even obstructive atherosclerotic lesions do not necessarily result in ischemia. With the increasing awareness of the mismatch between ischemia (MPI) and atherosclerosis/stenosis (MSCT and invasive angiography), one may even question the use of lesions on angiography as the gold standard.

The second issue the authors raise concerns our statement that in patients with abnormal MPI revascularization may be indicated. We fully agree with the authors that clinical presentation also should always be considered when deciding the need for revascularization. Nevertheless, in contrast to the opinion of Drs. Spevack and Levsky, we feel that assessment of the presence and extent of ischemia are of paramount importance in the prediction of benefit from revascularization. Recently, Hachamovitch et al. (2) published their observations in 5,366 consecutive patients without earlier revascularization who received either medical therapy or revascularization after initial MPI. In line with previous studies (3), the authors demonstrated that survival benefit from revascularization is proportional to the extent of ischemia. Although left ventricular ejection fraction was found to predict cardiac death, only inducible ischemia identified which patients had a short-term benefit from revascularization.

However, we fully agree with Drs. Spevack and Levsky that despite normal MPI results long-term outcomes may differ between patients with either minor or severe coronary artery disease (CAD). Indeed, the identification of considerable CAD in patients with still normal MPI may become an important advantage of using MSCT coronary angiography in addition to MPI. To this purpose, sequential imaging strategies could potentially be beneficial. Unfortunately at present, available data are too scarce to support such algorithms. Indeed, we fully agree with the authors that further investigations addressing patient outcomes as well as cost-effectiveness are highly warranted.

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Statins and Aortic Stenosis in the Context of Ratio of Low- to High-Density Lipoprotein Cholesterol

In a recent paper by Moura et al. (1), it was found that lipid-lowering therapy with a statin, namely, rosuvastatin, showed beneficial effects in slowing the progression of the aortic stenosis. Aortic stenosis has long been associated with atherosclerosis by many authors in the context of common risk factors with common pathophysiologic scenarios (2,3). The lipid hypothesis is one of the most enthusiastic ones, attracting attention after Otto et al. (2) showed that aortic valve disease behaved in an almost similar manner as atherosclerosis on microscopic samples, although there were some differences, particularly, more influence of calcification. This enthusiasm brought about a prospective study (4), which failed to show any beneficial effect on valve disease progression despite significant decrease in low-density lipoprotein (LDL) cholesterol with atorvastatin in a group of patients with heavily calcified aortic stenosis. This issue is also mentioned in the recent paper (1), and the potential difference is attributed to the difference in the severity of the aortic disease, which could definitely be accepted as one of the answers. In addition to this point, in the paper it was (1) stated that there was a significant correlation (1) between the LDL decrease, which was almost similar to that in the earlier study (4), and the progression of the aortic disease, which was definitely not correlated with LDL cholesterol in the previous study (4). On the other hand, what is not presented nor mentioned in either paper is that both statins are known to differ in terms of their effects on high-density lipoprotein (HDL) cholesterol, and the LDL to HDL cholesterol ratio (5). In our study (6), we had shown that there was a significant correlation between the rate of aortic valve disease progression and the total cholesterol to HDL cholesterol level ratio, with fast progression occurring in the group with higher ratios. It is rational within this concept to expect that better normalization, which has been shown to be significantly better with rosuvastatin (5), might yield better results. Neither of the 2 studies (1,4) pointed this out. We think that in addition to the severity of the aortic valve disease, a delicate balance of lipid profile with HDL cholesterol behaving in opposition to LDL cholesterol might have a significant role in aortic stenosis progression just as in atherosclerosis. However, this issue remains to be established.

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Reply

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.

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