

Interaction of Age With Lipoproteins as Predictors of Aortic Valve Calcification in the Multi-Ethnic Study of Atherosclerosis

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Background: Previous epidemiologic studies have shown that low-density lipoprotein is an independent risk factor for prevalent aortic valve calcification (AVC); however, to our knowledge, the interactions between plasma lipoprotein concentrations and age on the relative risks (RRs) for AVC prevalence and severity have not been examined in a large, racially and ethnically diverse cohort.

Methods: Using stepwise RR regression, the relationships of baseline fasting lipid levels and lipoprotein levels to baseline prevalence and severity of AVC were determined in 5801 non-statin-using participants in the Multi-Ethnic Study of Atherosclerosis (MESA).

Results: In age-stratified, adjusted analyses, the low-density lipoprotein-associated RRs (95% confidence intervals) for prevalent AVC were higher for younger compared with older participants (age 45-54 years, 1.69 [1.19-2.39]; age 55-64 years, 1.48 [1.24-1.76]; age 65-74 years, 1.09 [0.95-1.25]; and age 75-84 years, 1.16 [0.99-1.36]; *P* interac-

tion = .04]. There was a similar, significant interaction of age with total cholesterol-associated RR for prevalent AVC (*P* interaction = .04). In contrast, total- to high-density lipoprotein cholesterol ratio RRs were similar across all age strata (*P* interaction = .68). At multivariate analyses, no lipoprotein parameter was associated with AVC severity.

Conclusions: In this racially and ethnically diverse, pre-clinical cohort, low-density lipoprotein was a risk factor for AVC only in participants younger than 65 years, whereas the total cholesterol/high-density lipoprotein cholesterol ratio was associated with a modest increased risk of AVC across all ages. These findings may have important implications for the efficacy of and targets for dyslipidemia therapies in calcific aortic valve disease.

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CALCIFIC DEGENERATION OF the aortic valve, in the form of either aortic sclerosis or stenosis, is a common feature of aging and is associated with substantial morbidity and mortality.^{1,2} The presence of aortic sclerosis (ie, valvular calcification without hemodynamic obstruction) is associated with a 50% increase in the risk of cardiovascular events,² and the severity of calcification predicts worsened clinical outcome.³ However, while pathologic calcification is the defining feature of advanced degeneration, early-stage valvular lesions share many histologic similarities with vascular atherosclerosis, including lipid accumulation,^{4,5} inflammatory infiltrates,⁶⁻⁸ and the presence of renin-angiotensin system components.⁹ Epidemiologic studies also have suggested associations between aortic valve disease

and traditional cardiovascular risk factors, including male sex, smoking, hypertension, hyperlipidemia,^{10,11} and diabetes mellitus.^{10,12,13} Recently, metabolic syndrome also has been associated with increased prevalence¹³ and rate of progression¹⁴ of calcific aortic valve disease.

These findings, bolstered by retrospective analyses that infer a beneficial effect of statin use,¹⁵⁻¹⁹ have led to the hypothesis that statin therapy may reduce the morbidity and mortality associated with advanced aortic valve degeneration, akin to the benefits noted for coronary and peripheral vascular disease. However, the only randomized, placebo-controlled test of this hypothesis to date, the 155-participant SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) study, demonstrated no benefit of statin therapy in curbing the progressive natural history of the disease.²⁰ It is unclear whether these

null results were because of patient selection, small sample size, suboptimal timing or duration of therapy, or repudiation of the hypothesis.

One possibility is that statin therapy may be of little benefit in aortic valve disease if low-density lipoprotein cholesterol (LDL-C) is a weak risk factor in elderly patients such as those studied in SALTIRE.²⁰ The relationship between LDL-C and aortic valve calcification (AVC) was relatively weak in the Cardiovascular Health Study,¹¹ in which all participants were aged 65 years or older. Moreover, previous studies of coronary artery disease have consistently demonstrated an attenuation in LDL-C-associated risk with advancing age.²¹⁻²³

We reexamined the strengths of the relationship between total cholesterol (TC) level, lipoprotein levels, and AVC, with particular attention to the influence of age on AVC relative risk (RR). To test this association, we examined cross-sectional data from the Multi-Ethnic Study of Atherosclerosis (MESA), including baseline fasting lipoprotein levels and AVC scores, as determined using cardiac computed tomography (CT).

