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Plaque Regression and Stability Evaluated by Intravascular Ultrasound and Coronary Angioscopy: A Review

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1. Introduction

Although atherosclerosis seems to be continuously progressive and irreversible, it has been being demonstrated that substantial regression or stabilization of atherosclerotic lesions can occur by some interventions improving its determinants. However, the concepts of plaque regression or stabilization are not so new. It has been reviewed that the first reported observation of plaque regression could be found in the 1920s (Wissler, 1976), in which switching cholesterol-fed rabbits to low-fat chow over 2–3 years resulted in arterial lesions becoming more fibrous with a reduced lipid content. Later on, as the earliest prospective studies, a couple of previous studies in the 1950s have shown distinctive facts of plaque shrinkage or favorable change of its tissue components due to special diet therapy or some specific medications. In 1957 Friedman M et al. documented a result from prospective, interventional study demonstrating substantial shrinkage of atherosclerotic lesions performed in cholesterol-fed rabbits (Friedman, 1957). The dietary regimen raised total plasma cholesterol to around 1,000 mg/dl, and then animals received intravenous injections of phosphatidylcholine. They reported that after less than a week or so the size of the plaques as well as cholesterol stores within the arterial wall were significantly reduced. This striking report with some following supportive studies and reviews (Wissler, 1976; Armstrong, 1976; Malinow, 1983) has been surprisingly ignored for long years because of some beliefs regarding distinctive persistent characteristics of atherosclerosis, the negative history of which was reviewed by Stein Y, et al (Stein, 2001). However, various additional facts of plaque regression by some interventions have been demonstrated in other type of animal studies (Maruffo, 1968; Armstrong, 1970) since then without strong interests among general cardiologists.

The first prospective study demonstrating plaque regression in humans might be the one documented by Ost CR, et al. in 1967 (Ost, 1967). In the study, approximately 10% of patients treated with niacin showed improved femoral angiograms. Numerous additional larger trials of lipid lowering have then shown angiographic evidence of regression. However, though statistically significant, the resulted effects were very small (Brown, 1993), in which the improvement of percent stenosis of lumen were at most 2%. Accumulations of clinical evidences demonstrating the benefits of lipid-lowering in clinical outcome therefore yield

this kind of “angiographic paradox”. This paradox suggested that the improvement of clinical outcome was not necessarily associated with the improvement of arterial lumen diameter. However, various pathological findings have resolved this enigma. First, the answer came from the recognition of a phenomenon called as vascular remodeling (Glagov, 1987). The next answer was regarding the realization that lipid-rich, vulnerable plaques have a central role in acute coronary syndromes (Fuster, 1992; Libby, 1995). Vulnerable plaques are usually small in size and cause less than 50% occlusion. The vulnerable plaques are generally filled with intracellular and extracellular lipid, rich in macrophages and tissue factor, having low concentrations of smooth muscle cells as well as a thin fibrous cap (Shah, 2003; Falk, 1995). Rupture of a vulnerable plaque provokes the formation of a robust thrombosis causing critical lumen occlusion. It has been estimated that lipid lowering therapy does not induce lumen expansion but rather has most impact on risk reduction by the remodeling and stabilization of small, rupture-prone lesions.

Based on these past histories, a new era of medication strategy had come in late 1980s with an appearance of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) in clinical setting. Many large-scale pivotal clinical trials have then shown that statins remarkably reduced both atherogenic lipoproteins as well as cardiovascular morbidity and mortality (Scandinavian Simvastatin Survival Study Group, 1994; Sacks, 1996; The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998). However, the angiographic paradox still exists in this era even with a strong statin (Ballantyne, 2008). To overcome the paradox by in-vivo detection of plaque regression and stabilization, new development of commercially available intravascular imaging modalities contributed a lot to understanding the mechanism of statins for reducing cardiovascular events in patients with coronary artery disease. These modalities can visualize plaque size and its serial changes, and can even visualize tissue components within plaque to be able to estimate plaque vulnerability.

In this chapter, readers will be able to describe the imaging mechanisms of intravascular ultrasound and coronary angiography especially for observing plaque regression and stabilization. Then, a variety of important evidences of plaque regression and stabilization evaluated by these systems will be introduced in order to understand the clinical feasibility of these modalities as well as to recognize current clinical cutting edge of knowledge regarding plaque regression and stabilization.

