How does lipid lowering prevent coronary events? New insights from human imaging trials

Peter Libby*

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

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This editorial refers to ‘Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study’†, by L. Raber et al., on page 490.

Clinical trials conducted over the last two decades have firmly established that LDL lowering, particularly by statins, can reduce the risk of acute coronary syndromes and ischaemic stroke. Yet, the mechanisms that underlie these striking improvements in clinical outcomes remain controversial. It is now old news that lipid lowering only reduces lumenal stenoses assessed by angiography by an average of at most a few per cent. The fall in clinical events produced by statins dwarfs these small changes in angiographic stenoses by an order of magnitude. This apparent paradox has focused attention on alterations of other aspects of atherosclerotic lesions that might make them less prone to provoke thrombotic complications. Some have described such effects on plaques invisible on angiography as lesion ‘stabilization’.

Insights on effects of lipid lowering on atheroma from animal studies

Classical investigations in non-human primates with diet-induced atherosclerosis showed a decrease in the lesion lipid content leaving a fibrous component following withdrawal of the atherogenic diet.1 More recent experiments in rabbits probed biochemical and molecular changes in plaques produced by lipid lowering (reviewed in Libby2). In one series of experiments, animals with diet-induced atherosclerosis underwent a shift to a low-cholesterol diet. An increase in collagen content confirmed the morphological observations made in primates. Markers of inflammation also subsided with lipid lowering, in parallel with a reduction in the expression of interstitial collagenases implicated in collagen breakdown and the linking of inflammation with weakening of the plaque’s fibrous cap. Further studies showed a decrease in tissue factor expression, establishing a likely mechanism of reduced thrombogenicity of plaques following lipid lowering. Studies in rabbits with genetically determined hyperlipidaemia (the Watanabe heritable hyperlipidaemic rabbit) treated with statins showed directionally similar changes in plaques, consistent with ‘stabilization’ and reduced thrombogenic potential. Subsequently, many studies in hyperlipidaemic mice have shown that statins can reduce indices of inflammation. This ensemble of experimental data suggested that an increase in the fibrous content of plaques due to reduced inflammation could contribute to reduction in thrombotic events provoked by atherosclerotic plaques.

New insights from human imaging studies

While animal experiments permit the excision of lesions and probing gene expression and morphology using rigorous methods, the tools for the investigation of human atherosclerosis in situ remain indirect. Studies that used magnetic resonance imaging (MRI) in human carotids showed that long-term lipid-lowering therapy (2–10 years) reduced indices of lipid core area and increased the percentage of the plaque volume comprised of fibrous tissue.3–6 Using intravascular ultrasound, Nissen’s group first found reduction in the volume of atherosclerotic plaques in individuals receiving statin therapy.7 Conventional intravascular ultrasound cannot accurately assess fibrous cap thickness or rigorously characterize tissues. To this end, analysis of the radiofrequency signal from ultrasound examinations can provide additional information regarding tissue characterization. Algorithms known as ‘virtual histology’ have undergone some rudimentary validation as an approach to disclosing the content of lipid material, fibrous tissue, and calcium. A substudy of SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) evaluated the effect of aggressive statin treatment on characteristics of plaques disclosed by ‘virtual histology’.8 Compared with baseline observations, a 24-month period of treatment with rosvustatin 40 mg or atorvastatin 80 mg daily showed little or no change in the percentage of plaques occupied by tissue characterized as ‘fibrous’, but a striking...
increase in the percentage of plaque identified as densely calcified. SATURN enrolled individuals with stable atherosclerosis.

This issue of the *European Heart Journal* features IBIS-4, a substudy of the COMFORTABLE AMI trial of individuals that underwent stenting for ST-segment elevation myocardial infarction.9 This analysis of the ‘virtual histology’ in the non-target lesion vessels showed that high-intensity statin treatment (rosuvastatin 20–40 mg daily) was associated with a considerable reduction in lesion volume, as previously shown in the ultrasound studies of stable patients. As in the SATURN substudy, in IBIS-4, the percentage necrotic core did not change, but the proportion of calcified tissue increased significantly (Figure 1). Thus, while lesion volume falls consistently in these studies, ‘virtual histology’ reveals a striking increase in the estimated content of calcified tissue. The amount of tissue characterized as ‘fibrous’ not only did not increase, but actually trended down in these studies.