METHODS

STUDY POPULATION

The MESA trial was initiated by the National Heart, Lung, and Blood Institute to characterize subclinical cardiovascular disease and its progression. A full description of the design and recruitment process has been reported previously.²⁴ A total of 6814 free-living individuals without clinically apparent cardiovascular disease, aged 45 to 84 years, were recruited from 6 US communities, including Baltimore, Maryland (city and county); Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St Paul, Minnesota, between July 2000 and August 2002. Recruitment targeted 4 racial/ethnic groups: white, black, Hispanic, and Chinese. Participants were excluded if they had self-reported cardiovascular disease, including angina, or had undergone cardiovascular procedures such as percutaneous coronary interventions, coronary bypass or valvular surgery, or pacemaker or defibrillator implantation. The institutional review boards at each participating institution approved MESA, and each participant provided informed written consent before enrollment in the study.

Of the 6814 participants in MESA, 26 did not have cholesterol profiles and were, therefore, excluded from the study. To limit potential effect modification, the 987 subjects taking statins were also excluded. Thus, there were 5801 participants for these analyses. Baseline testing for and definitions of cardiovascular risk factors, including diabetes, hypertension, and impaired fasting glucose concentration, have been described previously.¹³

MEASUREMENTS

Lipoproteins

After a 12-hour fast, all participants had plasma samples drawn, prepared, and stored. Concentrations of TC, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured in a central lipid laboratory at Fairview-University Medical Center, Minneapolis, Minnesota, using the cholesterol oxidase method and a centrifugal analyzer (COBAS FARA; Roche Diagnostics, Indianapolis, Indiana). Full details of lipid quan-

tification have been reported previously.²⁵ Low-density lipoprotein cholesterol concentrations were estimated using the Friedewald equation.²⁶ Non-HDL-C and TC/HDL-C ratios were calculated from these primary data.

Aortic Valve Calcification

All participants underwent cardiac CT as part of MESA. Three institutions performed electron beam tomography (Imatron C150 scanner; GE Medical Systems, Milwaukee, Wisconsin), and 3 institutions used multidetector CT scanners (4-slice). Spatial resolution was 1.38 mm³ for electron-beam tomography (0.68 × 0.68 × 3.00 mm) and 1.15 mm³ for the multidetector CT (0.68 × 0.68 × 2.50 mm). Full details about the equipment, scanning methods, and quality control in MESA, including image calibration and interscanner reproducibility between the 2 scanning methods, have been reported previously.^{27,28}

All studies were sent to a central MESA CT scan reading center (Harbor-UCLA Research and Education Institute, Los Angeles, California), where they were retrospectively analyzed for AVC by a single blinded reader (J.T.) using the same method for all studies. Calcium strongly attenuates radiographs, appears bright on CT scans, and is easily differentiated from surrounding tissue. Aortic valve calcification was defined as any calcified lesion within the aortic valve leaflets, consistent with the definition of AVC used in other studies by our group.²⁹⁻³¹ Lesions involving the aortic annulus, sinuses, wall of the ascending aorta, or coronary arteries were not classified as AVC.²⁹⁻³¹ For each individual lesion, AVC was quantified using the method of Agatston et al,³² which factors in both lesion area and Hounsfield unit brightness, a reflection of calcium density. Single-lesion measurements were then summed to give an overall Agatston score. If aortic valve calcium was absent, the Agatston score was recorded as zero.

Demographic Information

Participant demographic data and medical history including medication use were obtained by questionnaire. While participants reporting cardiovascular disease were excluded from the study, screening for subclinical aortic stenosis was not specifically performed. Race/ethnicity was self-reported and those who identified themselves as white, black, Hispanic, or Chinese were eligible for inclusion.

