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REPLY

As a follow-up to our study on the effects of aggressive versus conventional lipid-lowering therapy by simvastatin in human atherosclerotic lesions (1), Dr. Spence stated that "Corti et al. found no difference in vessel wall area measured by magnetic resonance imaging (MRI)" and that "investigators wishing to measure effects of antiatherosclerotic therapy would be well served by measuring carotid plaque volume using three-dimensional ultrasound" on the importance of the methodology and location of atherosclerotic lesions when measuring the effect of antiarteriosclerotic therapies. Our study (1) was the second publication from a randomized, double-blind trial involving 51 newly diagnosed, clinically asymptomatic hyperlipidemic patients. Changes in atherosclerotic lesions were assessed by using high-resolution noninvasive MRI. The major conclusion of our study is the importance of lowering plasma low-density lipoprotein (LDL) cholesterol levels rather that the statin dose. As such, we reported that the observed changes in aortic plaque parameters were related to the reduction in LDL-cholesterol levels rather than to the doses of statin. The study design and early observations were published in 2001 (2).

Dr. Spence is partially correct in his statement that we found no differences in plaque volume in the study. We did observe a correlation with LDL-lowering and aortic lesion changes. Dr. Spence is correct in that we did not achieve statistically significant changes in the carotid lesions, although the percentages of volume change were identical in both the aorta and carotids. These observations strongly support the role of the severity/thickness of the lesions at baseline as a major determinant for detecting the effectiveness of the therapeutic interventions. In this regard, using an MRI-based imaging modality and the same treatments but in a population with more advanced disease (clinically documented coronary artery disease), Lima et al. (3) reached a conclusion similar to ours. In their study, the changes were significant after only six months of treatment (3). The importance of lesion severity for detecting treatment-induced changes in plaque volume is clearly emphasized by these two studies. Furthermore, these findings have been corroborated by studies performed more recently.

The major advantages of using MRI for plaque assessment are the noninvasive approach and the high sensitivity and specificity of this modality that permits a small sample size of subjects. This observation has been confirmed by a recent study with five sites that has reported sample size calculation for clinical trials using MRI for quantitative assessment of carotid atherosclerosis (4).

We do agree with Dr. Spence that MRI is not the only imaging modality capable of detecting changes in plaque lesions. The objective of our study was not to conclude that MRI is the only imaging modality to be used for such purpose. We want to emphasize that the important fact in inducing lesion regression is an effective and maintained lipid-lowering intervention. If the intervention is effective, MRI and any of the other imaging modalities should clearly validate the beneficial effects.

***Juan Jose Badimon, PhD, FACC, FAHA**
Roberto Corti, MD
Valentin Fuster, MD, PhD, FACC

*Cardiovascular Biology Research Laboratory
Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, New York 10029
E-mail: Juan.Badimon@mssm.edu

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Aspirin Resistance and Atherothrombotic Disease

We read with interest the comprehensive review of "aspirin resistance" by Mason et al. (1). We suggest, based on our recent experience, that two less well-explored mechanisms may contribute to what is clearly a composite of several processes.

Interindividual pharmacodynamic variability occurs with most drugs. Aspirin is no different; thus aspirin resistance assays may reflect pharmacodynamic heterogeneity. Mason et al. (1) identify genotypic variation in cyclooxygenase (COX)-1 as a potential but unproven pharmacodynamic mechanism. We recently explored this hypothesis in a population with stable coronary artery disease (CAD) and determined that COX-1 haplotype modulates platelet response to aspirin determined by two established laboratory assays of COX inhibition: arachidonic acid-induced platelet aggregation and thromboxane B_2 generation in serum. Much of the effect, however, was associated with a single COX-1 haplotype carried by 12% of the population, and thus, although contributing to the problem, this does not explain the higher rates of aspirin resistance reported in several studies (2).

Mason et al. (1) also discuss pharmacokinetic resistance to aspirin and specifically the role of drug interaction and dose response; however, variability in aspirin formulation is another possible factor. It is worth recalling that initial dose-finding studies were performed with plain aspirin, which is rapidly absorbed from the stomach and inhibits platelet cyclooxygenase in the presystemic circulation. As mentioned by Mason et al. (1) dosing with 100 mg is sufficient to completely inhibit platelet cyclooxygenase. Accordingly, current American College of Cardiology/American Heart