Chapter 19
Pharmacological Intervention

Masamichi Takano

Abstract Ischemic heart disease is a life-threatening disorder; especially acute coronary syndrome (ACS) is a major cause of death in the world. Coronary arteries of angiographic significant stenosis with patients' symptoms or certified myocardial ischemia are generally administered by revascularization therapies, such as coronary artery bypass surgery and percutaneous coronary intervention using balloon angioplasty or metallic stent deployment. However, ACS often arises from mild to moderate stenosis without the evidence of myocardial ischemia in a brief period. Accurate prospect of ACS is therefore complicated at the present, and pharmacological intervention as preventive insurance is extremely important. Among medical treatment for coronary risk factors, lipid-lowering therapy represented by administration of HMG-CoA reductase inhibitor (statin) is the most powerful, practical, and established way to prevent against ACS. From an angioscopic point of view, morphological changes in atherosclerotic coronary plaque focused on lipid-lowering intervention are reviewed in this chapter.

Keywords Vulnerable plaque • TCFA • Yellow plaque and statin

19.1 Pathogenesis of Acute Coronary Syndrome

In the clinical settings, ischemic heart disease is roughly classified into stable condition and unstable one. The former shows stable angina pectoris (stable coronary syndrome) and the later indicates acute coronary syndrome (ACS) including unstable angina pectoris, acute myocardial infarction, and sudden coronary death. Although they have severe lumen narrowing or complete occlusion of epicardial artery in common, their pathogenesis is decisively difficult according to previous histological investigations [1]. The remarkable findings in most ACS cases are the presence of atherosclerotic plaque disruption and massive thrombus at the culprit lesion. They are unusually found in stable coronary syndrome. Therefore, it is under-

M. Takano, M.D., Ph.D. (✉)
Cardiovascular Center, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamakari, Inzai, Chiba 270-1694, Japan
e-mail: takanom@nms.ac.jp

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stood that plaque disruption and subsequent formation of flow-limiting thrombus is the principal pathogenesis of ACS [2]. Plaque disruption is pathologically divided into its rupture and superficial intimal injury, so-called erosion [3]. In addition, ruptured plaque has large lipid core under a thin fibrous cap, and infiltration of inflammatory cells, such as monocyte, macrophage, and lymphocyte [4]. Lipid-rich plaque of the fibrous cap thickness <65 μm is specially designated thin-cap fibroatheroma (TCFA). Rupture of TCFA and plaque erosion approximately account for two thirds and one third of ACS, respectively. Other minority is shallow-calcified nodule with denudated endothelium [5].

19.2 Vulnerable Plaque

There is terminology of vulnerable plaque that is defined as a plaque to provoking its disruption or a high-risk plaque of future disruption in a narrow sense [6]. According to angiographic findings previous to the ACS event, ACS often arises from mild to moderate stenosis that invites neither chest symptoms nor myocardial ischemia on stress test [7], despite the fact that sever stenosis is one of the factors in plaque vulnerability. Expecting the time and site of plaque disruption as the motivating step toward the onset of ACS and rapid growth of thrombus as the final step is certainly complicated. Therefore, vulnerable features have been investigated fragmentarily applying the culprit plaque that had already caused ACS.

The characteristics of vulnerable plaque based on pathological analysis and clinical examinations by use of coronary imaging devices are shown in Table 19.1. The presence of TCFA and the absolute volume of atheroma play a key role in plaque vulnerability and that is demonstrated by a recent prospective study of virtual histology intravascular ultrasound (IVUS), PROSPECT trial [8]. Taken together with the pathogenesis of ACS and the frequency of TCFA in the culprit lesion, TCFA is unmistakably representative of vulnerable plaque. Great energy of researchers has been invested into detection of TCFA instead of identifying true vulnerable plaque [9].

19.3 Atherosclerotic Plaque Through Coronary Angioscopy

19.3.1 Coronary Angioscopy

Coronary angiogram is still gold standard for diagnosis of ischemic heart disease. However, this method is just luminology and powerless to estimate the quality of the vessel wall. To date several sorts of intracoronary imaging devices (e.g., conventional gray-scale IVUS, virtual histology IVUS, integrated backscatter IVUS, optical coherence tomography [OCT], near-infrared spectroscopy [NIRS])

Table 19.1 Characteristics of vulnerable plaque

Macro-morphological aspect
Thin cap with large lipid core (Thin-cap fibroatheroma: TCFA)
Positive remodeling
Glistening or intense yellow plaque
Fissured plaque
Superficial calcified nodule
Spotty calcification
Intraplaque hemorrhage
Severe stenosis
Micromorphological aspect
Infiltration of inflammatory cells
Endothelial denudation
Physiological or functional aspect
Endothelial dysfunction

have been developed, and they are available for evaluation of plaque composition [10–13]. Coronary angioscopy is a unique imaging system that provides direct visualization of vessel lumen. Information about forward-looking angioscopic image, such as color, three-dimensional, and detailed configuration of lumen surface, is capable of diagnosing macro-morphology of atherosclerotic plaque, thrombus, and proliferating neointima in coronary bare-metal and drug-eluting stents [14–21].

