Atherosclerosis Regression, Vascular Remodeling, and Plaque Stabilization*

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Improved characterization of the composition of plaque, advances in understanding the vascular biology of atherosclerosis progression, and the development of accurate imaging techniques that allow serial determinations of plaque morphology have created the opportunity for serious consideration of pharmacotherapeutic strategies to reverse atherosclerosis. Recent studies by Nissen et al. (1–3) show that atherosclerosis regression may be a realistic goal in some patients. Although the actual amount of plaque regression and compositional change is small, there may be substantial clinical benefit. Yet, the question arises: what is the therapeutic mechanism? Is it the reduced dimension of the plaque, the decreased atheroma burden, or the consequent compositional changes that confer the clinical improvement?

What Degree of Plaque Regression Has Been Achieved by Pharmacotherapy?

In the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial (1), median atheroma volume decreased (regressed) 0.4% in the high-dose statin group versus progressed 2.7% in the moderate-dose group over an 18-month period. In the ASTEROID (A Study to Evaluate the Effect of ROSuvastatin on Intravascular Ultrasound Derived Coronary Atheroma Burden) study (2), 63.6% of patients experienced regression and mean total atheroma volume decreased 7%, with a 1% decrease in percent atheroma volume, after 24 months of treatment. Intravenous recombinant apolipoprotein A1 Milano (3) administered in 5 weekly infusions showed a 4.1% decrease in total atheroma volume (p < 0.001).

Whether or not the small magnitude of plaque reduction that is observed leads directly to the improved outcomes in similarly designed clinical studies (4–6) is a provocative question. One possibility is that although the absolute amount of regression achieved is small, it may be sufficient to produce clinical benefit (7). However, the reduction in clinical events over the subsequent 1 to 2 years seems disproportionate to simply diminishing atheroma volume by <10% (8).

Which Components of the Plaque Are Most Likely to be Targets of Pharmacotherapy?

The lipid pool is a highly accessible target for statin therapy (8,9). Cholesterol esters can be mobilized if macrophage reverse cholesterol transport is activated (9,10). By increasing cholesterol efflux, either via the reverse cholesterol transport pathway (9) or by conversion to high-density lipoprotein esters via the cholesterol ester transfer protein pathway (11,12), an imbalance between the deposition and removal of vascular cholesterol after endothelial injury may be corrected.

Fibrous tissue and ground substance would seem to be irreversible despite metabolic manipulation. However, statins have been shown to diminish smooth muscle cell accumulation and collagen deposition (13). Calcification also seems to be a nonreversible change, but this has not been formally evaluated. Conversely, inflammatory reaction in the forms of cellular migration, humoral substance release, and edema are obviously potential targets. Statins decrease inflammation, an effect correlated with clinical benefit (14–16).

Regression and Stabilization: Is There a Relationship?

Decreasing endothelial injury, diminishing lipid content, and altering the cellular elements and inflammatory milieu in the subendothelial layer may ameliorate the susceptibility to plaque rupture. The targets of regression seem to be the same as those invoked in vulnerable plaque passivation. It is probably not coincidental that the smaller, lipid-rich plaques that are prone to rupture are also the ones most likely to regress (13), nor is it accidental that clinical trials evaluating the long-term effects of intensive pharmacotherapy identify study candidates as those with acute coronary syndromes (ACS) (3–7), or include them in large numbers (1,2).

An important consideration is that vulnerable plaque is associated with positive remodeling, whereas nonvulnerable plaque undergoes negative remodeling. Plaques that show positive remodeling contain “soft” noncalcified plaque with large lipid cores and an active inflammatory process (17). Outward (or positive) remodeling is strongly associated with ACS and plaque rupture, whereas constrictive (or negative)
remodeling is more common in patients with stable angina (17,18). Diminished lipid core, negative remodeling, and small changes in plaque size are observed in response to intensive lipid lowering (19). Progressors show positive remodeling, whereas regressors show negative remodeling (20). Progression can be associated with a paradoxical increase in lumen cross-sectional area, whereas regression is not associated with any change in lumen area, suggesting a complex relationship among these factors. Treatment with statins is associated with constrictive remodeling (21). Schartl et al. (22) found that the hyperechogenicity index (composed of dense fibrous or elastic tissue) increased in atorvastatin-treated patients, whereas calcification and hypoechogenic plaque (loose fibrous, lipid, and necrotic tissue) remained constant.

