transvalvular pressure gradient and SVi the stroke volume calculated in the LV outflow tract and indexed to body surface area.<sup>23</sup> LVEF was assessed using the biplane Simpson method.

## Study End Points

The primary end point for this study was the hemodynamic progression rate of AS measured as the change in  $V_{\text{peak}}$ : progression of  $V_{\text{peak}}$  was calculated as the difference between 2-year and baseline values. The secondary end point was the change in AS severity class (ie, change from mild to moderate or severe AS, or change from moderate to severe AS) during the 2-year follow-up.

## Statistical Analysis

Continuous data were expressed as mean  $\pm$  SD or median (interquartile range), and were tested for normality of distribution and homogeneity of variances with the Shapiro-Wilk and Levene tests, respectively. Continuous data were compared between the top tertile (ie,  $\geq 0.62$ ) and bottom and middle tertiles (ie,  $< 0.62$ ) of the apoB/apoA-I ratio with Student *t* test or Wilcoxon–Mann–Whitney test as appropriate. Categorical data were compared with the chi-square test or Fisher exact test as appropriate. Univariable and multivariable linear regression analyses were performed to examine

the association between apoB/apoA-I ratio and faster hemodynamic progression of AS. The log transformation of laboratory variables was used for each analysis including the variables in continuous format. Traditional risk factors and variables with a *P* value  $< 0.10$  in univariable analysis were included in the multivariable models. The variables entered in the multivariable models were age, sex, hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus, plasma levels of creatinine, corrected LDL-C and Lp(a), as well as baseline hemodynamic AS severity (ie, baseline  $V_{\text{peak}}$ ). Results were presented as standardized regression coefficients  $\pm$  standard error ( $\beta$  coeff.  $\pm$  SE). Univariable and multivariable logistic regression models were performed to determine the risk of progression to a more severe class of AS severity (ie, change from mild to moderate or severe AS, or change from moderate to severe AS). Results were reported as odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were done with Stata Software (V.14.2). A *P* value  $\leq 0.05$  was considered statistically significant.

## Results

### Population Characteristics

Baseline characteristics of the 159 patients included in this study are presented in Table 1. The mean age was  $66 \pm 13$  years, 73% were men, and 78% had a diagnosis of hypertension, 74% dyslipidemia, 32% metabolic syndrome, 22% diabetes mellitus, 35% coronary artery disease, and 15% were current smoker. The median levels of apoA-I, apoB and apoB/apoA-I ratio were 151 (132–170) mg/dL, 79 (69–100) mg/dL, and 0.53 (0.44–0.66), respectively. Seventy four percent of patients had mild ( $V_{\text{peak}} < 3.0$  m/s), 25% moderate ( $V_{\text{peak}} \geq 3.0$ – $3.9$  m/s), and 1% severe ( $V_{\text{peak}} \geq 4.0$  m/s) AS at baseline.

Compared with those in the middle and bottom tertiles of apoB/apoA-I ratio, patients in the top tertile were younger ( $63 \pm 13$  versus  $67 \pm 12$  years,  $P = 0.05$ ) and presented better overall cardiovascular risk profile, except for the prevalence of current smoking (Table 1). Patients in the top tertile of apoB/apoA-I ratio had also higher LDL-C, corrected LDL-C and triglycerides (all,  $P < 0.0001$ ), but lower Lp(a) and HDL-C (both,  $P \leq 0.0003$ ) (Table 1). With regards to the baseline echocardiographic data, there was no significant difference between patients in the top tertile versus those in the bottom and middle tertiles (Table 1).

### Association of ApoB/ApoA-I Ratio on AS Progression and Interaction With Age

After 2 years of follow-up, patients in the top tertile of apoB/apoA-I ratio had faster progression of AS compared with those

**Table 1.** Baseline Characteristics of the Study Population

	Entire Cohort (n=159)	ApoB/ApoA-I <0.62 Bottom and Middle Tertiles (n=106; 67%)	ApoB/ApoA-I ≥0.62 Top Tertile (n=53; 33%)	P Value
<b>Clinical</b>				
Age, y	66±13	67±12	63±13	0.05
Male, %	73	71	77	0.38
Height, cm	167±8	167±8	169±9	0.13
Weight, kg	79±15	78±15	81±15	0.23
Body surface area, m <sup>2</sup>	1.88±0.20	1.86±0.20	1.91±0.19	0.14
Body mass index, kg/m <sup>2</sup>	28±4	28±4	28±5	0.56
Waist circumference, cm	99±14	99±14	98±13	0.77
Systolic blood pressure, mm Hg	135±19	137±19	132±20	0.10
Diastolic blood pressure, mm Hg	75±10	74±10	76±9	0.37
Hypertension, %	78	84	66	0.01
Dyslipidemia, %	74	78	64	0.06
Smoking, %	15	9	26	0.005
Metabolic syndrome, %	32	30	38	0.30
Diabetes mellitus, %	22	26	13	0.06
Coronary artery disease, %	35	42	21	0.009
<b>Medication</b>				
Antihypertensive medication, %	58	67	42	0.002
ACE inhibitors, %	31	35	23	0.11
ARB, %	28	32	19	0.08
Statin, %	69	77	51	0.001
Antidiabetics, %	21	25	13	0.08
<b>Laboratory data</b>				
Total-C, mg/dL	164 (143–191)	153 (137–178)	190 (163–211)	<0.0001
LDL-C, mg/dL	84 (68–107)	79 (62–90)	110 (89–135)	<0.0001
Corrected LDL-C, mg/dL	76 (57–97)	67 (51–80)	105 (86–127)	<0.0001
Lp(a), mg/dL	15 (6–56)	24 (9–69)	12 (4–18)	0.0003
HDL-C, mg/dL	53 (46–64)	58 (49–66)	48 (40–54)	<0.0001
Triglycerides, mg/dL	108 (81–150)	96 (69–127)	146 (104–185)	<0.0001
Fasting glucose, mg/dL	95 (88–108)	95 (86–110)	95 (90–105)	0.88
Creatinine, mg/dL	0.92 (0.81–1.07)	0.94 (0.83–1.07)	0.89 (0.80–1.05)	0.32
apoA-I, mg/dL	151 (132–170)	160 (139–179)	137 (127–152)	<0.0001
apoB, mg/dL	79 (69–100)	74 (64–80)	104 (94–115)	<0.0001
apoB/apoA-I	0.53 (0.44–0.66)	0.48 (0.39–0.53)	0.75 (0.66–0.87)	...
<b>Doppler echocardiographic data</b>				
Bicuspid aortic valve, %	21	18	28	0.13
Peak aortic jet velocity, m/s	2.7±0.5	2.7±0.4	2.8±0.5	0.63
Mean transvalvular gradient, mm Hg	18±8	17±7	18±9	0.36
Aortic valve area, cm <sup>2</sup>	1.25±0.25	1.23±0.26	1.28±0.22	0.21
Indexed aortic valve area, cm <sup>2</sup> /m <sup>2</sup>	0.67±0.13	0.67±0.14	0.68±0.12	0.67