2. Assessment of plaque regression and stability

2.1 Assessment with intravascular ultrasound

Intravascular ultrasound (IVUS) can provide gray-scale images with an accurate representation of plaque cross-sectional areas and volumes. Therefore, IVUS can follow in-vivo plaque volumes serially in same patients. IVUS imaging is performed with an automatic catheter-pullback system to acquire consecutive cross-sections of arterial wall. Cross-sectional plaque area for each section can be measured by tracings of lumen-intima border as well as media-adventitia (External elastic membrane area: EEM area). The difference of the two areas corresponds to the plaque area (intima-media complex area). The product of a certain constant distance-related interval and the integration of these plaque areas calculated from each cross-section resulted in total plaque volume of interest. The certain interval varied from 0.1 mm to 10 mm according to the study concept. The IVUS indices used in major clinical trials were as follows: 1) Nominal Change of Percent Plaque

Volume: This is obtained from the absolute nominal change between the baseline and the follow-up period in percent value of plaque volume compared to EEM volume; 2) Percent Change in Plaque Volume: This is calculated from (follow-up plaque volume minus baseline plaque volume) divided by (follow-up plaque volume) times 100. It has been suggested that the former index might be more closely related to clinical outcome (Nicholls, 2010). However, this index would show “regression” even in case of increase in EEM volume (positive remodeling) without any change in plaque volume itself. The latter one may be more reflected to a particular change of a special plaque of interest. Although it has not yet been directly proved that these IVUS parameters are useful surrogate markers for clinical outcome, IVUS have demonstrated a remarkable change in plaque volume by use of statins. Furthermore, current technologies of IVUS can perform tissue characterization of plaque components with a color-coded image. In Japan, three color-IVUS systems are now commercially available. In addition, various other methods have been proposed with sophisticated mathematical models to detect tissue-specific acoustic properties. An overview of these methods is as follows.

It was originally expected that tissue components within plaque could be identified from the video-intensity pattern of IVUS images. Subsequent studies, however, demonstrated significant limitations of tissue characterization by IVUS intensity patterns alone, especially in discriminating fibrous and fatty tissues or in assessing plaque vulnerability (Hiro, 1996; Hiro, 1997; Kimura, 1995; Jeremias, 1999). To overcome this limitation, special attempts to analyze the echo-signals including the raw radiofrequency (RF) ultrasound signal that comes from plaque segments. The echo signal, which is originally emitted as a pulse wave from the ultrasound catheter tip, is produced at the interface between the two materials having different acoustic impedances. There are several interfaces within plaque, so time-series RF signal is then formed according to the degree of acoustic impedance mismatches and geometrical structure and distribution of each tissue components. Therefore, it can be expected that detection of special acoustic characteristics for each tissue component can allow us to visually identify it. Based upon this hypothesis, several successful studies have been reported, including the three commercially available machines.

2.1.1 Integrated backscatter analysis (IB-IVUS®)

This system visualizes the distribution of quantitative power or energy of echo for each segment of plaque using fast-Fourier transform of time-series RF signal. The total energy range is divided into four local ranges which correspond to four kinds of tissue components. This simple algorithm provides a high accuracy with a reliable sensitivity and specificity (Kawasaki, 2002).

2.1.2 Autoregressive spectral analysis (Virtual histology®)

The echo spectrum is first obtained by autoregressive spectral analysis for each portion of plaque. Autoregressive spectral analysis can obtain a spectrum of time-series signal, which has a different mathematical processing from fast-Fourier transform. Eight kinds of acoustic parameters are then measured for each spectrum. A classification tree which flows according to the values of the eight parameters makes the final diagnosis to discriminate four tissue types. The classification tree is already prepared with previous survey using tissue-known echo-samples (Nair, 2002). (Figure 1)

Fig. 1. VH-IVUS
A pre-defined classification tree according to eight acoustic parameters identifies four kind of tissues.

2.1.3 Attenuation-slope analysis

The ultrasound energy is attenuated when running through tissues. The degree of attenuation depends upon the frequency. It is hypothesized that the frequency-dependence of ultrasound attenuation is different according to the tissue type. This system colorized the degree of frequency-dependent of ultrasound attenuation (Wilson , 1994).