In the ESTABLISH (Early Statin Treatment in Patients With Acute Coronary Syndrome) trial (23), early statin treatment in patients with ACS resulted in regression of atherosclerotic lesions 6 months later. Plaque volume was reduced 13% from baseline in the atorvastatin-treated group, but increased 9% in the control group (p < 0.03). These data further suggest an overlap between the concepts of passivation and regression.

The qualities shared by drug-induced quiescence of the potentially vulnerable plaque and regression of soft plaque suggests that stable atheromas would be more resistant to regression. However, because current studies exclude lesions with >50% luminal narrowing, whether or not high-grade lesions are less responsive to medical therapy cannot be addressed directly (8). Also, obstructive stenoses do remain capable of compensatory remodeling, and have been shown to have the potential for the greatest degree of regression (24,25). In the Stary classification (26), regression of types I to III (early and preatheroma) to normal is possible, whereas decreasing lipid content in lesion types IV to VI (atheromas, fibroatheromas, and complicated lesions) results in transformation to types VII to VIII (calcific and fibrotic lesions).

### New Findings

In this context, the findings of Nicholls et al. (27) in this issue of the Journal are extraordinarily relevant to understanding the vascular response to statin and antihypertensive therapy. The investigators re-examined the intravascular ultrasound (IVUS) findings in the REVERSAL and NORMALIZE studies (28), and determined that the more calcified atheromas were resistant to change, either progression or regression. Conversely, less calcification was a sign of potential for significant changes over time, either progression or regression. The findings suggest that the various components of atheroma respond differently to treatment with medical therapies, and can be used to target plaques that are likely to respond. A secondary conclusion is that imaging techniques that assess clinical response to therapy on the basis of changes in the degree of calcification may be theoretically flawed.

An important drawback of the study is that the investigators did not analyze whether constrictive remodeling is ascribable to diminished volume of hypolucent plaque on the IVUS. They did not describe whether the luminal dimension increased, or whether atheroma volume decreased because of compression or actual decreases in atheroma tissue. Because the remodeling index is calculated at the worst single site but atheroma volume is summed in multiple slices, the relationship between atherosclerosis regression and constrictive remodeling is ambiguous. It is intuitive that remodeling is probably one aspect of regression, but the data analysis implies that these are inseparable processes. In the investigators’ defense, IVUS is not the best imaging technique for reconciling these relationships, and it is not the most accurate method for quantifying calcification.

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<th>Table 1</th>
<th>Questions Regarding Location of Soft and/or Vulnerable Plaques</th>
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<td>Do vulnerable plaques manifest in a focal or diffuse manner within an atherosclerotic coronary segment?</td>
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<td>How frequently do they occur compared to stable or hard plaques?</td>
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<td>How far in advance of clinical events do they appear?</td>
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<td>Do they herald plaque rupture or progression routinely or just occasionally?</td>
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<td>What is the probability of a vulnerable plaque becoming active in the future? Over what time frame? Can they heal spontaneously without clinical significance or events?</td>
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### How May These Observations Alter the Diagnostic and Therapeutic Approach to Patients?

If potentially vulnerable plaque is the form of atherosclerosis most amenable to regression, then improved imaging techniques that reliably identify it are required. A better comprehension of where soft and vulnerable plaques are located within a field of atherosclerosis is necessary to develop imaging techniques most apt to reliably find them. Then, the natural history of these plaques must be definitively established for therapeutic judgments to be made once they are found (Table 1).

It will also be important to correlate traditional risk factors with mechanisms of disease and potential response to therapy. For example, male gender, diabetes, and a history of prior revascularization are independent predictors of atherosclerotic burden (25). There is also an association between negative remodeling, calcification, and age >80 years, suggesting that the elderly may be less responsive to medical therapy (29).

The work of Nissen et al. sets the stage for the development of a pharmacologic approach to producing regression of coronary atherosclerosis. In the future, patients could be treated acutely with intravenous infusions of various agents to induce stabilization and regression, and then placed on long-term oral therapy for further improvement and maintenance. The development of therapeutic programs of the future depend on understanding the mechanisms of disease...
quiescence and being able to identify which plaques and which patients are likely to have a response.

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REFERENCES