Continued

**Table 1.** Continued

	Entire Cohort (n=159)	ApoB/ApoA-I <0.62 Bottom and Middle Tertiles (n=106; 67%)	ApoB/ApoA-I ≥0.62 Top Tertile (n=53; 33%)	P Value
Valvulo-arterial impedance, mm Hg/mL per m <sup>2</sup>	3.6±0.7	3.7±0.7	3.6±0.7	0.29
LV ejection fraction, %	65±5	65±5	65±5	0.58

Values are mean±SD, %, or median (interquartile range). ACE indicates angiotensin-converting enzyme; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; ARB, angiotensin receptor blockers; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a) LV, left ventricular; Total-C, total cholesterol.

in the middle and bottom tertiles ( $V_{\text{peak}}$  progression: 0.30 [0.09–0.49] versus 0.16 [0.01–0.36] m/s,  $P=0.02$ ) (Figure 1A). When compared with patients in the middle versus those in the bottom tertile of apoB/apoA-I ratio, hemodynamic progression of AS was similar between both groups ( $P=0.72$ ) (Figure S2). We thus elected to merge together the bottom and middle tertiles for further analyses (Figure S2). In multivariable analysis adjusted for age, sex, hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus, plasma levels of corrected LDL-C, Lp(a), and creatinine, as well as baseline  $V_{\text{peak}}$ , top tertile of apoB/apoA-I ratio or apoB/apoA-I ratio as a continuous variable did not reach statistical significance for association with AS progression (both,  $P\leq 0.28$ ) (Table 2). Similar results were obtained with the analysis of the progression of MG or AVAi instead of the progression of  $V_{\text{peak}}$ .

There was a significant interaction between baseline apoB/apoA-I ratio and age for the progression of AS ( $P=0.007$ ), despite a similar hemodynamic progression rate of AS between younger (ie, aged <70 years [median age of the cohort],  $n=80$ ) and older (ie, aged ≥70 years,  $n=79$ ) patients ( $V_{\text{peak}}$  progression: 0.16 [0.01–0.43] versus 0.22 [0.04–0.46] m/s,  $P=0.86$ ). Indeed, in younger patients, those in the top tertile of apoB/apoA-I ratio had a 3.4-fold faster AS progression compared with patients in the middle/bottom tertiles ( $V_{\text{peak}}$  progression: 0.34 [0.13–0.69] versus 0.10 [–0.03–0.31] m/s,  $P=0.002$ ) (Figure 1B); whereas in older patients, there was no significant difference between patients in the top tertile versus those in the middle/bottom tertiles ( $V_{\text{peak}}$  progression: 0.21 [0.04–0.49] versus 0.22 [0.04–0.43] m/s,  $P=0.83$ ) (Figure 1C). The stenosis progression was similar in patients with a bicuspid aortic valve versus those with a tricuspid aortic valve ( $V_{\text{peak}}$  progression: 0.22 [0.05–0.40] versus 0.21 [0.01–0.44] m/s,  $P=0.65$ ). On multivariable analysis adjusted for sex, hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus, levels of corrected LDL-C, Lp(a), creatinine, and baseline  $V_{\text{peak}}$ , higher apoB/apoA-I ratio (ie, as tertiles or in continuous format) remained significantly associated with faster AS progression in the subset of younger patients (all,  $P\leq 0.01$ ) (Table 2). Further adjustment for the aortic valve phenotype (ie, bicuspid versus tricuspid aortic valve) or statin therapy instead of dyslipidemia provided comparable results. The results were also similar

when progression of MG and AVAi were analyzed instead of  $V_{\text{peak}}$  progression.

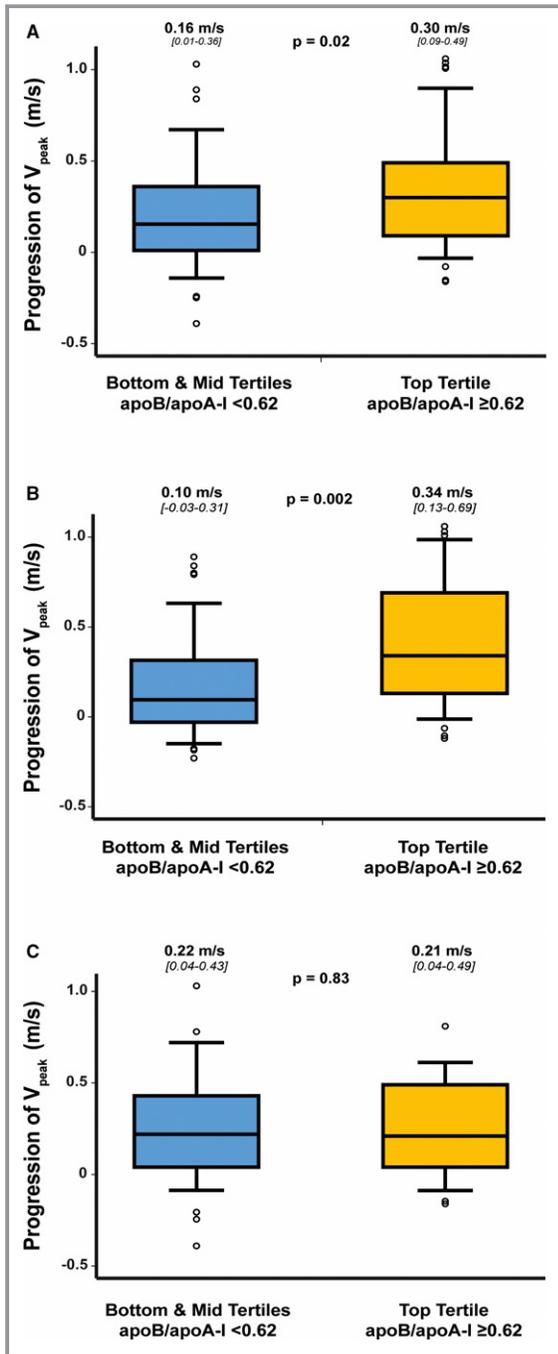
### Association of ApoB/ApoA-I Ratio on the Progression of AS Severity

During the 2-year follow-up, 44 (28%) patients progressed to a more severe class of AS severity. Thirty-seven (84%) patients changed from mild to moderate or severe AS, and 7 (16%) patients from moderate to severe AS (Figure 2). In the entire cohort, patients in the top tertile of apoB/apoA-I were at 2.4-fold increased risk (OR: 2.37; 95% CI: range 1.15–4.86];  $P=0.02$ ) to progress to higher severity class at 2 years compared with the other tertiles. After adjustment for age, sex and baseline  $V_{\text{peak}}$ , patients in the top tertile of apoB/apoA-I ratio remained at higher risk of the worsening of AS severity class ( $P=0.03$ ) (Figure 3).

In the subset of younger patients, being in the top tertile of apoB/apoA-I ratio significantly increased the risk of worsening of AS severity class (OR: 4.31; 95% CI: range 1.61–11.52;  $P=0.004$ ) (ie, 17 [63%] patients had a worsening of severity class), but not in the subset of older patients ( $P=0.75$ ). The adjustment for sex and baseline  $V_{\text{peak}}$  provided consistent results ( $P=0.005$ ; Figure 3). Similar results were obtained using apoB/apoA-I ratio in continuous format.

