Coronary artery disease is a result of atherosclerosis, a progressive disorder that forms plaques throughout the arterial system. Intravascular imaging modalities, with recent significant advances, have literally provided an insight from within the vessel. With its ability to visualize the vessel wall structure as well as luminal border, intravascular ultrasound (IVUS) has many potential advantages as a research tool for characterizing atherosclerotic plaques. IVUS has allowed us to appreciate that atherosclerotic plaque formation is not a unidirectional process, but rather the plaques do dynamically change in size and dimensions. IVUS has been used to examine the effect on plaque progression/regression with a number of different drugs including statins, aspirin, a high-density lipoprotein analogue, a thiazolidinedione, and anti-hypertensive agents.

In this issue of the Journal, Hiro et al have reported on a substudy of the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) trial comparing diabetic patients vs. non-diabetic patients. They sought to clarify the impact of diabetes on the plaque progression/regression following vigorous statin therapy. In brief, the JAPAN-ACS trial was a prospective randomized open-label parallel group study with a blind endpoint evaluation to compare the effect of 8–12 months of treatment with pitavastatin and atorvastatin. Changes in atheroma burden were examined on serial IVUS, which was performed at baseline and at 8–12 months with the use of several IVUS volumetric parameters. The main results of the JAPAN-ACS study are that there was a 16.9% reduction in percent change in plaque volume with 4 mg of pitavastatin and an 18.1% reduction with 20 mg of atorvastatin. In the substudy published in this issue of the Journal, Hiro et al found that percent change in plaque volume was significantly less in diabetic patients as compared with non-diabetic patients. The authors also found that there was a significant correlation between percent change in plaque volume and low-density lipoprotein-cholesterol (LDL–C) levels only in diabetic patients. Diabetes mellitus is a strong independent risk factor for cardiovascular mortality and morbidity, but the best means to reduce the excess cardiovascular risk has not yet been identified. Although statins are highly effective in reducing the cardiovascular events, diabetic patients still do not fare as well as non-diabetic patients even on optimal medical therapy or with invasive revascularization measures. This study has shown that reduction in plaque volume by statins is less in diabetic patients although there was a similar degree of LDL-C lowering as seen in non-diabetic patients. These results confirm that diabetic patients are at higher risk for atherosclerosis progression, and that the plaques in diabetic patients, once formed, are resistant to vigorous lipid-lowering therapy. Based upon their findings, the authors recommend a more aggressive lipid-lowering approach in diabetic patients.

There are several intriguing findings from their clinical observations. Figure 2 in their article shows that the reduction in plaque volume significantly varies among patients. There are even patients who had 50–70% reduction in plaque volume during the follow-up period. Do these patients have different clinical characteristics from other patients? Or in contrast, there are some patients who had plaque progression even when the optimal LDL-C level was reached. Do these patients have other morbidities that makes them more prone to plaque progression? Further analysis of these individual patients might yield another insight into plaque progression/regression following acute coronary syndrome. Another important finding from their Figure 2 was that a significant proportion of patients did not achieve the optimal LDL-C level of <100 mg/dl even on 4 mg of pitavastatin or 20 mg of atorvastatin. Apparently a higher dose is needed, other medications, or significant lifestyle modification in those patients to achieve the optimal level of LDL-C to reduce coronary event recurrence.

A methodological issue may merit mentioning. The authors have shown that there was a significant correlation between percent plaque reduction and LDL-C levels at follow up, and argued that vigorous reduction in LDL-C may induce a greater degree of plaque regression in acute coronary syndrome patients with diabetes mellitus. Does the result mean that vigorous LDL-C reduction is necessary only in diabetic patients? Caution should be exercised whenever looking at subgroup analyses. It is not always easy to state that there was a significant correlation in a subgroup of patients when there was no such correlation in the overall patient population. The pitfalls of subgroup analysis have been repeatedly shown since the famous example of the ISIS-2 study. Singling out a group from a clinical trial may sometimes unearth important subgroup findings, but subgroup analysis should basically be viewed as hypothesis generating, unless prespecified and appropriately powered, or unless backed up by solid scientific ground. The authors are implying how the treatment should be different between diabetic and non-diabetic patients, but it may still be important to apply aggressive treatment in non-diabetic patients as well.
Another important issue is that we have yet to fully determine whether a reduced amount of plaque can be translated into better clinical outcomes. Cardiologists are well aware that surrogate endpoints are not exactly the same as the true clinical endpoints, as exemplified by the classic CAST trial, which demonstrated that reducing a surrogate endpoint was not necessarily associated with better clinical outcomes. Although plaque progression/regression on IVUS may infer the efficacy of a given therapeutic option, we can only judge the impact of the therapy based upon clinical endpoints, which can be obtained only from large-scale randomized clinical trials. A large-scale randomized clinical endpoint trial comparing different doses of pitavastatin is currently under way (REAL-CAD trial: UMIN000002680), which may be able to answer some of the hypotheses and questions presented in this paper.

Nonetheless, the authors should be commended for their meticulous and detailed analysis using serial invasive coronary imaging with a fairly large number of patients. Although non-invasive measures (eg, multidetector computed tomography or magnetic resonance imaging) have been rapidly integrated into clinical practice, invasive imaging technologies have still many more advantages as research tools with their higher resolution and definition. IVUS will continue to play an important role in testing the effect of a drug with anti-atherosclerotic actions. In the future, qualitative IVUS analysis in addition to quantitative analysis will be of interest to further characterize changes in plaque composition following anti-atherogenic medical treatment.

References