Data Analyses

Participants were categorized by the presence or absence of AVC, and differences between the baseline characteristics of these groups were determined using *t* tests for continuous variables and χ^2 analysis for categorical variables. Severity of AVC was determined using the log transformation of Agatston scores.

Because the prevalence of calcification was more than 10% in the cohort, odds ratios overestimate RR. Therefore, RR estimates are presented from the regression model $y = \exp(X^T\beta)$. The exponentiated parameters are interpreted as RRs. We assumed gaussian error and used robust standard error estimates. Because AVC scores required log transformation based on the nature of the underlying data structure, the percent change in AVC score was calculated per unit increase in normalized risk factors. Risk factors were normalized by dividing their values by their standard deviations.

Statistical analyses were performed with commercially available software (SPSS for Windows, version 13.0.1; SPSS Inc, Chicago, Illinois; or STATA for Windows, version 8.0; StataCorp, College Station, Texas). Statistical significance was defined as $P < .05$, and RRs are reported with 95% confidence intervals.

Table 1. Baseline Characteristics Stratified by Aortic Valve Calcification AGS

Characteristic	No. (%) of Participants		P Value
	AGS=0 (n=5101)	AGS>0 (n=700)	
Age, mean (SD), y	60.3 (9.9)	70.4 (8.2)	<.001
Female sex, No. (%)	2792 (55)	269 (38)	<.001
Race, No. (%)			
White	1872 (37)	314 (45)	<.001
Chinese	654 (13)	46 (7)	
Black	1425 (28)	178 (25)	
Hispanic	1150 (23)	162 (23)	
Cholesterol level, mean (SD), mg/dL			
TC	196.0 (35.2)	198.9 (38.6)	.06
LDL-C	119.1 (30.9)	122.9 (34.7)	.006
HDL-C	51.4 (15.1)	48.3 (14.6)	<.001
Triglycerides	129.3 (91.3)	138.2 (73.1)	.01
Non-HDL-C	144.6 (35.7)	150.6 (37.7)	<.001
TC/HDL-C ratio	4.1 (1.3)	4.4 (1.2)	<.001
Diabetes mellitus, No. (%)			
Normal	3124 (61)	355 (51)	<.001
Impaired fasting glucose	1371 (27)	199 (29)	
Untreated	213 (4)	39 (6)	
Treated	376 (7)	102 (15)	
Hypertension, No. (%)	1991 (39)	425 (61)	<.001
Smoking status, No. (%)			
Never	2614 (51)	305 (44)	<.001
Former	1758 (35)	315 (45)	
Current	711 (14)	78 (11)	
CRP, ^a median (IQR), mg/L	1.92 (0.83-4.37)	2.18 (1.01-4.24)	.09
Medication use, No. (%)			
ACE inhibitor	465 (9)	121 (17)	<.001
β-Blocker	373 (7)	82 (12)	<.001
Calcium channel blocker	488 (10)	117 (17)	<.001
Aspirin	1044 (21)	242 (35)	<.001
Hip circumference, mean (SD), cm	105.5 (11.6)	104.9 (10.4)	.17
BMI, mean (SD)	28.2 (5.6)	28.3 (5.0)	.69

Abbreviations: ACE, angiotensin-converting enzyme; AGS, Agatston score; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

SI unit conversions: To convert all cholesterol levels to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; C-reactive protein to nanomoles per liter, multiply by 9.524.

^aMedian (interquartile range).

RESULTS

PARTICIPANT CHARACTERISTICS

The MESA cohort included in these analyses comprised 5801 subjects with a mean age of 62 years (age range, 45-84 years). Of this cohort, 3061 participants (53%) were women, while 2186 participants (38%) were white, 1603 (28%) were black, 1312 (23%) were Hispanic, and 700 (12%) were Chinese. Seven hundred thirty participants (13%) had diabetes, with impaired fasting glucose levels in 1570 (27%), hypertension in 2416 (42%), current smoking for 789 (14%), and former smoking for 2073 (36%). At baseline, of these participants not receiving statin therapy, few (586 [10%]) were taking angiotensin-converting enzyme inhibitors or β-blockers (455 [8%]).