Why does lipid lowering seem to produce different effects in human atherosclerosis from those in animal experiments?

In contrast to the animal studies, during the 13–24 months of high intensity statin therapy in the virtual histology analyses from SATURN and IBIS-4 no increase in the fibrous tissue in atheroma was shown following lipid lowering. Why might this be? First, the degree of hyperlipidaemia produced in experimental situations exaggerates rather than replicates the dyslipidaemia in the patients enrolled in the intravascular ultrasound studies. Secondly, the human lesions have probably formed over decades, while the experimental lesions occur rapidly in response to intense interventions such as arterial injury or the extreme abnormalities in lipids used to produce lesions in the laboratory. The human lesions have a much more complex character than those in animals. Indeed, the increases in tissue characterized as calcified in both SATURN and IBIS-4 may reflect the more advanced character of the lesions in patients with established atherosclerosis. The human intervention trials change the lipid environment of the plaque for only a year or two. In the generally prolonged time course of human atherogenesis, the morphological changes wrought by this relatively brief period of drug treatment may not suffice to produce the type of increases in fibrous content observed in the exaggerated animal preparations. Yet, intensive lipid lowering can reduce events even during a brief follow-up period, particularly in high-risk patients.

We must also bear in mind that ‘virtual histology’ may have much less fidelity in reporting the characterization of tissue than the more rigorous morphological analysis permitted in the experimental situation. Also, the cross-sectional imaging modalities provide a much more limited view of functional characteristics of plaques that may relate to acute coronary events. MRI techniques have shown a decrease in microvessels during lipid lowering, an aspect of plaque biology not disclosed by ultrasound studies.10 Magnetic resonance studies have also shown decreases in phagocytic activity in rabbits treated with intensive statin therapy as disclosed by uptake of phagocytosable nanoparticles.11 The probing of indices of inflammation, including fluorodeoxyglucose uptake, reports on the metabolic activity of cells in the atherosclerotic plaque, aspects of lesions not assessed by intravascular ultrasound.12 These distinctions between human and animal studies serve as a stern reminder to temper facile extrapolation of animal results to humans. This concern has particular importance given the increasing reliance of experimentalists on atherosclerosis in genetically altered mice. The caveats regarding the exaggerated hyperlipidaemia and the short time course should heighten our vigilance regarding the direct translatability of findings in animal atherosclerosis to humans. While experimental atherosclerosis indubitably provides ways of testing mechanisms and raising hypotheses, translational studies such as those reported in the SATURN and IBIS-4 trials help to place experimental results in a clinical context.

Cautions for calcium imaging from these new lipid-lowering trials

The ultrasound results from SATURN, IBIS-4, and other accumulating data indicate that statin therapy actually increases the calcium
content of atherosclerotic plaques (Figure 1). While the coronary calcium score strongly predicts prospective cardiovascular events, the clinical significance of changes in calcium content of coronary arteries has not undergone validation as a marker of altered risk. The ultrasound results from SATURN and IBIS-4 show that increases in the lesion calcification actually correlate with conditions that improve clinical outcomes. This discordance between a change in calcium content and clinical outcomes requires consideration in those who advocate following coronary calcium scores serially to determine risk.

**Conclusion**

The results of IBIS-4 and SATURN underscore the necessity of translating the results of animal studies to humans. Including substudies such as the advanced imaging substudies represented by these two investigations illustrates how to gain new insight into human atherosclerosis to help us translate our experimental observations to humans. Ultimately, laboratory investigations and human studies go hand in hand to advance our understanding of pathobiology and the mechanisms of benefit of therapies.

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**References**