Can a Potent Statin Actually Regress Coronary Atherosclerosis?

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Since the initial report by Sones and Shirey in 1962, coronary angiography has been the standard method used to define the severity and extent of coronary atherosclerosis. By only providing a silhouette of the coronary lumen, however, coronary angiography frequently underestimates the true burden of atheroma in the arterial wall. In this issue of JAMA, Nissen et al present important new data on coronary atherosclerosis based on their findings from the ASTEROID (A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial. This multicenter, intravascular ultrasound (IVUS) study assessed the extent of coronary atheroma at baseline and after 2 years of treatment with the maximally approved dose (40 mg) of rosuvastatin, the statin most effective at reducing levels of low-density lipoprotein cholesterol (LDL-C). Each pair of baseline and 24-month IVUS studies was analyzed in blinded fashion.

The investigators found that 349 of 507 participants had “evaluable” serial IVUS studies. After 2 years of treatment with rosuvastatin, mean LDL-C levels decreased by 53% (from 130 to 61 mg/dL) and mean high-density lipoprotein cholesterol (HDL-C) levels increased by 15% (from 43 to 49 mg/dL). Rosuvastatin therapy was associated with a modest decrease in mean percent atheroma volume (from 39.6% to 38.6%) and mean atheroma volume in the most diseased 10-mm subsegment (from 65 to 59 mm³). Importantly, all patients either had no statin therapy for more than 3 months during the preceding year or required a 28-day washout period before enrollment to obtain accurate baseline lipid values prior to the initiation of therapy.

The authors conclude that very aggressive LDL-C lowering in the setting of a moderate increase in HDL-C results in regression of coronary atherosclerosis. While the results of this study are exciting, they are tempered by the lack of a control group receiving a somewhat less intensive LDL-C lowering regimen, the absence of paired IVUS measurements in less diseased coronary segments to demonstrate reproducibility of atheroma volume measurements, and exclusion of patients with coronary stenoses measuring greater than 50% throughout a target segment. Furthermore, the study design raises questions about whether differences in the amount of atheroma regression depend on whether a patient is “statin naïve” in comparison with those previously receiving statin therapy. This is particularly important when trying to evaluate the findings of this study in the context of the Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, in which patients were allowed to be taking lipid-lowering therapy prior to study enrollment.

The authors of the ASTEROID trial deemed it “ethically unacceptable to randomize patients in this high-risk group to low-intensity treatment.” However, it appears that most enrolled patients were not at extremely high risk (eg, the clinical indication for angiography typically consisted of stable or unstable ischemic chest pain syndromes or abnormal exercise testing results for angina and only 13% had diabetes mellitus). Furthermore, the baseline LDL-C level for enrolled patients was only mildly elevated, the HDL-C level was average, and 17% of individuals were not taking aspirin at baseline. Given current guidelines, such patients would not necessarily be considered high risk and treatment with a less aggressive lipid-lowering regimen (target LDL-C level of approximately 90-100 mg/dL) would be accepted as standard of care.

Unfortunately, the ASTEROID study does not provide definitive information regarding the relationship of LDL-C lowering and extent of coronary atherosclerosis regression to determine if high-intensity treatment is required to achieve regression. Since the authors report a similar magnitude of regression for patients above and below the median HDL-C and LDL-C levels (Table 4 in the article), less intensive changes in LDL-C levels, non–HDL-C levels, or both, and HDL-C levels also may have led to modest regression.

Comparison of high-dose rosuvastatin with simvastatin—which performed well in the Heart Protection Study (even in patients with baseline LDL-C levels <100 mg/dL)—would have been a more informative study design. The choice of simvastatin would have been a good one because...
it is significantly more potent than pravastatin, which was used in the REVERSAL trial\(^1\) and in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22 [PROVE IT-TIMI 22]) trial.\(^6\) Moreover, after simvastatin becomes a generic medication in the United States later this year, it likely will be the preferred initial lipid-lowering therapy in many managed care formulas.

Several large clinical outcome trials have shown that aggressive LDL-C reduction with high-dose atorvastatin or moderate-dose simvastatin reduces hard end points and also slows the progression of atherosclerosis.\(^3,5-7\) Although moderate-dose simvastatin reduces hard end points and aggressive LDL-C reduction with high-dose atorvastatin or initial lipid-lowering therapy in many managed care formulas in the United States later this year, it likely will be the preferred initial lipid-lowering therapy in many managed care formulas. Future studies are needed to determine if at-risk patients derive more clinical benefit from treatment with rosuvastatin than other statins, and if these benefits are attributable to the extent of atherosclerotic regression.

Current data suggest that the predominant benefit derived from statins is through stabilization of lipid-laden plaques, rather than regression of atherosclerosis. Although the ASTEROID study showed that 24 months of high-dose rosuvastatin therapy is associated with modest regression of atherosclerosis, there are no clinical trial data reporting the effect of rosuvastatin on adverse clinical events either alone or in comparison with other less potent statins. Although rosuvastatin is being evaluated in a primary prevention trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin [JUPITER]), future studies are needed to determine if at-risk patients derive more clinical benefit from treatment with rosuvastatin than other statins, and if these benefits are attributable to the extent of atherosclerotic regression.

Furthermore, a recent substudy of the REVERSAL trial examined the effects of plaque progression and regression on coronary lumen size.\(^7\) In patients manifesting plaque regression, a decrease in the cross-sectional area of the external elastic membrane was associated with no change in coronary lumen area. No data regarding changes in lumen volume or size are reported in the ASTEROID study, leaving open the possibility that changes in atheroma volume may be due to reduced cross-sectional area of the external elastic membrane with potentially unchanged or reduced coronary lumen size (suggested by Figure 2 in the article\(^2\)). By excluding coronary lesions with greater than 50% luminal narrowing, the clinical impact of statin-induced reductions in atheroma volume on high-grade lesions in this study remains undetermined.

Whether comparable changes in LDL-C and HDL-C levels, which may be obtained with combination therapy, will produce similar effects on atherosclerotic coronary lesions also is unknown. One such product that combines simvastatin with ezetimibe is currently being studied in 9000 patients with chronic renal disease, 1800 with moderate aortic stenosis, and 10,000 with acute coronary syndromes. In addition, the combination of simvastatin with niacin will be evaluated by the National Institutes of Health in a large study of patients with stable coronary heart disease.

Importantly, increases in plasma HDL-C either by infusion of native HDL-C or lipid-free apolipoprotein A-1 (apo A-1) reduced plaque size in animal models of atherosclerosis.\(^10\) In addition, weekly infusions of the recombinant mutant apolipoprotein apo A-1 Milano for as little as 5 weeks resulted in modest plaque regression in humans after an acute coronary syndrome.\(^11\) Based on these findings, several trials are currently using IVUS to examine the effects of administering apo A-1-like mimetics, phospholipid vesicles, or selectively delipidated plasma to individuals with at least moderate atherosclerotic vascular disease. Whether IVUS-based end points will be sufficient to support the approval of these treatment strategies remains to be seen.

Clearly a multimodality approach to the management of risk factors in patients with coronary artery disease is needed.\(^12,13\) While IVUS-documented atherosclerotic regression is an intriguing finding, clinicians must remember that this may not be the best measure of the treatment’s effect on hard cardiovascular end points. Nevertheless, the pioneering work of Nissen et al has revolutionized the current approach to understanding the anatomy and pathophysiology of coronary atherosclerosis as well as its responsiveness to medical therapy. The results of several ongoing trials will help determine what agent or combination of pharmacologic agents is most efficacious in the long-term management of at-risk patients.

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