The mean (SD) lipoprotein levels were as follows: TC, 196 (36) mg/dL; LDL-C, 120 (31) mg/dL; HDL-C, 51 (15) mg/dL; triglycerides, 130 (89) mg/dL; non-HDL-C, 145 (36) mg/dL; and TC/HDL-C ratio, 4.1 (1.3). (To convert all cholesterol values to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.) Aortic valve calcification, that is, an Agatston score higher than zero, was present in 700 participants (12%). This group had a median Agatston score of 57 (interquartile range, 18-148).

The baseline characteristics of the study population, stratified by the presence (Agatston score >0) or absence (Agatston score 0) of AVC, are given in **Table 1**. Participants with AVC were older, were more likely to be white men, had higher prevalences of diabetes and hypertension, and were more likely to be taking cardiovascular medications than were those without AVC. While differences in TC levels were not statistically significant, there were significant between-group differences in all lipoprotein subclasses, including LDL-C, HDL-C, triglycerides, and non-HDL-C levels, and the TC/HDL-C ratio.

PREVALENCE OF AVC AND LIPOPROTEINS

Univariate Analyses

The associations between lipoprotein quartiles and the presence of AVC are given in **Table 2**, and the corresponding quartile cutoff values are given in **Table 3**. Univariate predictors of the presence of AVC include LDL-C, HDL-C, and triglyceride levels, and the TC/HDL-C ratio. The TC level was not a univariate predictor of the presence of AVC.

Multivariate Analyses

Because age interacted with LDL-C-associated RR for prevalent AVC (*P* interaction = .04), all lipoprotein analyses were age-stratified in stepwise multivariate regressions (**Figure**), with adjustments for sex, race/ethnicity, site of enrollment, body mass index, smoking status, diabetes, hypertension, and medication use. There were no significant interactions between age and any of the other lipoprotein-associated RRs examined. No significant interactions were found for sex (*P* interaction = .39) or race/ethnicity (*P* interaction = .45).

Total Cholesterol. The fully adjusted TC-associated RR for prevalent AVC was higher in younger participants compared with older participants (*P* interaction = .04; **Figure, A**).

Low-Density Lipoprotein. The fully adjusted LDL-C-associated RR for prevalent AVC was also higher in younger compared with older participants (*P* interaction = .04; **Figure, B**).

High-Density Lipoprotein. In contrast, HDL-C was not associated with RR for prevalent AVC in participants younger than 65 years (**Figure, C**). Rather, HDL-C was associated with decreased RR for AVC in participants aged 65 to 74 years and 75 to 84 years, though the RR did not reach significance in the latter group.

Table 2. Prevalence of Aortic Valve Calcification (AGS > 0) Stratified by Lipoprotein Quartiles

Lipoprotein Factor	Quartile, No. (%)				P Value for Linear Trend
	1	2	3	4	
TC	141 (11)	182 (13)	175 (12)	199 (13)	.14
LDL-C	139 (11)	173 (12)	173 (12)	208 (14)	.04
HDL-C	239 (16)	173 (12)	152 (10)	133 (10)	<.001
Triglycerides	143 (10)	162 (11)	189 (13)	203 (15)	<.001
Non-HDL-C	123 (9)	169 (12)	197 (13)	208 (14)	<.001
TC/HDL-C ratio	115 (8)	149 (11)	185 (13)	248 (16)	<.001

Abbreviations: AGS, Agatston score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant; TC, total cholesterol.