### Individual Effect of ApoB, ApoA-I, and Other Lipid Variables on AS Progression

In individual analysis, apoB/apoA-I ratio showed the strongest association with the progression of AS in the entire cohort and the subset of younger patients (Table S2). The analyses regarding the association between individual plasma levels of apoB and apoA-I and the progression of AS are presented in Figures S3 and S4, and Tables S3 and S4. In younger patients, those in the top tertile of apoB and apoA-I were at higher risk of faster AS progression compared with the middle and bottom tertiles (Figures S3B and S4B). After multivariable adjustment, baseline levels of apoB and apoA-I (in continuous format) remained significantly associated with AS progression (Tables S2 and S3).



**Figure 1.** Hemodynamic progression rate of aortic valve stenosis according to tertiles of apoB/apoA-I ratio. Comparison of progression of  $V_{\text{peak}}$  in the entire cohort ( $n=159$ ) (A), in patients with age  $<70$  years (ie, median age for the entire cohort;  $n=80$ ) (B), and in patients with age  $\geq 70$  years ( $n=79$ ) (C) according to top tertile of apoB/apoA-I ratio (ie,  $\geq 0.62$ ) vs bottom and middle tertiles (ie,  $<0.62$ ). The box shows the 25th to 75th percentiles, the median line on the box shows the median value, and the error bars the 10th and 90th percentiles; circles are outliers; the numbers of the top of the graph are median (25th percentile to 75th percentile). apoA-I indicates apolipoprotein A-I; apoB, apolipoprotein B;  $V_{\text{peak}}$ , peak aortic jet velocity.

## Discussion

The main finding of this study is that higher apoB/apoA-I ratio is significantly associated with faster hemodynamic progression of AS and the worsening of AS severity class over a 2-year follow-up period in younger patients. This finding reinforces the hypothesis that abnormal levels of LDL and/or HDL particles, as reflected by increased apoB/apoA-I ratio, are involved in the pathogenesis and progression of AS mainly in younger/middle-aged patients.

The results of the present study highlight the age-dependent effect of apoB/apoA-I ratio on AS progression in younger/middle-aged patients (aged  $<70$  years in this study). Higher ratio was associated with much faster AS progression rate and increased the risk of worsening of AS severity class over a 2-year follow-up, whereas, in older patients, this association was no longer present. These findings are in line with several previous studies reporting significant associations between lipid factors, such as LDL and Lp(a), and faster AS progression in the subset of younger or middle-aged patients but not in the older patients.<sup>4,14</sup> A potential hypothesis to explain this age-related difference is a survival bias.<sup>20,24,25</sup> This hypothesis is supported by a recent sub-analysis of the INTERHEART study, showing an inverse relationship between patient's age and the risk of myocardial infarction.<sup>25</sup> Exposure to atherogenic lipoproteins may predispose to early development of coronary artery and/or aortic valve disease and ensuing death or need for coronary artery bypass graft or aortic valve replacement, earlier in life. Elderly patients with AS often have more favorable lipid risk profile than younger patients, and in these patients other mechanisms, such as calcium-phosphorus metabolism, osteoporosis, and other age-related processes, may play a predominant role in the development and/or progression of the disease.<sup>20,26–28</sup>

The plasma level of apoB/apoA-I ratio is known to reflect the balance between pro- versus anti-atherogenic properties of lipoprotein particles.<sup>29,30</sup> Indeed, apoB is a key component of atherogenic lipoprotein particles,<sup>30</sup> whereas apoA-I is the major protein component of HDL particles, that have anti-atherogenic properties.<sup>31</sup> Hence, an increased ratio of apoB/apoA-I might reflect a predominance of pro-atherogenic effects over anti-atherogenic effects of lipoprotein lipids, thus contributing to lipid-mediated inflammation in the arteries and the valves. Experimental studies have reported an accumulation of apoB and several other apolipoproteins within surgically explanted stenotic aortic valves, suggesting an infiltration of atherogenic apoB-containing lipoproteins into the valve leaflets.<sup>32</sup> Interestingly, apoA-I was also found in explanted stenotic aortic valves.<sup>33</sup> The latter finding could be related to the modification of apoA-I by proteins such as matrix metalloproteinases, increasing its affinity to proteoglycans, and altering its reverse cholesterol transport function, leading to its accumulation

**Table 2.** Association Between apoB/apoA-I Ratio and Hemodynamic Progression of Aortic Valve Stenosis

	Entire Cohort (n=159)				Aged <70 y (n=80)				Aged ≥70 y (n=79)	
	Individual Analysis		Multivariable Analysis*		Individual Analysis		Multivariable Analysis†		Individual Analysis	
	β±SE	P Value	β±SE	P Value	β±SE	P Value	β±SE	P Value	β±SE	P Value
<b>Model with tertile</b>										
apoB/apoA-I (Tertile 3)	0.18±0.05	0.02	0.14±0.06	0.14	0.34±0.07	0.002	0.36±0.09	0.009	-0.02±0.07	0.84
<b>Model with continuous format</b>										
Log (apoB/apoA-I)	0.20±0.08	0.01	0.12±0.11	0.28	0.38±0.10	0.001	0.42±0.16	0.01	-0.04±0.11	0.71

β are standardized regression coefficient±SE.

\*Adjustment for age, sex, diagnosis of hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus, corrected LDL-C, Lp(a), creatinine level, and baseline  $V_{peak}$ .

†Multivariable adjustment for sex, hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus, corrected LDL-C, Lp(a), and baseline  $V_{peak}$ . apoA-I indicates apolipoprotein A-I; apoB, apolipoprotein B.

within tissues.<sup>33–36</sup> Therefore, this lipid accumulation and retention, may act as a “warning” signal triggering the pathophysiologic processes involved in the development and progression of AS.<sup>4,37</sup> To this effect, autotaxin transported by lipoproteins promotes the production of lysophosphatidic acid, a lipid metabolite that drives inflammation and an osteogenic program in the aortic valve.<sup>38,39</sup> An increased apoB/apoA-I ratio may also be a marker for small, dense lipoprotein particles.<sup>29,40,41</sup> High proportion of small, dense lipoproteins is one of the key features of visceral obesity and is closely associated with the hypertriglyceridemic state of insulin resistance.<sup>40</sup> Numerous studies have demonstrated that the small, dense lipoprotein particles have greater susceptibility to oxidation, a process promoting the inflammation and fibrocalcific remodeling of the aortic valve.<sup>42–44</sup> In the present study, we found a strong association between increased apoB/apoA-I ratio and faster hemodynamic progression of AS. Of note, we also previously reported an association between increased apoB/apoA-I ratio and the risk of structural degeneration of aortic bioprosthetic valves.<sup>45</sup> However, this previous study was not stratified by age.

