Calciﬁc aortic valve disease (CAVD) is the most common indication for valve intervention in the world.1 The cellular mechanisms, cardiovascular risk factors, and therapeutic interventions have been under intense investigation in the 21st century. In the study published in Arterioscler Thromb Vasc Biol, Cao et al2 tested the Multi-Ethnic Study of Atherosclerosis (MESA) database to deﬁne the calcification phenotype associated with unique lipoprotein mechanisms in the development of calcification. MESA was designed to test subclinical atherosclerosis markers and measure calcification burden in the aortic valve using computed tomography measurements. The study group included individuals from age 45 to 84 years, who were free of any clinical cardiovascular disease and treated diabetes mellitus.3,4 The database is robust to test for subclinical risk factors in the development of calciﬁc aortic valve disease.

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Lipoproteins as Novel Risk Factors in Calciﬁc Aortic Valve Disease
O’Brien et al5 and Otto et al6 publish studies to deﬁne the role of lipoproteins in ex vivo calciﬁed aortic valves. Over the next 20 years, studies in the ﬁeld of calciﬁc aortic valve disease have determined that the calciﬁc aortic valve disease is not a degenerative process, but an active cellular biology.7 This hypothesis was conﬁrmed using animal models, which tested the role of hypercholesterolemia as an initiating event for calciﬁc aortic valve disease.7 In 2009, the National Heart, Lung, and Blood Institute convened a working group on the cellular mechanisms of calciﬁc aortic valve disease.8 The working hypothesis for the development of calciﬁc aortic valve disease emphasized the role of lipoproteins and oxidative stress in the initiation of the disease.8 Calciﬁcation ensues over time as aortic valve myoﬁbroblasts differentiate into an osteogenic phenotype.9–11

Role of MESA in CAVD
MESA has played an important role in studying the development of calcification in the aortic valve and coronary artery.12–15

In this study by Cao et al,2 they deﬁne the cutoffs for Lp(a) and the effect of ethnicity in the development of CAVD. Lp(a) concentrations were measured using a turbidimetric immunoassay, and subclinical CAVD was measured by quantifying aortic valve calcification (AVC) through computed tomographic scanning in 4678 participants of the Multi-Ethnic Study of Atherosclerosis. Relative risk (RR) and ordered logistic regression analysis determined cross-sectional associations of Lp(a) with AVC and its severity, respectively. The conventional 30 mg/dL Lp(a) clinical cutoff was associated with AVC in white (RR, 1.56; 95% conﬁdence interval, 1.24–1.96) and was borderline signiﬁcant (P=0.059) in black study participants (RR, 1.55; 95% conﬁdence interval, 0.98–2.44). Whites with levels ≥50 mg/dL also showed higher prevalence of AVC (RR, 1.72; 95% conﬁdence interval, 1.36–2.17) than those below this level. Significant associations were observed between Lp(a) and degree of AVC in both white and black individuals. The degree of AVC in Asians and Hispanic is not signiﬁcant, but this could be because of the results being underpowered in these populations tested.

Lipoprotein Analysis in Coronary Artery Calcification
The presence of existing coronary artery calcification did not affect these associations of Lp(a) and CAVD. There were no signiﬁcant ﬁndings in Hispanics or Chinese. In contrast, CAC was only associated with AVC in the subcohort using a regression model and adjusting for age, sex, education, diabetes mellitus, systolic blood pressure, hypertension meds, smoking, low-density lipoprotein, high-density lipoprotein, and triglycerides (RR, 1.71; P<0.001). All of the traditional risk factors important in the development of CAVD.12 Importantly, CAC was not associated with Lp(a) in this MESA data set, and the inclusion of CAC into statistical models did not appreciably inﬂuence relations of Lp(a) and AVC in the subcohort or among races/ethnicities.

Lp(a) in Calciﬁc Aortic Valve Disease
In 2016, Cao et al2, discovery of Lp(a) in MESA as a risk factor for CAVD teases out the role of traditional risk factors versus Lp(a). The MESA data set, and the inclusion of CAC into statistical models, did not appreciably inﬂuence relations of Lp(a) and AVC in the subcohort or among races/ethnicities. This finding differentiates the role of Lp(a) in the progression of AVC, which is not related to the presence of CAC in the population. This may be because of the mechanism of coronary artery calcification16 versus AVC9 versus the role of embryonic cell lineage17 in the mechanism of calcification. Previous investigations have also deﬁned the importance of Lp(a) in the development of CAVD in genetic.
studies. Thanassoulis has further proposed that targeted therapy of Lp(a) may be a novel target for treating calcific aortic valve disease.

The role of multiple lipoproteins in the progression of CAVD, may further aid in understanding the outcomes of the clinical trials in CAVD designed to lower lipids in calcific aortic valve disease. ASTRONOMER specifically addressed this question by determining the role of oxidized phospholipids and Lp(a) in the progression of calcific aortic valve disease. It is well known that traditional risk factors play a role in the majority of patients with CAVD; however, genetics and lipoprotein Lp(a) are also critical in the development of CAVD. The Figure demonstrates cardiovascular risk factors, genetic factors, and the final calcification phenotype critical in the development of calcific aortic valve disease. Future studies evaluating the role of Lp(a) in patients in CAVD may help to further understand the role of lipoprotein driving early atherosclerosis and eventual calcification in the aortic valve.

Disclosures

The author is the inventor on a patent for methods to slow progression of valvular heart disease. The Mayo Clinic owns the patent. The author (NMR) does not receive any royalties from this patent.

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The Lipid Hypothesis in Calcific Aortic Valve Disease: The Role of the Multi-Ethnic Study of Atherosclerosis
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