Table 3. Quartile Cutoff Values

Lipoprotein Factor	Quartile			
	1	2	3	4
TC, mg/dL	≤ 170	171-192	193-215	≥ 216
LDL-C, mg/dL	≤ 96	97-116	117-136	≥ 137
HDL-C, mg/dL	≤ 40	41-48	49-59	≥ 60
Triglycerides, mg/dL	≤ 78	79-111	112-161	≥ 162
Non-HDL-C, mg/dL	≤ 119	120-141	142-164	≥ 165
TC/HDL-C ratio	≤ 3.18	3.19-3.92	3.93-4.78	≥ 4.79

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. SI conversion factors: To convert all cholesterols to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

Triglycerides. In addition, triglyceride levels were not associated with RR for prevalent AVC in participants younger than 65 years (Figure, D). However, triglyceride levels were associated with increased RR for AVC in participants aged 65 to 74 years and 75 to 84 years, although, again, the RR did not reach significance in the latter group.

Total Cholesterol to HDL-C Ratio. Overall, the most consistent relationship of a lipoprotein variable with AVC risk was the TC/HDL-C ratio (Figure, E). The TC/HDL-C ratio RRs were similar across all age strata (*P* interaction = .68), though the RR did not reach significance in the youngest group.

AVC SEVERITY AND LIPOPROTEIN LEVELS

Univariate Analyses

To examine the relationship between individual lipoprotein factors and AVC severity, the log(Agatston score) for each of the lipoprotein quartiles was examined (**Table 4**). Only TC showed a linear trend in AVC severity with increasing lipoprotein levels.

Multivariate Analyses

To exclude the possibility of masked interactions, the relative change in log(Agatston score) per unit increase in normalized risk factors was examined (**Table 5**). Despite the apparent association of TC with AVC severity at univariate analysis, no significant associations with AVC severity were identified at multivariate analysis.

COMMENT

To our knowledge, this study is the largest to date to examine potential associations of plasma lipoproteins with the prevalence and severity of calcific aortic valve disease. The MESA cohort is notable for its diversity in age and race/ethnicity and for the absence of clinical cardiovascular disease at baseline. Our findings show that, even within this relatively young, healthy, and racially and ethnically diverse population, AVC is common, with a prevalence of 12% among subjects not taking statins. Our findings are consistent with those of previous studies that demonstrated associations of AVC with advanced age, male sex, and hypertension.^{10,11} Furthermore, they extend the results of studies that demonstrated a relationship between lipoprotein levels and aortic valve disease^{10,11} by emphasizing that, similar to coronary artery disease,^{21,23,33} the overall association of LDL-C with AVC prevalence is particularly weak in persons older than 65 years. They suggest that the TC/HDL-C ratio, a composite measure of dyslipidemia, may be a better marker of lipid-attributable risk for prevalent AVC across the full age range of MESA participants.

INTERACTION OF AGE AND LIPOPROTEIN-ASSOCIATED RELATIVE RISK

Two of the most striking findings of this study are the interactions of age with both TC-associated and LDL-C-associated risk for prevalent AVC. For every 31-mg/dL (ie, 1-SD) increase in the level of LDL-C, the youngest cohort

