

## EDITORIAL COMMENT

# MR Imaging-Verified Plaque Delipidation With Lipid-Lowering Therapy

## Important Questions Remain\*

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Numerous studies over the past 2 decades have demonstrated the benefit of low-density lipoprotein (LDL) cholesterol lowering on heart attack, stroke, and cardiac death (1). Both invasive and noninvasive imaging approaches have been used as surrogate markers to demonstrate benefits of LDL lowering on atherosclerosis. Studies using intravascular ultrasonography (IVUS) of the coronary arteries have demonstrated that statin initiation is associated

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with halting of plaque progression, and, in fact, with more potent statins, evidence of plaque regression (2). Carotid intima-media thickness studies with ultrasonography have likewise demonstrated benefit of statin therapy (3). These studies have primarily been conducted over the first year or 2 after initiation of statins, and the endpoint used has been coronary plaque volume or greatest plaque area in the case of IVUS and carotid wall thickness in the case of carotid intima-media thickness. Noninvasive imaging with magnetic resonance imaging (MRI) of the carotid and aorta (4–6) and superficial femoral artery (7) have demonstrated the plaque regression capabilities of these powerful drugs.

A decade ago, Crisby et al. (8) showed that statin treatment was associated with lower lipid components in atherosclerosis in ex vivo carotid specimens excised at the time of endarterectomy. Clear demonstration of this effect in vivo in humans required further development in noninvasive imaging of plaque components. The groups at the University of Washington and at Mount Sinai, among others, have validated the technique of plaque composition delineation by carotid MRI over the past 10 to 15 years, specifically the ability to differentiate lipid, fibrous, calcified, and hemorrhagic components (9–12). The benefits of lipid lowering on plaque morphology was suggested in a carotid MRI study from Zhao et al. (13) in a post-hoc study of 16 patients at the end of the FATS (Familial Atherosclerosis Treatment Study) study, in which patients treated with an aggressive lipid-lowering regimen had less lipid and more calcium in their plaque as compared to control subjects. A prospective study from this group (14) in another small study of 18 patients showed that rosuvastatin in either high dose or low dose reduced the extent of lipid-rich necrotic core (LRNC) by 41%, although plaque volume did not change in either group. However, the effect of lipid-lowering therapy on changes in atherosclerotic plaque composition measured by MRI over time has not been fully delineated. In addition, the relative effect of statins compared to other lipid-lowering drugs has not been previously illustrated.

This sets the stage for the Zhao et al. (15) paper in this issue of *JACC*. They present intriguing data with regard to the effect of lipid-lowering therapy on changes in atherosclerotic plaque composition measured by carotid MRI over time. Patients in this study comprise part of a 3-arm study of lipid-lowering strategies involving 123 patients. To be

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entered into the study, patients had to have established coronary or carotid disease, elevated apolipoprotein B, and prior lipid-lowering therapy of <1-year duration. Patients were then randomly assigned to either atorvastatin alone, atorvastatin plus extended-release niacin, or triple therapy with the addition of colesvelam to the regimen. Serial MRI scans were performed at baseline, and yearly for 3 years. Only the 33 patients who had evidence of LRNC in their carotid plaque at baseline were evaluated in this paper. Plaque volume in the carotid decreased in the patients as a whole. The investigators documented a 38% reduction in the volume of LRNC in the carotid plaque; the LRNC fell from 14.2% to 7.4% of the wall area in those regions. Importantly, they demonstrated that the majority of delipidation occurred in the first 2 years and then slowed significantly in the third year. This is the first prospective demonstration of the time course of plaque delipidation with lipid lowering demonstrated using noninvasive imaging.

There are some important limitations of the study. We are not told what happened to the other 90 patients without lipid in their plaque. Did their plaque progress or regress? How did their plaque components change? The robustness and reproducibility of the LRNC measurements over multiple time points have not been demonstrated and require further validation. Issues related to image registration and partial volume-averaging artifacts could potentially bias the results of this small dataset. That is particularly crucial as, in the current study, data from the internal carotid, carotid bulb, and common carotid arteries were combined.

The authors also correlate the imaging findings with lipid biomarkers and find relatively poor and nonsignificant correlations. This study, therefore, does not present a clear picture with regard to the roles of such traditional measures with respect to carotid MRI. Hence, the link between LDL lowering and plaque delipidation cannot be extracted on the basis of the data presented in this study.

Most important, the treatment code is not yet available for this study, so we do not know if 1 or 2 of the therapeutic arms showed more benefit than the others or even if there was benefit in all 3 arms. We cannot, therefore, draw any conclusion regarding the effect of statins specifically on plaque de-

lipidation. It should be noted that the 33 subjects were allocated to 3 groups, resulting in small sample sizes for each treatment. Therefore, this study may also lack the power to discriminate any differences between statin treatment compared to other lipid reduction approaches with regard to plaque lipid depletion. This is increasingly important given the recently stopped AIM-HIGH (Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes) trial in which niacin offered no clinical benefit above statins in patients with a starting low-density lipoprotein of approximately 70 (16). We need to know the relative benefit of agents that are potential add-ons to statins as, to date, the imaging results of drugs such as ezetimibe have been disappointing in this regard (7,17,18). Although the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis) study (18) and the Oxford Niaspan MRI study (6) suggested plaque regression benefits of niacin that was not borne out in the clinical results of the AIM-HIGH trial (16).

Despite these limitations, the current study does present the first in vivo evidence of the time course of lipid depletion in carotid plaques in patients undergoing lipid-lowering therapy. Most of this effect is in the first 2 years. Is there a statute of limitations on the delipidation benefits of plaque regression therapies? More long-term serial studies are needed to confirm this finding. In addition, the present study by Zhao *et al.* (15) does not elucidate the effect of various forms of lipid-lowering therapy on plaque delipidation. Moreover, as no link could be established between any changes in lipid biomarkers and plaque delipidation, additional studies with adequate statistical power are still needed to better understand the mechanism of plaque compositional changes and their relationship to clinical outcomes of atherosclerosis therapy.

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