A recent study using a Mendelian randomization design reported an association between the genetic predisposition for elevated LDL-C and the presence of aortic valve calcification as well as incident AS.<sup>15</sup> Previous studies have also reported an association of elevated serum LDL-C with development and faster progression of AS.<sup>6,46–48</sup> In the present study, higher apoB/apoA-I ratio was associated with faster AS progression independently of the level of LDL-C, which did not reach significance level. In patients with coronary artery disease, several studies reported that apoB/apoA-I ratio is a powerful predictor of adverse events and is superior to conventional lipid parameters, especially in patients with LDL-C within normal ranges.<sup>29,49,50</sup> In our study, the level of LDL-C was within normal limits in the vast majority of patients, and apoB/apoA-I ratio outweighed LDL-C to predict disease progression in this series. This could be

explained by the fact that apoB/apoA-I ratio captures both dyslipidemia and a dysmetabolic state often typified by lower HDL levels.

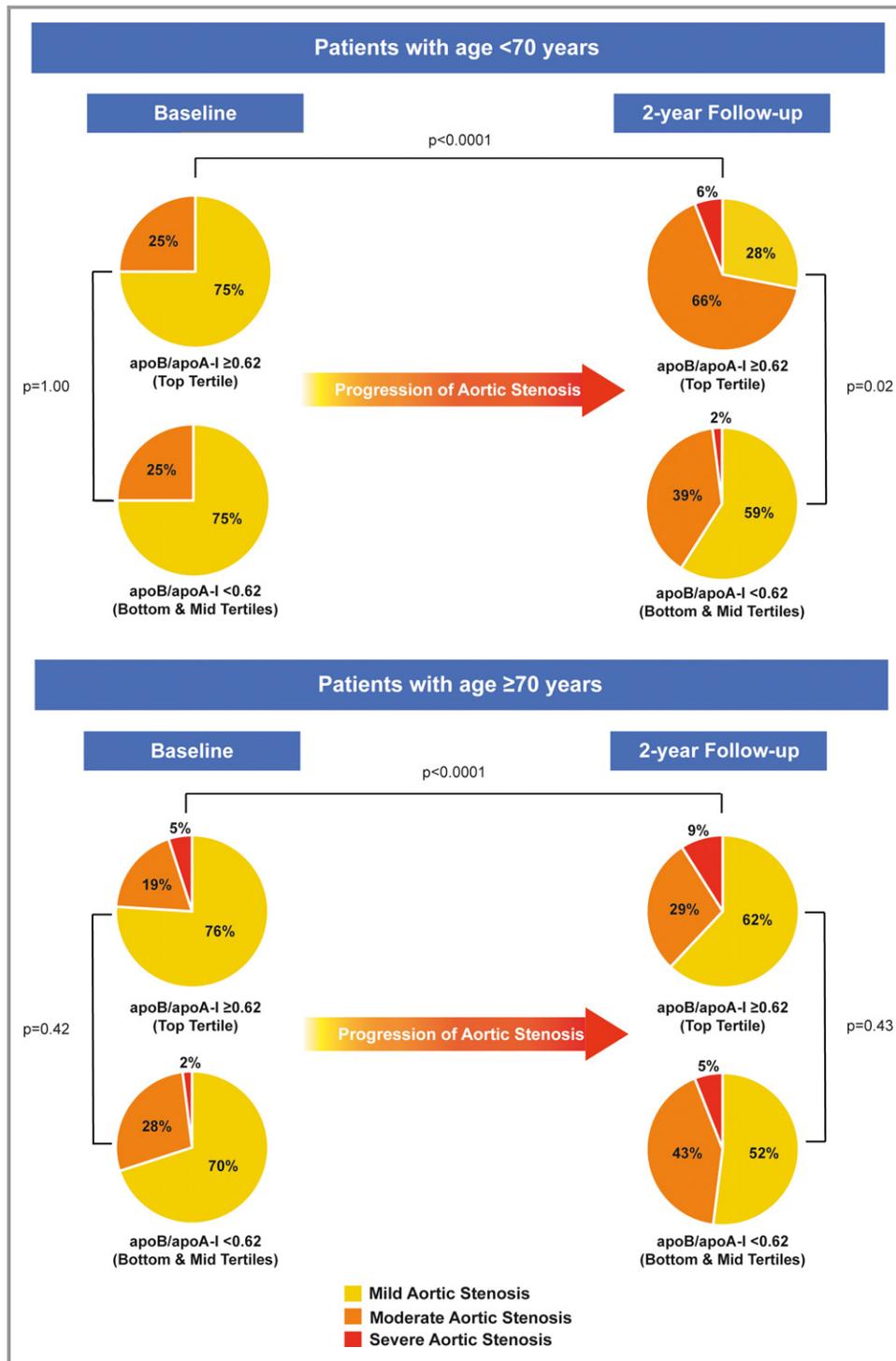
### Clinical Implications

There is compelling evidence suggesting that calcific AS is an active and multifaceted disease involving lipid deposition, chronic inflammation, and active mineralization.<sup>1,4,5</sup> However, three randomized clinical trials focused on lipid-lowering therapy to prevent AS progression have failed to demonstrate any benefit regarding AS progression or occurrence of AS-related events,<sup>16–18</sup> and currently there is no effective pharmacological therapy to slow the progression of AS. The lack of effect of statins on AS progression in these trials may be explained by: (1) the study populations included predominantly older patients with moderate AS; (2) the benefit of LDL-lowering by statins may have been counterbalanced by some negative effects including increase in insulin resistance and associated deterioration in LDL particle phenotype as well as increase in Lp(a) plasma levels; these factors have been shown to be associated with a faster progression rate of AS.<sup>9,14</sup>