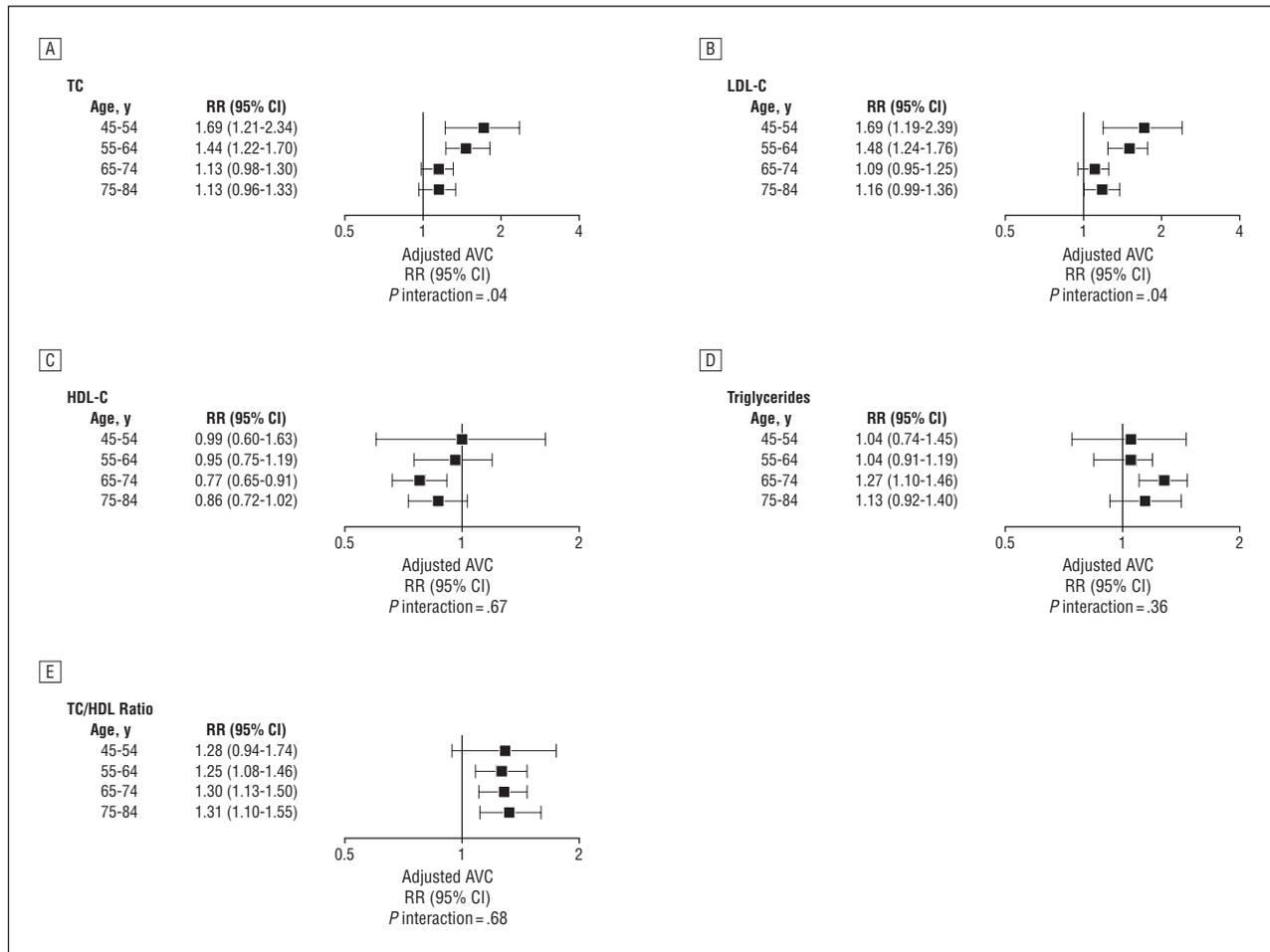


Figure. Lipoprotein-associated relative risk (RR) of prevalent aortic valve calcification (AVC). Shown are point estimates (squares) and 95% confidence intervals (CIs) for adjusted RR per 1-SD increase in lipoprotein levels (A-D) and total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C) (E), stratified by decade of age. LDL-C indicates low-density lipoprotein cholesterol.

Table 4. Disease Severity (Log[AGS]) Stratified by Lipoprotein Quartiles in 700 Participants With AVC (AGS > 0)

Lipoprotein Parameter	Quartile Log(AGS) (SD)				P Value for Linear Trend
	1	2	3	4	
TC	4.2 (1.6)	4.1 (1.5)	4.2 (1.5)	3.8 (1.6)	.03
LDL-C	4.1 (1.5)	4.2 (1.6)	4.0 (1.5)	3.9 (1.6)	.07
HDL-C	4.1 (1.5)	4.0 (1.6)	3.8 (1.6)	4.1 (1.6)	.27
Triglycerides	4.1 (1.7)	4.1 (1.6)	4.1 (1.5)	3.9 (1.5)	.42
Non-HDL-C	4.2 (1.6)	4.2 (1.5)	4.0 (1.5)	3.9 (1.6)	.07
TC/HDL-C ratio	4.1 (1.6)	4.0 (1.6)	4.0 (1.6)	4.1 (1.6)	.97

Abbreviations: AGS, Agatston score; AVC, aortic valve calcification; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant; TC, total cholesterol.

