We appreciate the letter discussing the importance of high-density lipoprotein (HDL) in the pathogenesis of aortic valve disease. We agree with the author that there are many mechanisms involved in aortic stenosis. The work of Dr. Otto was the first to define the atherosclerotic risk factors in the development of calcific aortic stenosis (1). This important study set up the hypothesis that calcific aortic stenosis is an active biologic disease.

Since then, there have been a number of experimental models implicating the potential mechanisms by which calcification develops. The primary hypothesis has been proposed by Rajamannan et al. (2) and Mohler et al. (3), that an active osteoblast bone formation is present in the calcifying aortic valve. The field of valvular heart disease is now poised for large-scale clinical trials to define the pharmacologic targets for this disease process. Our design for the RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium) trial (4) was to test the effect of low-density lipoprotein (LDL) lowering in the treatment of aortic valve stenosis. We designed the trial and powered the statistical analysis in terms of LDL lowering and echocardiographic monitoring. In the study by Yilmaz et al. (5), they demonstrated the importance of HDL and its predictive value in treating aortic valve disease. However, that study was published after the initiation of the RAAVE trial, and therefore the importance of HDL was not emphasized in our final analysis. However, HDL is an important predictor and we plan to perform a subanalysis.

Calcific aortic stenosis has been a surgical disease for the past 40 years since the landmark 1968 paper of Ross and Braunwald (6) defined surgical valve replacement at the onset of symptoms. The RAAVE trial (4) is the first trial of medical therapy to demonstrate prospectively that LDL lowering and improvement in inflammatory markers slow the progression of this disease. The issues that will need to be considered are not only the effect of increasing HDL and lowering LDL, but also the cellular biology of this disease. Future clinical trials will need to take into account all of these aspects in their design.

Luis M. Moura, MD
José L. Zamorano, MD, PhD
Sandra F. Ramos, MSc
Isabel M. Barros, MD
Luis F. Azevedo, MD
F. Rocha-Gonçalves, MD, PhD
*Nalini M. Rajamannan, MD
*Northwestern University Feinberg School of Medicine
303 E Chicago
Tarry 12-717
Chicago, Illinois 60611
E-mail: n-rajamannan@northwestern.edu

doi:10.1016/j.jacc.2007.04.037

REFERENCES