2.1.4 Angle-dependence analysis

It has been demonstrated that intravascular ultrasound (IVUS) backscatter from fibrous tissue is strongly dependent on the ultrasound beam angle of incidence (Picano , 1985). It was found that this technique provides an accurate representation of the thickness of the fibrous cap in atherosclerotic plaque, the echo-intensity of which is highly angle-dependent (Hiro , 2001). (Figure 2)

Fig. 2. Angle-dependence analysis
Highly angle-dependent area (yellow) is accurately corresponded to fibrous cap. Incited from (Hiro, 2001)

2.1.5 Fractal analysis

This method obtained the value of fractal dimension, which represents how complex the echo-segment is from each plaque portion. It was found that the echo-signal was more complex from lipidic tissue compared to fibrous tissue (Hiro, 2000).

2.1.6 Wavelet analysis

Wavelet analysis of RF IVUS signals is a novel mathematical model for assessing focal geometrical differences within arterial walls. Color coding of the wavelet correlation coefficient derived from the RF signal allows detection of changes in the geometrical profile of time-series signals to derive an image of plaque components (Figure 3). Murashige et al. showed that lipid-rich plaques could be detected with acceptable sensitivity and specificity using this method (Murashige, 2005). (Figure 3)

Fig. 3. Wavelet analysis

Wavelet correlation mapping of the RF signal from lipid-rich plaque revealed a unique stripe pattern. Incited from (Murashige, 2005)

2.1.7 Neural network theory

This method analyzes the RF signal with a self-learning system that resembles real neural actions in humans or animals. Kubota used a k-nearest neighbor method to classify tissue types of coronary plaque (Kubota, 2007). The k-nearest neighbor method is like a decision-making system by a majority vote. When a time-series signal is evaluated, there are numerous parameters obtained by a signal-processing system. The parameters (total number = n) from a signal area of interest, therefore, can yield a coordinate as: $(x_1, x_2, x_3, \dots, x_n)$ (Let's call now point P). In such space, previously prepared coordinates obtained from the tissue-known signal exist around the point P. When you look around the point P for a constant distance, you can count the number of tissue-known points. If the majority of tissue-known points is from lipidic tissue, then the point P- corresponded tissue area is considered to be a lipidic tissue. Kubota R et al. modified this k-nearest method to enhance the accuracy of tissue characterization by IVUS. Sathyanarayana S, et al. performed

this kind of analysis in analyzing spectral similarity of the RF signal (Sathyanarayana , 2009). It was hypothesized that each tissue component has a special characteristic spectrum shape. This system is now commercially available with a system name, iMap ® (Figure 4). This system can identify four kinds of tissue, which definitions are slightly different from the one used in VH-IVUS. The imaging system is unique, in which the confidence level of identification of tissue types is represented the brightness of each color corresponded to each tissue type. The brightness of confidence level represents the degree of majority in the decision-making space of the k-nearest neighbor method.

Fig. 4. iMap system.
The system of iMap perform color mapping of four different tissue types. Confidence level of each tissue identification is reflected on the brightness of each color. CL:Confidence level

2.2 Assessment with coronary angiography

Coronary angiography provides a full-color perspective of the intravascular surface morphology of plaque. This technique also accurately represents the presence of thrombi. In this method, vulnerable plaques are detected as yellow plaques compared to the normal surface which is depicted as white. The degree of yellow grade of the plaque surface is corresponded to how rich lipidic components are under the plaque surface or how thin the thickness of fibrous cap is within the plaque. It has been documented that the degree of yellowness of plaque as well as the number of yellow plaque observed are related to plaque vulnerability and poor patient prognosis in cardiovascular outcome (Kodama , 2000; Ueda , 1997; Ueda , 2004; Naghavi , 2003; Asakura , 2001; Ohtani , 2006; Mizuno, 1992). This modality together with IVUS has provided various aspects of plaque regression and its stability.

2.3 Problems in assessing plaque vulnerability

Naghavi M, and a lot of famous investigators collaborated to try to establish the criteria for defining vulnerable plaques(Naghavi , 2003). As the major criteria, the plaque with the following characteristics can be identified as vulnerable plaque:

- Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)
- Thin cap with large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured plaque
- Stenosis more than 90%

As the minor criteria:

- Superficial calcified nodule
- Glistening yellow by coronary angioscopy
- Intraplaque hemorrhage
- Endothelial dysfunction
- Outward (positive) remodelling

So what criteria can we examine generally in all patients?

