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EDITORIAL COMMENT

Should CMR Become the New Darling of Noninvasive Imaging for the Monitoring of Progression and Regression of Coronary Heart Disease?*

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Over the past several decades, we have made tremendous progress in understanding the pathogenesis of atherosclerotic coronary artery disease (CAD), knowledge that has helped to reduce morbidity and mortality. In the past few years, the maturation of noninvasive imaging modalities, such as computed tomography angiography (CTA) with a resolution of 0.5 to 1.0 mm and cardiac magnetic resonance (CMR) with and without contrast and a lower resolution of 1.0 to1.5 mm (with 1.5-T), has introduced an additional dimension for predicting patients at increased risk of future cardiovascular events (1). Multiple randomized studies have demonstrated the benefit of statins in reducing mortality in patients with and without CAD (2). It has been hypothesized that low-density lipoprotein-cholesterol (LDL-C) reduction leads to plaque modification, and small studies of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have shown reduction in plaque volume, inflammation, and necrotic core after statin treatment (3-5).

In this issue of the *Journal*, Noguchi et al. (6) report a small prospective study that they conducted involving 48 patients on 12 months of pitavastatin treatment that showed a decrease in plaque-to-myocardium signal-intensity ratio (PMR) of high-intensity plaques (HIPs) detected on 1.5-T noncontrast T1-weighted CMR imaging (T1WI), especially in patients with a PMR of ≥1.4. These impressive findings were accompanied by a significant reduction in LDL-C to <80 mg/dl as well as a decrease in major adverse cardiac events (MACE) compared with propensity-matched controls (2.1% vs. 16.7%). In context, MACE were defined as a composite of cardiac death, ST-segment elevation myocardial infarction, cardiac troponin T-positive unstable angina/non-ST-segment elevation myocardial infarction, and ischemia-driven percutaneous coronary intervention. Acknowledging this accomplishment, large randomized, prospective trials will be required to further assess the capability of this innovative methodology to help identify patients at risk of future cardiovascular events.

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DO PREVIOUS CLINICAL TRIALS PROVIDE SUFFICIENT EVIDENCE THAT INITIATION OF STATIN THERAPY EXPLAINS THE OBSERVED BIOLOGICAL EFFECTS?

Statins have been commercially available since 1987 and are currently prescribed for an estimated 30 million people worldwide (7). Many statin trials have been conducted for both primary and secondary prevention of coronary heart disease. Indeed the landmark 4S study (Scandinavian Simvastatin Survival Study) was a secondary prevention trial showing

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a significant reduction in total mortality and coronary events (8). This was soon followed by a successful primary prevention study: PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), which enrolled individuals with a history of or risk factors for vascular disease. Active therapy was associated with a 24% reduction in mortality from coronary disease (5,9). These 2 studies had a follow-up of 5.4 and 3.2 years, respectively, which is very different from the current study of only 12 months of pitavastatin (4 mg/day) treatment. The current study showed that LDL-C decreased from 125 ± 25 mg/dl to 70 ± 11 mg/dl (percentage of change from baseline: −42.1 ± 14.1%; $p < 0.001$). The earlier studies shared sufficient power and duration to detect meaningful mortality differences, whereas the current study was not appropriately sized nor designed to prospectively assess risk stratification of patients with CAD. This study's main inadequacy is its use of a propensity score–matched control group in the absence of statin treatment, which cannot replace prospective, randomized trials. Today, the standard of care for patients with CAD is statin therapy for all, and studies without statin treatment are no longer considered ethical to perform; therefore, we have to assess low- versus high-dose statin therapy.

Initial animal studies have contributed enormously to our understanding of the response to statin treatment (10) by showing a definite reduction in plaque area and macrophage infiltration with an increase in fibrous tissue (11). Later mechanistic studies demonstrated that statins quench nuclear factor kappa B while increasing peroxisome proliferator–activated receptor alpha and gamma activation, processes that affect inflammation and angiogenesis (12). Overall, the hypolipidemic effects of statins are weak in mice because of differences in circulating lipoproteins, whereas the response to statins in the Watanabe heritable hyperlipidemic (WHHL) animal model may be more representative of human plaques (13). In this context, a study in WHHL rabbits treated with statins over a 1-year period showed a 20% reduction in circulating cholesterol and stabilization of coronary plaques. This was the end product of a decrease in the ratio of foam cells to macrophages and extracellular lipid content as well as an increase in the stabilization components of collagen and smooth muscle cells (13).

In the current study (6), the primary endpoint at 12 months was a change in the PMR value of HIP, which was accompanied by a decrease in the total and percentage of atheroma volume, total low attenuated plaque (LAP) volume of <30 Hounsfield units, and percentage of LAP volume on CTA compared with a matched control group. On the contrary, propensity-matched controls showed the opposite trends. Moreover, there were a significant lowering of LDL-C and a reduction in high-sensitivity C-reactive protein, both of which correlated with the percentage of change in the PMR. The underlying mechanism for this effect is not well understood, especially given the relatively short 12-month follow-up. Similarly, a small OCT study (resolution of 10 to 15 μm) of 35 patients presenting with unstable angina and untreated dyslipidemia who were then treated with 5 or 20 mg atorvastatin revealed a significant increase in fibrous cap thickness, a reduction in lipid core arc, and a reduction in macrophage intensity within 12 months but only for those treated with the high-dose statin (4). Reductions in circulating LDL-C were 69 mg/dl and 78 mg/dl for high- and low-dose atorvastatin, respectively (4). Despite these remarkable accomplishments, we have to bear in mind that these are selected studies with imaging surrogate endpoints and insufficient power to make meaningful recommendations without seeing hard clinical outcomes or large prospective, randomized trials. Indeed, some of these findings may arise from chance alone and may be disallowed in large prospective studies.

In a 2009 report, the same authors (14) showed that HIP detected by noncontrast T1WI is associated with positive coronary remodeling and mirrored by low density on CTA and ultrasound attenuation. In a subsequent paper, Noguchi et al. (15) reported that plaques with a PMR ≥1.4 were significant independent predictors of coronary events within 55 months of follow-up. The event rate (25.8%) was significantly higher in patients with a PMR ≥1.4 compared with patients with a PMR of 1.0 to 1.4 (event rate of 8.4%) and was lowest (1.1%) in those with a PMR <1.0 (15). The best predictors of coronary events were age, male sex, glycosylated hemoglobin, proven CAD, and a PMR ≥1.4 (15). However, the positive predictive value for a future coronary event (PMR: ≥1.4 vs. <1.4) was low (26%), but sensitivity, specificity, and negative predictive value were high (80%, 77%, and 87%, respectively). On the other hand, Motoyama et al. (16) showed that the diagnostic accuracy of CT-derived plaque characteristics such as positive remodeling, LAP (<30 Hounsfield units), and spotty calcification demonstrated a high positive predictive value, and the absence of all 3 had a high negative predictive value for culprit plaques associated with acute coronary syndrome (ACS).

Sudden coronary death attributed to plaque rupture, as we described in an autopsy study in 1997 (17), showed the highest frequency of vulnerable plaques (thin-cap fibroatheromas [TCFAs]) defined as fibrous cap thickness of <65 μm with macrophage infiltration and an underlying large necrotic core