Atherosclerotic plaque is broadly divided into white plaque and yellow one according to its surface color. Similarly, intracoronary thrombus is classified into white, red, mixed (white and red), and pinkish thrombus [22, 23]. On the basis of superficial form of the plaque, that is also categorized into simple plaque with smooth surface and complex one of irregularity. Findings of complex plaque include intimal flap, dissection, fissuring, ulceration, and disruption.

It is noticeable that coronary angioscopy can sensitively detect a tiny thrombus in comparison with other imaging [24]. Although thrombus transformed digital signals on the other imaging may be missed, visual color on the angioscopy simplifies diagnosis of the thrombus. By contrast, there is some weakness in angioscopic evaluation; quantification of distance or volume is impossible and its diagnosis is limited only to the lumen surface. They are compensated by cross-sectional IVUS or OCT images.

19.3.2 Angioscopic Findings of Plaque Vulnerability

Disrupted plaque in the culprit lesion of ACS is no longer vulnerable in the narrowest sense. Nevertheless, observation of the culprit plaque surely makes us understand plaque vulnerability before the conclusive event. At angioscopic

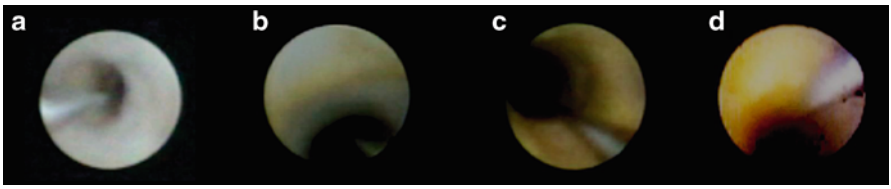

Fig. 19.1 Color of atherosclerotic coronary plaque. Semiquantitative color classification of coronary plaque is shown. Intense yellow plaque sometimes has glisten in the lumen. (**a**) White plaque (grade 0). (**b**) Light yellow plaque (grade 1). (**c**) Medium yellow plaque (grade 2). (**d**) Intense yellow plaque (grade 3)

examination in the case of ACS, massive thrombus covering disrupted plaque is commonly found as pathological reports have proved [25]. The plaque usually has yellow surface, and so yellow plaque is considered to be vulnerable. The degree of yellow color is really various, and its grading or scoring system is often used for semiquantitative analysis as the following: grade 1 = light yellow, grade 2 = medium yellow, grade 3 = intense or dark yellow, and grade 0 = no yellow (white) [26, 27] (Fig. 19.1).

In pathological validation, angioscopically yellow plaque corresponds with fibrolipidic atheroma [28]. Integrated backscatter IVUS, virtual histology IVUS, and OCT demonstrate that the majority of yellow plaques are composed of lipid-laden elements including necrotic core [11, 29–32]. Also, yellow plaque is relevant to positive vessel remodeling on IVUS images [33]. The yellow plaque with positive remodeling has large plaque burden, and that probably contributes to local vulnerability. Thickness of fibrous tissue covering lipidic content is determinant of the plaque color, and yellow grade is conversely correlated with the fibrous cap thickness (Fig. 19.2) [31, 32]. These data suggest that intense yellow plaque is identical with TCFA of pathological definition. In contrast, white plaque is a lipidic plaque with thick fibrous cap (thick-cap fibroatheroma) or a complete fibrous plaque without lipid. With regard to thrombogenicity, the frequency of thrombus adhesion gradually increases according to the yellow grade [34]. Some intense yellow-plaque, angioscopy-derived TCFA is located in the segment of a large lumen area measured by OCT [32]. The phenomenon implies that vulnerable plaque may hide in the lesion of nonsignificant stenosis. Few small-scale prospective researches exhibit that the incidence of ACS is higher in patients having glistening yellow plaque or plural yellow plaques than in patients without those [35, 36]. Hence, it is generally believed that white plaque achieves clinically stable condition and intense yellow plaque may have potential for its disruption and thrombus formation in the future.