IVUS and coronary angioscopy can actually represent the thickness of thin fibrous cap and the volume of lipid-rich core. However, Imoto K, et al demonstrated in the study with a biomechanical simulation of in-plaque stress distribution that plaques with the same thickness of fibrous cap does not necessarily indicate the same vulnerability to rupture (Imoto, 2005). Ambrose JA documented a get-to-the-point criticism in search of the vulnerable plaque(Ambrose, 2008). He proposed several prerequisites to establish the way to identify vulnerable plaque for distinctive improving patient vulnerability.

1. "Vulnerable plaque" caused by a thin-capped fibroatheroma can be identified with modern technology.
2. A "vulnerable plaque" caused by plaque erosion should be identifiable.
3. The number of "vulnerable plaques" is known, and the number is limited.
4. The natural history of a "vulnerable plaque" has been identified in patients treated with optimal systemic therapies.
5. An interventional approach applied locally or regionally to an asymptomatic "vulnerable plaque" is proven to reduce future events relative to the best systemic medical therapy.

He criticized that among these prerequisites, only the first is currently possible, but the others are not yet established and require further study. We have to realize that thin-capped fibro-atheroma is not a single cause of acute coronary syndrome. Erosion, inflammatory cell infiltration, intraplaque hemorrhage or local endothelial dysfunction should be also evaluated. Fukumoto Y, et al. has reported that color mapping of shear stress along plaque surface using IVUS images is useful for identifying future rupture point(Fukumoto, 2008), since it was found that local concentration of shear stress is related to a trigger of plaque rupture. Therefore, numerous local risk factor should be considered for identifying the vulnerable plaque. Even when the method is established, still we have additional problems. We have to possess a detailed data on the likelihood of a cardiac event for a proven "vulnerable plaque." For example, if only 5% of a given plaque type as identified will develop an event on follow-up, all 20 of these plaques will need to be treated with a new procedure to prevent 1 event, that is, NNT=20(Ambrose, 2008). Is this allowed in using the expensive stent therapy? Therefore, a well-designed clinical trial should be performed to prove the clinical feasibility of preventive therapy for a particular plaque which is identified as vulnerable.

3. Clinical evidences using intravascular imagings

A number of human studies in a single center demonstrated the beneficial effects of statin or other lipid-lowering drugs in plaque progression/regression and stabilization. For example, Takagi T, et al. documented in 1997 as one of the earliest reports on IVUS observation that administration of pravastatin reduced serum lipid levels and progression of coronary artery atherosclerotic plaque (Takagi, 1997). Kawasaki et al. reported with use three-dimensional color mapping of tissue components with IB-IVUS system that statin therapy reduced the lipid component in patients with stable angina without reducing the degree of stenosis (Kawasaki, 2005). Previous coronary angioscopic studies have demonstrated that statin therapy stabilizes yellow color grade of coronary plaques (Takano, 2003).

Using IVUS and/or coronary angioscopy, various human multicenter trials with statins have offered important information on plaque regression. In the following paragraphs, the trials including REVERSAL (Nissen, 2004), ASTEROID (Nissen, 2006), ESTABLISH (Okazaki, 2004), JAPAN-ACS (Hiro, 2009), COSMOS (Takayama, 2009), TWINS (Hirayama, 2009) and TOGETHAR (Kodama, 2010) are overviewed and discussed. These trials demonstrated not only the degree of regressive effects of statins on plaque, but also key determinants and mechanisms of plaque regression.