(age 45-54 years) had a 69% (95% CI, 19-139) increase in adjusted RR for prevalent AVC. In contrast, the LDL-C-associated risk was a nonsignificant 12% increase for those 65 years or older. This magnitude of LDL-C-associated risk for AVC is similar to that seen for aortic valve disease in the Cardiovascular Health Study, in which all participants were 65 years or older.¹¹ In that study, the odds ratio (25th vs 75th percentile) for LDL-C was 1.12 (95% CI, 1.03-1.23).¹¹ A similar age attenuation in the li-

poprotein-associated risk for coronary artery disease was seen in the Whitehall Study,²¹ Cardiovascular Health Study,²² and Honolulu Heart Study²³ cohorts.

In participants 65 years or older, the level of HDL-C was associated with a modest decrease in RR for prevalent AVC, and the levels of triglyceride were associated with a modest increase in RR for prevalent AVC. Why increased age is associated with a shift in the associations of particular lipoprotein classes with AVC risk is

unclear, but one possible explanation may be the age-related increase in prevalence of central obesity and metabolic syndrome.³⁴ Development of metabolic syndrome is characterized, in part, by an increase in levels of triglyceride-rich very-low-density lipoprotein and a decrease in levels of HDL-C.^{35,36} We recently reported an association between metabolic syndrome and AVC prevalence in the MESA cohort.¹³

While there are many age-related differences in lipoprotein-associated RRs for prevalent AVC, the RR for AVC associated with the TC/HDL-C ratio remains largely age-independent. The TC/HDL-C ratio serves as an estimate of the degree of atherogenic dyslipidemia and has been found to be superior to either TC or LDL-C in predicting cardiovascular risk in both the Framingham Offspring Study³⁷ and the Lipid Research Clinics Coronary Primary Prevention Trial.³⁸ Some studies have suggested that the apolipoprotein B/apolipoprotein A-I ratio may be a superior predictor of lipoprotein-associated cardiovascular risk than the TC/HDL-C ratio,^{39,40} but an updated evaluation from the Framingham cohort recently has reported that the apolipoprotein B/apolipoprotein A-I and TC/HDL-C ratios have nearly identical predictive values for coronary heart disease.⁴¹

SEVERITY OF AVC AND LIPOPROTEIN LEVELS

While our results identified significant associations between specific lipoprotein classes and prevalent AVC in specific age groups, we found no association between any lipoprotein class and AVC severity in fully adjusted analyses. Thus, while dyslipidemia may contribute to the presence of AVC, the primary determinants of calcification progression may be independent of the lipoprotein classes we examined. Further conclusions are limited by the cross-sectional nature of these analyses.

BIOLOGY OF VALVULAR CALCIFICATION

The past decade has brought a growing understanding of the pathologic mechanisms underlying aortic valve sclerosis and subsequent calcification. It is now seen as an active process characterized by cellular infiltration⁶⁻⁸; deposition of atherogenic lipoproteins, primarily LDL-C and lipoprotein A^{4,5}; extracellular proteoglycan accumulation⁴²; and renin-angiotensin system components.⁹ Calcific nodules form in areas of previous lipoprotein deposition,⁴ particularly in those with oxidized lipids,⁵ and elegant studies in hypercholesterolemic rabbit models have implicated specific signaling pathways in this process.⁴³⁻⁴⁵ In addition, studies have shown that statins inhibit the calcification process both in valve fibroblasts in vitro⁴⁶ and in hypercholesterolemic rabbits in vivo.⁴³⁻⁴⁵ These studies suggest a plausible role for lipoproteins in the pathogenesis of aortic valve calcification. However, despite these findings, clinical trials of statin therapy in aortic stenosis have shown mixed results,^{20,47} perhaps a testimony to our incomplete understanding of the disease process.