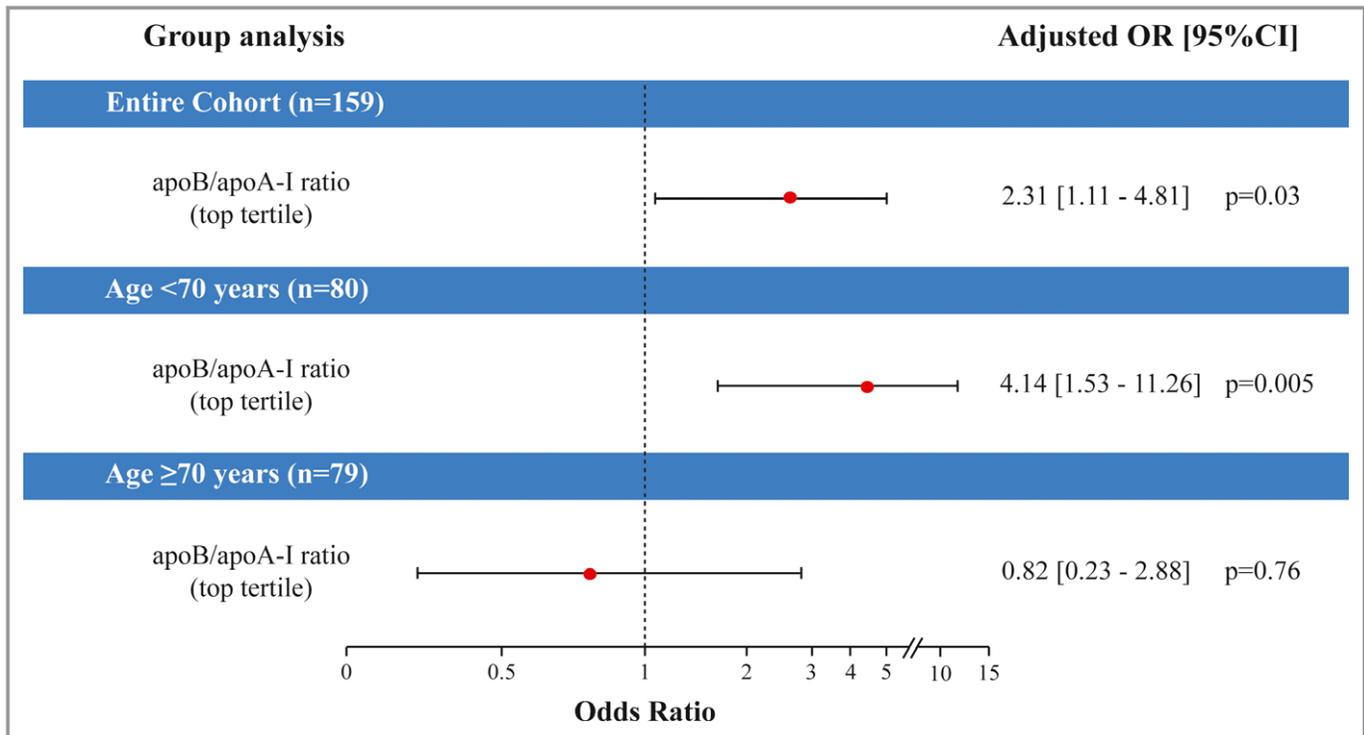
In this context, the results of this study may have important clinical implications. Indeed, independently of traditional risk factors, increased apoB/apoA-I ratio, which reflects altered lipid metabolism linked to visceral fat accumulation, predicts the progression rate of AS in younger patients. Though the present work does not establish a cause-and-effect relationship, it provides further impetus to investigate the links between lipids and visceral obesity-associated metabolic factors with the pathobiology of AS.

### Study Limitations

Our data were derived from a prospective observational cohort study, and a causality between higher apoB/apoA-I



**Figure 2.** Comparison of the change in severity class of aortic valve stenosis according to tertiles of apoB/apoA-I ratio and age. Baseline aortic valve stenosis severity was similar when comparing patients with higher (top tertile) vs those with lower (bottom/middle [mid] tertiles) plasma level of apoB/apoA-I ratio, in patients aged <70 years and patients aged ≥70 years, respectively. However, in the subset of patients aged <70 years, after 2 years of follow-up, those with higher apoB/apoA-I ratio had significant change in class of aortic valve stenosis severity. Indeed, at baseline, 75% of these patients had mild aortic valve stenosis, but only 28% remained with mild aortic valve stenosis after 2-year follow-up. While, in patients aged ≥70 years, those with higher apoB/apoA-I ratio did not have significant change in class of aortic valve stenosis severity when compared with those with lower apoB/apoA-I ratio. apoA-I indicates apolipoprotein A-I; apoB, apolipoprotein B;  $V_{peak}$ , peak aortic jet velocity.



**Figure 3.** Association of higher apoB/apoA-I ratio with the worsening of AS severity class. Risk of the worsening of AS severity class (ie, change from mild to moderate or severe defined as  $V_{\text{peak}} > 3.0$  m/s, or change from moderate to severe defined as  $V_{\text{peak}} \geq 4.0$  m/s) after 2 years of follow-up according to top tertile vs bottom and middle (mid) tertiles of apoB/apoA-I ratio, in the entire cohort, the patients aged <70 years, and the patients aged  $\geq 70$  years, respectively. In the entire cohort, the logistic regression analysis was adjusted for age, sex, and baseline  $V_{\text{peak}}$ . In both age groups, the analyses were adjusted for sex and baseline  $V_{\text{peak}}$ . CI indicates confidence interval; OR, odd ratio; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B;  $V_{\text{peak}}$ , peak aortic jet velocity.

ratio and AS progression cannot be established. In this low-risk cohort with mild-to-moderate AS, the rates of cardiac events were low and it was thus not possible to assess the association between higher apoB/apoA ratio and clinical events. Adjustment for the baseline value of the outcome in the analyses of change can be problematic when the exposure of interest is related to the baseline outcome value, leading to biased estimates of association of change in the outcome with the exposure.<sup>51</sup> In the present study, tertile of apoB/apoA-I ratio was unrelated to baseline AS severity, and the unadjusted association of the ratio with AS progression was similar to the adjusted association. Hence, the potential for biased estimates from baseline AS severity adjustment appears to be low.

## Conclusion

This prospective study is the first to report a significant association between increased apoB/apoA-I ratio and faster hemodynamic progression of AS in middle-aged patients. These findings further support the concept that lipid-mediated processes play a predominant role in disease progression in the younger/middle-aged patients, whereas other factors may

be involved in the elderly ones. Further studies are needed to elucidate whether apoB/apoA-I ratio is a causative factor or a marker in the initiation and progression of AS.

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## Disclosures

None.

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# **Supplemental Material**

**Table S1.** Baseline Characteristics of Included versus Excluded Patients.

	Included Patients (N = 159)	Excluded Patients (N = 156)	p Value
<b>Clinical</b>			
Age, years	66 ±13	63 ±15	0.15
Male, %	73	71	0.63
Height, cm	167 ±8	167 ±9	0.69
Weight, kg	79 ±15	81 ±16	0.21
Body surface area, m <sup>2</sup>	1.88 ±0.20	1.89 ±0.22	0.42
Body mass index, kg/m <sup>2</sup>	28 ±4	29 ±5	0.08
Waist circumference, cm	99 ±14	102 ±14	0.07
Systolic blood pressure, mmHg	135 ±19	134 ±17	0.10
Diastolic blood pressure, mmHg	75 ±10	76 ±8	0.33
Hypertension, %	78	74	0.45
Dyslipidemia, %	74	72	0.82
Smoking, %	15	6	<b>0.007</b>
Metabolic syndrome, %	32	46	<b>0.01</b>
Diabetes, %	22	27	0.31
Coronary artery disease, %	35	27	0.14
<b>Medication</b>			
Antihypertensive medication, %	58	54	0.47
ACE inhibitors, %	31	26	0.31
ARB, %	28	29	0.72
Statin, %	69	65	0.55
Antidiabetics, %	21	27	0.25
<b>Laboratory data</b>			
Total-C, mg/dl	164 (143 - 191)	168 (144 - 200)	0.47
LDL-C, mg/dl	84 (68 - 107)	84 (68 - 109)	0.94
Corrected LDL-C, mg/dl	76 (57 - 97)	74 (56 - 103) (75/156)	1.00
Lp(a), mg/dl	15 (6 - 56)	16 (4 - 45) (77/156)	0.45
HDL-C, mg/dl	53 (46 - 64)	56 (46 - 67)	0.64
Triglycerides, mg/dl	108 (81 - 150)	114 (82 - 158)	0.39
Fasting glucose, mg/dl	95 (88 - 108)	99 (92 - 115)	<b>0.006</b>
Creatinine, mg/dl	0.92 (0.81 - 1.07)	0.90 (0.80 - 1.06)	0.59
apoA-I, mg/dl	151 (132 - 170)	149 (134 - 170)	0.88
apoB, mg/dl	79 (69 - 100)	83 (70 - 99)	0.52
apoB/apoA-I	0.53 (0.44 - 0.66)	0.56 (0.46 - 0.67)	0.36
<b>Doppler echocardiographic data</b>			
Bicuspid aortic valve, %	21	27	0.26
Peak aortic jet velocity, m/s	2.7 ±0.5	2.8 ±0.7	0.17
Mean transvalvular gradient, mmHg	18 ±8	20 ±10	<b>0.04</b>
Aortic valve area, cm <sup>2</sup>	1.25 ±0.25	1.24 ±0.36	0.74
Indexed aortic valve area, cm <sup>2</sup> /m <sup>2</sup>	0.67 ±0.13	0.65 ±0.18	0.40