3.1 The REVERSAL study (The Reversal of Atherosclerosis with Aggressive Lipid Lowering trial) (Nissen, 2004)

This was to compare the 18-month effect of regimens designed to produce intensive lipid lowering or moderate lipid lowering on coronary artery atheroma burden and progression. Patients with stable coronary artery disease were randomly assigned to receive a moderate lipid lowering regimen consisting of 40 mg of pravastatin or an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin. The primary efficacy parameter was the percentage change in atheroma volume (follow-up minus baseline). Baseline low-density lipoprotein cholesterol level (mean, 150.2 mg/dL in both treatment groups) was reduced to 110 mg/dL in the pravastatin group and to 79 mg/dL in the atorvastatin group ($P < 0.001$). It was shown that progression of coronary atherosclerosis occurred in the pravastatin group (median change = 2.7%; 95% CI: 0.2% to 4.7%; $P = 0.001$) compared with baseline. Progression did not occur in the atorvastatin group (-0.4%; CI -2.4% to 1.5%; $P = 0.98$) compared with baseline. It was concluded that for patients with coronary heart disease, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. In this study, remarkable regression of plaque by statin was not yet clearly indicated.

3.2 The ASTEROID study (A study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) (Nissen, 2006)

This study was to assess whether very intensive statin therapy could regress coronary atherosclerosis as determined by IVUS imaging. Patients with stable coronary artery disease received intensive statin therapy with rosuvastatin, 40 mg/day. Two primary efficacy parameters were prespecified: the change in percent atheroma volume (PAV) and the change in nominal atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline (observation period: 24 months). Baseline low-density lipoprotein cholesterol level (mean, 130.4 mg/dL) was reduced to 60.8 mg/dL ($P < 0.001$). For the

primary efficacy parameter of PAV, the mean decrease was -0.98% and the median was -0.79% ($P<0.001$ compared with baseline). For the second primary efficacy parameter, change in atheroma volume in the 10-mm subsegment with the greatest disease severity, the mean change was -6.1 mm^3 , and the median change was -5.6 mm^3 ($P<0.001$ compared with baseline). This change represents a median reduction of 9.1% in atheroma volume in the 10-mm segment with the greatest disease severity. It was concluded that very high-intensity statin therapy using rosuvastatin 40 mg/day achieved significant regression of atherosclerosis. In this study, remarkable regression of plaque by statin was first clearly indicated as a multicenter study result. Regression can be considered to be a completely different process from inhibition of progression, so this result was striking.

3.3 The ESTABLISH study (Early Statin Treatment in Patients with Acute Coronary Syndrome: Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis during Half a Year after Coronary Event) (Okazaki, 2004)

This was a single-center, but should be discussed, since the results were historical. Most unique part of this study was study population. This study investigated the 6-month effect of early statin treatment by atorvastatin of 20 mg daily on plaque volume of a nonculprit lesion by serial volumetric intravascular ultrasound in patients with ACS. All patients who underwent emergency coronary angiography and percutaneous coronary intervention were randomized to intensive lipid-lowering therapy ($n=35$; atorvastatin 20 mg/day) or control ($n=35$) groups after PCI. Volumetric intravascular ultrasound analyses were performed at baseline and 6-month follow-up for a non-PCI site in 48 patients (atorvastatin, $n=24$; control, $n=24$). LDL-C level was significantly decreased by 41.7% (124.6 to 70.0 mg/dL) in the atorvastatin group compared with the control group, in which LDL-C was not significantly changed (123.9 to 119.4 mg/dL) (atorvastatin vs. control : $P<0.0001$). Plaque volume was significantly reduced in the atorvastatin group (mean 13.1% decrease) compared with the control group (8.7% increase; $P<0.0001$). These results of the degree of plaque regression by statin were surprisingly remarkable compared to the former reports from foreign countries for patients with stable coronary artery disease. This evidence was then proved by the JAPAN-ACS study which is discussed next.

3.4 The JAPAN-ACS study (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) (Hiro, 2009)

This study had almost similar protocol for selecting patients with acute coronary syndrome and measuring protocol to the ESTABLISH study. Major difference was that this was a non-inferiority test with randomization between patients with taking atorvastatin 20 mg/day and patients with pitavastatin of 4 mg/day . Therefore, based on the ESTABLISH study, the objective of this study was to evaluate whether the regressive effects of aggressive lipid-lowering therapy with atorvastatin on coronary plaque volume in patients with acute coronary syndrome are generalized for other statins in multicenter setting (observation period: 8-12 months). The primary end point was the percentage change in nonculprit coronary plaque volume. Baseline low-density lipoprotein cholesterol level (mean, 133.8 and 130.9 mg/dL in atorvastatin, and pitavastatin groups, respectively) was reduced to 84.1 mg/dL (-35.8% decrease: $P<0.001$, compared to the baseline) in the atorvastatin group and to 81.1 mg/dL (-36.2% decrease: $P<0.001$) in the pitavastatin group. The mean percentage change in plaque volume was -18.1% and -16.9% ($p=0.5$) in the pitavastatin and atorvastatin

