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oronary atherosclerosis is a chronic inflammatory disease of the vessel wall, frequently leading to vascular morbidity and premature mortality. Intravascular ultrasound (IVUS) allows accurate quantitative assessment of coronary plaque burden. Serial IVUS studies to assess the progression and/or regression of coronary atherosclerotic plaques indicate only modest effects of pharmacological intervention on plaque burden, even when clinical efficacy is documented. In the REVERSAL trial, after 18 months of therapy in 654 patients with coronary artery disease, atheroma volume decreased by 0.4% in patients receiving atorvastatin 80 mg but increased by 2.7% in those receiving pravastatin 40 mg. In a Japanese population, after 12 months of therapy in 307 patients with acute coronary syndrome, plaque volume in non-culprit lesions had significantly declined by 16.9% in patients receiving 4 mg of pitavastatin and by 18.1% in those receiving 20 mg of atorvastatin. That study demonstrated that coronary plaque is more likely to show regression in Japanese patients than in Western patients. However, IVUS studies of progression/regression of coronary atherosclerosis have been limited by several issues that have not yet been resolved.

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In this issue of the Journal, Takashima et al\(^1\) report on their subanalysis of data collected from groups other than the control group over a prolonged period in the JAPAN-ACS study\(^2\) to evaluate whether the degree of plaque regression was attenuated with individual risk factors of metabolic syndrome (MetS), rather than the presence of MetS itself, using IVUS. From their findings, the degree of plaque regression was similar between patients with and without MetS. In patients with MetS, however, the number of MetS components was associated with the degree of plaque regression. They show that the degree of plaque regression was significantly attenuated with increasing number of MetS components (0 component: -24.0±14.3%; 1 component: -20.8±14.0%; 2 components: -16.1±10.0%; 3 components: -18.7±11.2%; 4 components: -13.5±13.8%; \(P=0.037\)).

It is recognized that statins have anti-inflammatory and antioxidant properties, and it has been suggested that these so-called “pleiotropic” effects may account for some of the benefits of statins beyond low-density lipoprotein cholesterol lowering alone.\(^4\) Moreover, previous clinical randomized studies demonstrated that lipid-lowering therapy with statins has an effect on the primary and secondary prevention of cardio-vascular events.\(^5,6\) Recently, the availability of several intracoronary imaging techniques for use as surrogate markers of atherosclerotic burden has enabled the effects of pharmacologic intervention by statins to be examined at the vascular level in unselected Japanese populations with coronary artery disease.\(^7,8\) During the past decade, the progression and complications of coronary artery atherosclerosis has been intensively studied and stages of plaque progression have been defined.\(^9\) Because coronary atherosclerosis is a systemic, multifaceted, and multifocal disease, optimal care is likely to require systemic therapy. Statins, have pleiotropic effects that are independent of cholesterol-lowering and significantly affect the development and progression of coronary atheroma.\(^10\) However, in patients exposed to systemic risk factors, including diabetes mellitus, hypertension, dyslipidemia, and MetS, focal plaques progress, remain quiescent, or regress in an independent manner, largely because of the concomitant effect of locally acting factors. It is necessary to clarify the relationship between systemic risk factors of cardiovascular disease and coronary plaque progression and regression in response to statins. The investigators report that the number of MetS components was associated with the degree of plaque regression in patients with MetS, although the degree of plaque regression was similar between patients with and without MetS.

The study adds new insights to an important clinical issue, but several methodological issues have not yet been resolved. The first issue is that it is still controversial which arterial segments should be analyzed. In accordance with previous studies, angiographically non-significant stenotic segments were selected in this study to eliminate patients in whom coronary surgery or intervention was likely within the follow-up period. However, pharmacological effects of statin (plaque progression and regression) may be heterogeneous, because plaque accumulation is not homogeneous throughout the vessel. Problems can occur if plaque regresses in the analyzed segment but progresses in the non-analyzed segment, leading to an acute coronary event. Therefore, it should be clarified whether the pharmacological effects of statin on non-significant stenotic segments represent those on all coronary segments. The second issue is that it is still unclear which parameters (plaque volume or plaque composition) are a more suitable surrogate or have more effect on clinical outcomes. Although quantitative measurements such as volume and percentage change of plaque were used as endpoints in this study, some studies have used qualitative parameters such as plaque characterization.\(^11\) Despite these limitations, their report provides potentially...
important information that needs to be validated prospectively in larger cohorts of patients. Several questions remain: Which risk factors of cardiovascular disease are the most important in terms of plaque progression/regression? Which arterial segments should be analyzed? Which parameter is the most important surrogate: plaque volume or plaque composition? Furthermore, it remains possible that focusing on MetS alone is insufficient. That point remains uncertain and warrants further investigation.

References