Valvulo-arterial impedance, mmHg/ml/m <sup>2</sup>	3.6 ±0.7	3.8 ±0.8	<b>0.03</b>
LV ejection fraction, %	65 ±5	64 ±6	0.14

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Value are mean ± SD, %, or median (interquartile range).

ACE = angiotensin-converting enzyme; apoA-I = apolipoprotein A-I; apoB = apolipoprotein B; ARB = angiotensin receptor blockers; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a) LV = left ventricular; Total-C = total cholesterol.

**Table S2.** Association between Lipid Variables and Hemodynamic Progression of Aortic Valve Stenosis.

	Entire Cohort (n = 159)		Age <70 years (n = 80)		Age ≥70 years (n = 79)	
	Individual Analysis		Individual Analysis		Individual Analysis	
	β ±SE	p Value	β ±SE	p Value	β ±SE	p Value
Log (LDL-C)	<b>0.18 ±0.07</b>	<b>0.03</b>	<b>0.23 ±0.10</b>	<b>0.04</b>	0.10 ±0.10	0.39
Log (Corrected LDL-C)	<b>0.18 ±0.05</b>	<b>0.02</b>	0.20 ±0.07	0.07	0.14 ±0.08	0.21
Log (Lp[a])	-0.03 ±0.02	0.67	0.03 ±0.03	0.82	-0.11 ±0.03	0.33
Log (HDL-C)	-0.06 ±0.10	0.43	<b>-0.22 ±0.15</b>	<b>0.05</b>	0.12 ±0.13	0.29
Log (TG)	0.09 ±0.05	0.24	0.13 ±0.07	0.25	0.02 ±0.09	0.86
Log (Total-C/HDL-C)	<b>0.19 ±0.09</b>	<b>0.02</b>	<b>0.32 ±0.13</b>	<b>0.004</b>	-0.006 ±0.14	0.96
Log (nonHDL-C/HDL-C)	<b>0.19 ±0.06</b>	<b>0.02</b>	<b>0.33 ±0.08</b>	<b>0.003</b>	-0.01 ±0.09	0.93
Log (TG/HDL-C)	0.10 ±0.04	0.23	0.18 ±0.05	0.10	-0.04 ±0.06	0.70
Log (apoB/apoA-I)	<b>0.20 ±0.08</b>	<b>0.01</b>	<b>0.38 ±0.10</b>	<b>0.001</b>	-0.04 ±0.11	0.71

β are standardized regression coefficient ± SE. Text in bold highlights the statistically significant associations.

apoA-I = apolipoprotein A-I; apoB = apolipoprotein B; C = cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp[a] = lipoprotein(a); TG = triglycerides.

**Table S3.** Association between apoB and Hemodynamic Progression of Aortic Valve Stenosis.

	Entire Cohort (n = 159)				Age <70 years (n = 80)				Age ≥70 years (n = 79)	
	Individual Analysis		Multivariable Analysis*		Individual Analysis		Multivariable Analysis <sup>†</sup>		Individual Analysis	
	β ±SE	p Value	β ±SE	p Value	β ±SE	p Value	β ±SE	p Value	β ±SE	p Value
<i>Model with tertile</i>										
apoB (Top Tertile)	0.08 ±0.05	0.31	0.12 ±0.06	0.15	0.20 ±0.08	0.08	<b>0.27 ±0.08</b>	<b>0.04</b>	-0.07 ±0.07	0.52
<i>Model with continuous format</i>										
Log (apoB)	<b>0.19 ±0.09</b>	<b>0.02</b>	<b>0.22 ±0.10</b>	<b>0.01</b>	<b>0.28 ±0.12</b>	<b>0.01</b>	<b>0.40 ±0.15</b>	<b>0.003</b>	0.06 ±0.13	0.58

β are standardized regression coefficient ± SE. \*Multivariable adjustment for age, sex, diagnosis of hypertension, dyslipidemia, metabolic syndrome, diabetes, lipoprotein(a), creatinine level, and baseline  $V_{\text{peak}}$ . <sup>†</sup>Multivariable adjustment for sex, hypertension, dyslipidemia, metabolic syndrome, diabetes, lipoprotein(a), and baseline  $V_{\text{peak}}$ .

apoB = apolipoprotein B.