groups, respectively, which was associated with negative vessel remodeling. The upper limit of 95% confidence interval of the mean difference in percentage change in plaque volume between the two groups did not exceed the pre-defined noninferiority margin of 5%, suggesting noninferiority between the two groups. It was thus proved that the efficacies of both group were equivalent in the percent change of plaque volume. This results supported the data of the ESTABLISH study that early administration of statins after the onset of ACS has the potential to reverse the process of atherosclerosis. This observation also generalized the effect of statins other than atorvastatin on plaque volume in the setting of ACS. The reason why plaques in Japanese patients with ACS shows greater regression by statin compared to the foreign patients with stable coronary artery disease might be shown by the COSMOS study which is summarized later.

Recently interesting results came from a sub-analysis of the JAPAN-ACS study (Hiro, 2010). It demonstrated that the regression of coronary plaque induced by statin therapy after ACS was weaker in diabetic patients than their counterparts, although the reduction of LDL-C level was similar between diabetic group and non-diabetic group. In addition, it was also interesting that significant correlation between % change of PV and low-density lipoprotein cholesterol (LDL-C) level was found in patients with diabetes mellitus ($n=73$, $P<0.05$, $r=0.4$), whereas there was no significant correlation between the 2 parameters in patients without diabetes mellitus ($n=178$). This study was suggesting that there might be LDL-C dependent mechanism and LDL-C non-dependent mechanism in plaque regression by statin. It might be possible that in diabetic patients LDL-C non-dependent mechanism is inhibited by unknown mechanism resulting smaller regression of plaque volume. The mechanism of plaque regression may have various steps and pathways.

3.5 The COSMOS study (The Coronary Atherosclerosis study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) (Takayama, 2009)

This study was the first multicenter study on IVUS observation of plaque with use of statin for Japanese patients with stable coronary artery disease. This was as a single arm 76-week study to investigate the effect of rosuvastatin on plaque volume in such patients. The patients received first rosuvastatin 2.5mg/day, which could be increased at 4-week intervals to ≤ 20 mg/day. The primary end point was the percentage change in nonculprit coronary plaque volume. The change in the serum low-density lipoprotein-cholesterol level from baseline to end of follow-up was $-38.6 \pm 16.9\%$ (mean: 140.2 to 82.9 mg/dL, $P<0.0001$). Percent change of plaque volume, the primary endpoint, was $-5.1 \pm 14.1\%$ ($P<0.0001$). The degree of plaque regression compared to the degree of reduction of LDL-C level was just in-between the results from the foreign patients with stable coronary artery disease and the ones from Japanese patients with acute coronary syndrome (Figure 5). Therefore, Japanese patients as well as patients with acute coronary artery disease can easily show regression of plaque volume compared to the foreign patients and patients with stable coronary artery disease, respectively. This might be due to the difference in plaque tissue characteristics. It has been reported that patients with ACS have many greater-risk nonculprit plaques (Asakura, 2001; Burke, 1997).

3.6 The TWINS study (Hirayama, 2009)

This study as well as the TOGETHAR study were using not only IVUS but also coronary angiography to examine the effect of statin on plaque characteristics. The aim of this study

Fig. 5. Meta-regressive analysis of the relationship between LDL-C level and the percent change of plaque volume.

Some data was not the result as the primary endpoint of the study, which was re-estimated by documented data. Black line represents the meta-regression curve for the foreign patients with stable coronary artery disease. Red line represents the one for Japanese patients with ACS. The data of the COSMOS study is just in-between the two lines. See each protocol and result for each study from the papers by (Takano , 2003; Nissen , 2004; Nissen , 2006; Okazaki , 2004; Hiro , 2009). The data of A-PLUS was obtained from the paper by (Berry , 2007). ATV:atorvastatin, PRV:pravastatin, RSV:rosuvastatin, PTV:pitavastatin.