ASSESSMENT OF AVC

While MESA centers used either electron beam tomography or multidetector CT to assess the severity of AVC, the

Table 5. Relative Change in Disease Severity^a in Persons With Aortic Valve Calcification (AGS > 0)

Variable ^b	Percent Change (95% CI)	P Value
TC	1.01 (0.90-1.13)	.87
LDL-C	1.02 (0.91-1.13)	.78
HDL-C	1.05 (0.94-1.20)	.41
Triglycerides	0.97 (0.84-1.12)	.70
Non-HDL-C	0.99 (0.89-1.11)	.89
TC/HDL-C ratio	0.96 (0.85-1.09)	.56

Abbreviations: AGS, Agatston score; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

^aPer unit increase in normalized risk factors.

^bEach variable entered separately and adjusted for age, sex, race/ethnicity, site, body mass index, smoking status, diabetes, hypertension, and medications.

equivalency of these techniques within the MESA population has been established.⁴⁸ These methods have been shown in both echocardiographic^{29,31} and ex vivo pathologic^{49,50} validation studies to provide reliable quantification of calcification severity and have demonstrated good correlation with the presence of echocardiographically determined aortic stenosis.^{30,51,52} However, results for the correlation between CT-determined AVC severity and the hemodynamic severity of aortic stenosis are mixed,^{30,52,53} likely because the location of calcification and its effects on restricting leaflet mobility influence valvular hemodynamics above and beyond severity of calcification. Despite this limitation, data suggest that CT-determined AVC scores are useful in their extremes, with threshold values (eg, Agatston scores >1100) above which clinically significant aortic stenosis is likely.^{30,52} Moreover, worsening calcification, measured by either echocardiography or CT, has been associated with worsened clinical outcomes in patients with asymptomatic aortic stenosis.^{3,54}

STUDY LIMITATIONS

This study has several limitations. First, this is a cross-sectional study of the MESA cohort that was not pre-specified during trial design, thus limiting conclusions about causality and potentially affecting analytic power. Second, the exclusion from MESA of individuals with baseline cardiovascular disease may both subject the study to survival bias and diminish strengths of association when compared with studies that included individuals with established cardiovascular disease. Thus, our data need to be corroborated in other populations. Third, other lipoprotein variables that have been associated with atherosclerotic risk such as lipoprotein(a), LDL particle size, apolipoprotein B or apolipoprotein A-I levels, and oxidation status were not measured in MESA. Third, MESA participants who were receiving statin therapy were excluded from these analyses. However, reanalysis of the data including MESA participants receiving statin therapy did not substantially alter our findings, and we were unable to detect an effect modification by statin therapy.

CONCLUSIONS

This cross-sectional analysis demonstrates an age-dependent decrement in the LDL-C-associated RR for AVC among otherwise healthy subjects without known cardiovascular disease. In contrast, there was a statistically significant, though modest, association between a composite measure of dyslipidemia, the TC/HDL-C ratio, and the presence but not severity of AVC. These findings may have important implications about pharmacologic lipid-lowering therapy in calcific aortic valve disease. To date, trials examining the benefits of statin therapy have shown mixed results.^{20,47} Our results suggest that alternative treatment strategies may include targeting dyslipidemia therapies to earlier-stage disease (eg, aortic sclerosis), especially in younger individuals, or testing dyslipidemia therapies that substantially raise HDL-C levels and lower triglyceride levels, thereby improving the TC/HDL-C ratio.

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MESA Group Members: A full list of investigators and participating institutions for MESA is available at <http://www.mesa-nhlbi.org>.

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