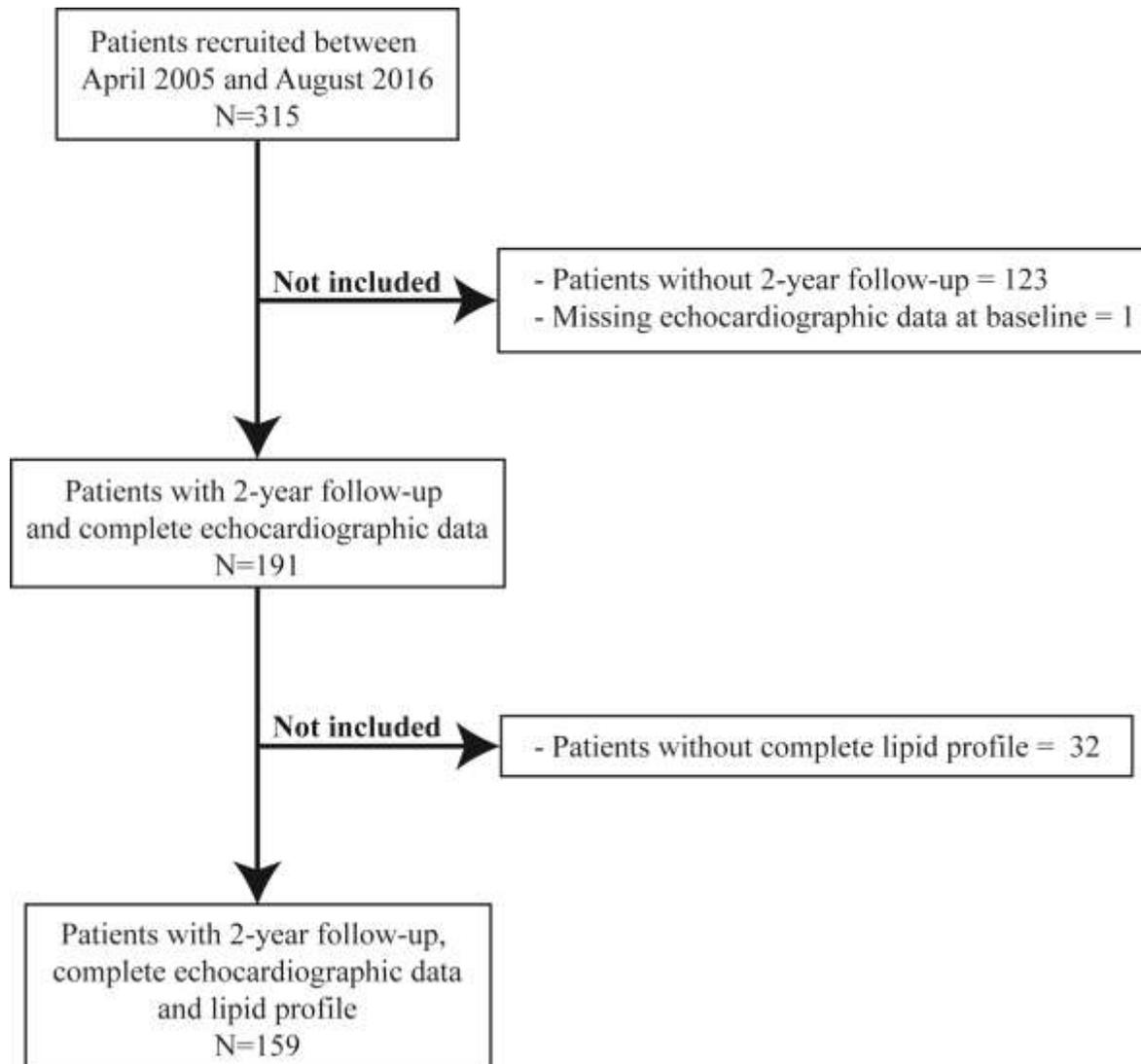
**Table S4.** Association between apoA-I and Hemodynamic Progression of Aortic Valve Stenosis.

	Entire Cohort (n = 159)				Age <70 years (n = 80)				Age ≥70 years (n = 79)	
	Individual Analysis		Multivariable Analysis*		Individual Analysis		Multivariable Analysis†		Individual Analysis	
	beta ±SE	p Value	beta ±SE	p Value	beta ±SE	p Value	beta ±SE	p Value	beta ±SE	p Value
<b><i>Model with tertile</i></b>										
apoA-I (Bottom & Mid Tertiles)	0.07 ±0.05	0.40	0.08 ±0.05	0.33	<b>0.27 ±0.08</b>	<b>0.01</b>	<b>0.29 ±0.09</b>	<b>0.02</b>	-0.17 ±0.07	0.14
<b><i>Model with continuous format</i></b>										
Log (apoA-I)	-0.07 ±0.14	0.36	-0.08 ±0.15	0.38	<b>-0.28 ±0.21</b>	<b>0.01</b>	<b>-0.30 ±0.24</b>	<b>0.02</b>	0.16 ±0.18	0.15

beta are standardized regression coefficient ± SE. \*Multivariable adjustment for age, sex, diagnosis of hypertension, dyslipidemia, metabolic syndrome, diabetes, lipoprotein(a), creatinine level, and baseline  $V_{peak}$ . †Multivariable adjustment for sex, hypertension, dyslipidemia, metabolic syndrome, diabetes, lipoprotein(a), and baseline  $V_{peak}$ .

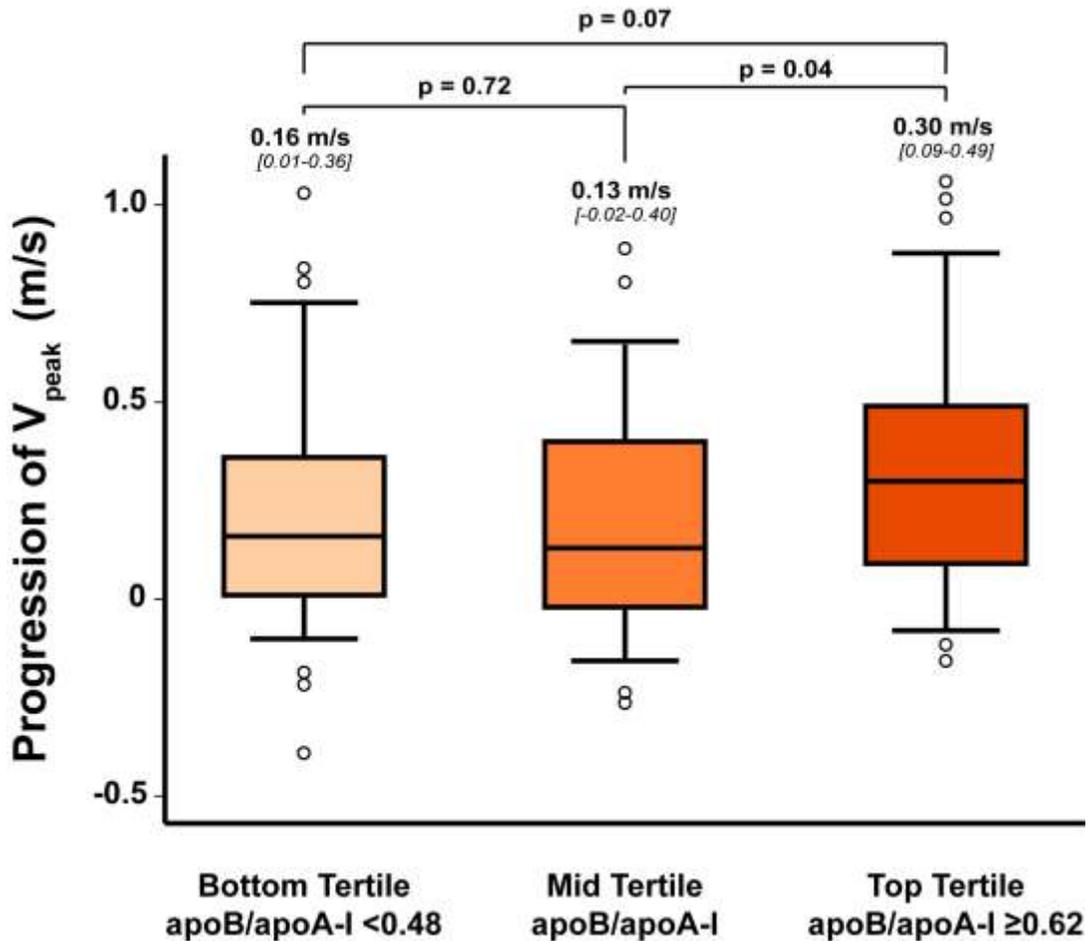
apoA-I = apolipoprotein A-I.