was to elucidate 80-week time course of atorvastatin-induced changes in vulnerable plaque using angioscopy and intravascular ultrasound (IVUS). Patients with coronary artery disease received atorvastatin of 10-20 mg/day. Mean baseline LDL-C level of 144.4 mg/dL was significantly reduced to 86.4 mg/dL at week 28 and to 89.4 mg/dL at week 80. Angioscopic images were classified into 6 grades (0-5) based on yellow color intensity. The mean angioscopic grade of 58 yellow plaques significantly decreased from 1.5 (95% confidence CI: 1.2 to 1.8) to 1.1 (95%CI 0.9 to 1.3, $P=0.012$) at week 28 and 1.2 (95%CI :0.9 to 1.4, $P=0.024$) at week 80, compare to the baseline (no significant difference between week 28 and week 80). Mean volume of 30 lesions, including the 58 yellow plaques, significantly reduced -8.3% (95%CI: -11.5 to -5.2) at week 28 ($P<0.001$ for baseline vs week 28) and -17.8% (95%CI -23.9 to -11.8) at week 80 ($P<0.001$) for baseline vs week 80. It should be noted

that qualitative changes in plaque occurred relatively early after the beginning of atorvastatin therapy (by week 28), and that quantitative changes in atheroma volume occurred continuously, even after week 28, up to week 80. These non-parallel results suggest that there may be two different, probably independent, mechanisms involved in the reduction of vulnerability, improvement in characteristics, and reduction of the volume of yellow plaques. These different time courses suggested that the improvement in plaque characteristics occurs early, whereas atheroma volume regression occurs over a prolonged period of time.

3.7 The TOGETHAR study (Kodama, 2010)

This multicenter study also revealed that the stabilization and regression of atherosclerotic plaques by statin may differ. This study was performed to assess coronary plaque regression and stabilization following 52 weeks of pitavastatin treatment (2 mg/day). Low-density lipoprotein-cholesterol (LDL-C) was reduced 34.5% (mean: 145.0 to 93.6 mg/dl, $P < 0.001$). Yellow grade decreased (2.9 ± 0.8 to 2.6 ± 0.7 , $P = 0.040$) during 52 weeks. However, percent atheroma volume on IVUS did not change during 52 weeks. It was concluded that fixed dose pitavastatin stabilized vulnerable coronary plaques by the reduction of yellow grade without significant reduction of plaque volume. The fact that plaque volume was not significantly changed was probably due to the characteristics patient populations that did not include patients with ACS. These results suggested that plaque stabilization and plaque regression reflect independent processes mediated by different mechanisms, which has been previously reported (Kawasaki, 2005; Scharf, 2001).

4. Future perspectives

Recently new intravascular imaging modalities have been proposed, including optical coherence tomography. Furthermore, noninvasive imaging system, such as multi-detector CT and MRI, can visualize coronary plaques more vividly than before. Therefore, brilliant future in terms of plaque imaging can be expected. We may have to produce the following future as: Fully understanding of the plaque regression and stabilization in terms of changes in tissue component; Perfect prediction of plaque rupture with an absolute value of its likelihood within a certain period; More detailed elucidation of mechanism of acute coronary syndrome, which is fully imaged by some imaging modalities; Best therapeutic ways which are clarified based on the data of plaque imaging. Therefore, the research world of plaque imaging for plaque regression and stability has still a wide variety of clinical goals.

5. Conclusion

Advanced developments in the field of intravascular ultrasound and angioscopy are offering their capabilities of accurately measuring plaque volume as well as identifying tissue components. These technologies significantly help understand in vivo pathological reactions of plaque by lipid-lowering therapy especially in plaque regression and stabilization. Furthermore, these technologies are providing numerous reliable evidences with multicenter studies.

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Intravascular ultrasound (IVUS) is a cardiovascular imaging technology using a specially designed catheter with a miniaturized ultrasound probe for the assessment of vascular anatomy with detailed visualization of arterial layers. Over the past two decades, this technology has developed into an indispensable tool for research and clinical practice in cardiovascular medicine, offering the opportunity to gather diagnostic information about the process of atherosclerosis in vivo, and to directly observe the effects of various interventions on the plaque and arterial wall. This book aims to give a comprehensive overview of this rapidly evolving technique from basic principles and instrumentation to research and clinical applications with future perspectives.

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