Dyslipidemia is an important arteriosclerotic risk factor, and much research has shown that lipid-lowering therapy, primarily with a statin, can prevent both ischemic cerebral infarctions and ischemic heart disease. It was in the WOSCOPS\(^2\) and 4S\(^2\) studies that the use of evidence-based medicine in the treatment of dyslipidemia was pioneered. The results of those studies show that statins exert beneficial effects that can persist over periods as long as 10 years.

**In 2005, the results of a meta-analysis of 14 large-scale clinical trials in Europe and America showed that, as a class, statins reduced the incidence of cardiovascular events.**\(^3\) During follow-up for an average of 5 years, statins significantly reduced total deaths by 12% and coronary deaths by 19%, and reduced the relative risk of coronary events by reducing low-density lipoprotein (LDL) cholesterol by 1 mmol (38 mg/dl). This inhibitory effect on the incidence of cardiovascular events was already significant 1 year after beginning statin therapy, and the effect increased yearly thereafter. Moreover, statins exert their beneficial effects, regardless of the patient’s age, sex or history of coronary artery disease, hypertension or diabetes mellitus.

So how do statins contribute to the suppression of cardiovascular events? Many critical events in acute coronary syndrome (ACS) are explained by rupture of an unstable plaque and the resultant thrombogenesis. Plaques are defined as unstable based on the presence of a lipid deposition-related necrotic core, thinning of the fibrous capsule and inflammatory cell permeation. Stabilizing such plaques entails both quantitative and qualitative stabilization. In previous studies, which entailed screening plaques using conventional intravascular ultrasound (IVUS), quantitative stabilization of plaques by statins (ie, plaque regression) was the main concern.

In the REVERSAL study, plaque volume was compared over 18 months in patients with stable coronary artery disease who were divided into a standard treatment group, in which LDL cholesterol was reduced 25.2% using pravastatin (40 mg), and a active treatment group, in which LDL cholesterol was reduced 46.3% using atorvastatin (80 mg).\(^4\) It was found that plaque volume increased 2.7% with the standard treatment, but declined 0.4% with the active treatment.

In Japan, the ESTABLISH study reported on changes in plaque volume in ACS patients on active lipid-lowering therapy.\(^5\) They compared a control group that was not taking a statin and showed a LDL cholesterol increase of 0.7% with a group that was taking atorvastatin (20 mg) and showed a 41.7% reduction in LDL cholesterol. After 6 months of treatment, plaque volume had increased 8.7% in the control group, but had declined 13.1% in the treatment group. Because of the small sample size (70 cases) in that study, the JAPAN-ACS study subsequently started a multi-institution joint large-scale randomized controlled trial.\(^6\) They randomly assigned ACS patients who had high cholesterol and had previously undergone PCI to a pitavastatin group (4 mg/day) or an atorvastatin group (20 mg/day) and then followed the changes in plaque volume using IVUS. They found that after 8–12 months of therapy, plaque volume in nonculprit lesions had significantly declined by 16.9% in the pitavastatin group and by 18.1% in the atorvastatin group. Based on the results of the ESTABLISH and JAPAN-ACS studies, it was suggested that atheromas were more likely to show regression in Japanese ACS patients with stable coronary artery disease than in Western patients, and it was speculated that the Japanese had more soft plaque against which statins were effective.

In the COSMOS study, reported in 2009, changes in coronary plaque volume induced by rosuvastatin were followed using IVUS in Japanese patients with hypercholesterolemia who had undergone elective CAGB or PCI.\(^7\) The initial dosage of rosuvastatin was 2.5 mg/day, and it was increased gradually to a maximum of 20 mg/day to reduce LDL cholesterol to less than 80 mg/dl. Changes in plaque volume were then estimated 76 weeks later using IVUS. The average last rosuvastatin dosage was 16.9 mg/day, which elicited a significant 38.6% reduction in LDL cholesterol and a 5.1% reduction in plaque volume.

In addition, the recently presented SATURN study reported on the effect of strong statins on coronary plaque regression.\(^8\) Patients were randomly assigned to an atorvastatin (80 mg/day) group or a rosuvastatin (40 mg/day) group, and the effect of both drugs on the progress of the coronary atherosclerosis was assessed. After 104 weeks of therapy, LDL cholesterol was reduced more in the rosuvastatin group than in the atorvastatin group (70.2 vs. 62.6 mg/dl, P<0.001), and high-density lipoprotein (HDL) cholesterol was increased more by rosuvastatin than atorvastatin (50.4 vs. 48.6 mg/dl, P<0.01). However, there was no significant difference in the reduction of atheroma volume (PAV) between the 2 groups (1.22% vs. 0.99%, P=0.17).

A key question is, will quantitative plaque regression improve long-term prognosis? In the Extended-ESTABLISH
study, in which patients with ACS were followed for 4 years, the average LDL cholesterol was reduced to 72.2 mg/dl in the atorvastatin group (n=89), and the incidence of cardiovascular events were reduced to half that seen in the control group (incidence of cardiovascular events: 11 vs. 22). However, because the control group in this study took no statin at all, there was the possibility that it was the statin itself that caused the reduction in cardiovascular events. To test that idea, it is necessary to directly compare quantitative plaque regression with the reduction in cardiovascular events.

In this issue of the Journal, Miyauchi et al analyze data collected from groups other than the control group over a prolonged period in the JAPAN-ACS study to assess whether plaque regression influences the incidence of cardiovascular events. From their findings, it is clear that among ACS patients, regression of plaque in the coronary artery resulting from intensive lipid-lowering therapy did not suppress the incidence of cardiovascular events. In addition, it was suggested that the initial HDL cholesterol value and reverse remodeling of the coronary artery might affect the incidence of cardiovascular events. These are very important findings.

In the first place, plaque evaluation using IVUS is only a surrogate endpoint; the hard endpoint is the suppression of cardiovascular events, which is another thing. Because most ACS patients have multiple plaques in addition to a culprit lesion, and because 70% of ACS cases are caused by a rupture, plaque regression was connected directly to the reduction in event risk. This makes plaque regression in ACS patients an extremely useful surrogate marker. However, although lipid-lowering therapy improves vascular remodeling, as revealed on coronary arteriography, the change is extremely small and does not account for the reduction in cardiovascular events elicited by statins. This suggests that for the improvement obtained with intensive lipid-lowering therapy, quantitative improvement of coronary lesions is not a primary factor, but rather that qualitative improvement is essential.

In that regard, Otagiri et al evaluated plaques using an integrated-backscatter-IVUS system, which we developed previously, in ACS patients treated with intensive lipid-lowering therapy and found that the make-up of the plaque tissue changed from lipid to fibrous with regression of the plaque. In the future, the relation between stabilization of unstable plaques and changes in their composition should become a subject of discussion.

References