**Figure S1.** Study Flow Chart



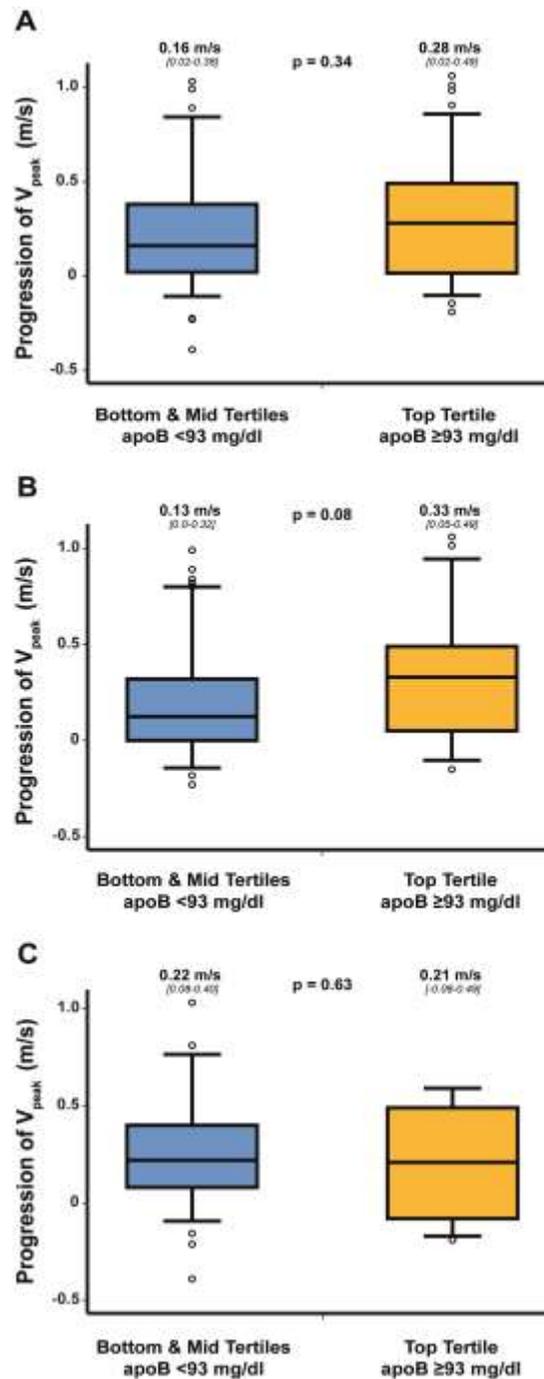
Description of the inclusion of the study population.

**Figure S2.** Hemodynamic Progression of Aortic Valve Stenosis According to Tertiles of apoB/apoA-I.



Comparison of the progression of  $V_{peak}$  according to tertiles of apoB/apoA-I ratio in the entire cohort. The box shows the 25<sup>th</sup> to 75<sup>th</sup> percentiles, the median line on the box shows the median value, and the error bars the 10<sup>th</sup> and 90<sup>th</sup> percentiles; circles are outliers; the numbers of the top of the graph are median [25<sup>th</sup> percentile - 75<sup>th</sup> percentile]. apoA-I = apolipoprotein A-I; apoB = apolipoprotein B;  $V_{peak}$  = peak aortic jet velocity.

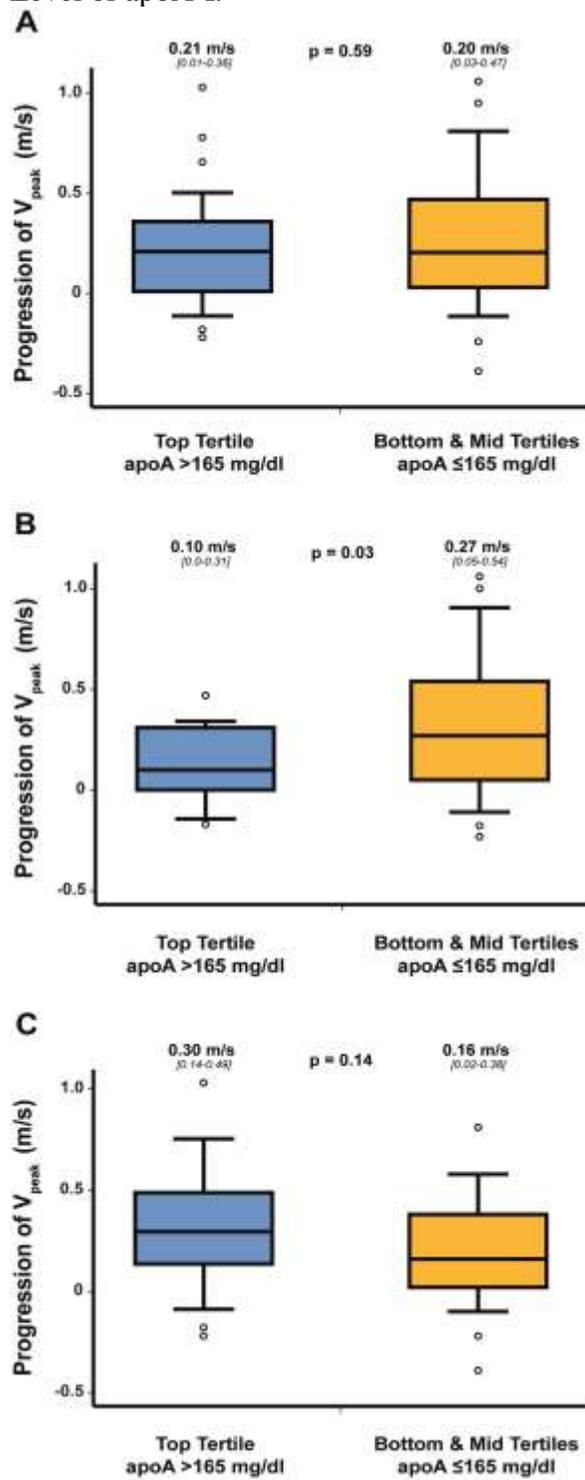
**Figure S3.** Hemodynamic Progression of Aortic Valve Stenosis According to Tertiles of Plasma Level of apoB.



Comparison of progression of  $V_{peak}$  in the whole cohort ( $n = 159$ ) (A), in patients with age <70 years (i.e. median age for the whole cohort) ( $n = 80$ ) (B), and in patients with age  $\geq 70$  years ( $n = 79$ ) (C) according to top tertile of apoB (i.e.  $\geq 93$  mg/dl) versus bottom and mid tertiles (i.e. <93 mg/dl).

apoB = apolipoprotein B;  $V_{peak}$  = peak aortic jet velocity.

**Figure S4.** Hemodynamic Progression of Aortic Valve Stenosis According to Tertiles of Plasma Level of apoA-I.



Comparison of progression of  $V_{\text{peak}}$  in the whole cohort ( $n = 159$ ) **(A)**, in patients with age  $<70$  years **(B)**, and in patients with age  $\geq 70$  years **(C)** according to bottom and mid tertiles of apoA-I (i.e.  $\leq 165$  mg/dl) versus top tertile (i.e.  $>165$  mg/dl).

apoA-I = apolipoprotein A-I;  $V_{\text{peak}}$  = peak aortic jet velocity.