Complex plaque features, intimal injury recognized by the naked eye through angioscopy, reflect microscopic endothelial denudation, and they are often accompanied with attachment of mural thrombus [37, 38]. Therefore, complexity is regarded as a factor of plaque vulnerability as well as color of the high-intense yellow.

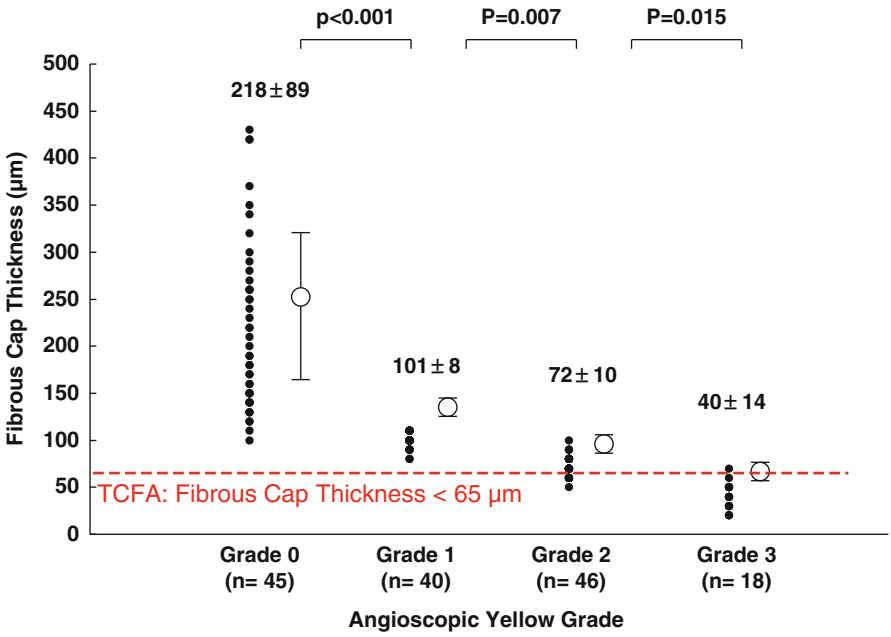

Fig. 19.2 The relationship between angioscopic yellow grade and fibrous cap thickness measured by OCT. Yellow grade of the plaque is conversely correlated with its fibrous cap thickness. Pathological thin-cap fibroatheroma (TCFA) is identical with intense yellow plaque on coronary angioscopy

19.4 Lipid-Lowering Therapy by Statin

Numerous researches of epidemiology conducted several coronary risk factors promoting atherosclerosis of systemic arteries including ischemic heart disease. Diabetes mellitus, hypertension, dyslipidemia, family history, and cigarette smoking are well known as conventional risk factors. From standpoint of preventive medicine, control of each factor and risk factor reduction are performed for primary and secondary prevention of cardiovascular disease.

Since HMG-CoA reductase inhibitor (statin) has been utilized for the treatment of dyslipidemia, serum level of low-density lipoprotein cholesterol (LDL-C) is reduced absolutely. According to basic researches, macrophage takes in oxidized LDL through scavenger receptor and changes into foam cell [39]. The cells themselves constitute lipid-rich plaque and they secrete various inflammatory cytokines advancing atheroma to inflamed condition. Activated macrophage also releases metalloproteinase and collagenase, and these proteinases thin down and weaken fibrous cap [40]. Statin displays not only direct effect on LDL-C lowering but also pleiotoropic effects, such as improving endothelial function, decreasing oxidative

stress and inflammation, and inhibiting thrombogenic response [41]. Consequently, statin helps to suppress formation and development of atherosclerosis.

Large-scale clinical researches revealed that statin therapy dramatically reduces cardiovascular events including ACS [42, 43]. Considering pharmacological effects of statin, the phenomenon is reasonable. However, findings of coronary angiography disappointedly showed the minimum regression of stenosis in atherosclerotic lesion [44]. Angiogram as lumen silhouette thus failed to declare alternation of the plaque quantity and quality resulting from statin therapy.

19.5 Angioscopic Changes in Coronary Plaque After Pharmacological Intervention

The culprit plaque of ACS, stable angina pectoris, and silent myocardial ischemia usually undergoes invasive therapy such as percutaneous coronary intervention. Disrupted, thrombotic, and/or yellow plaque is sometimes located in the non-culprit lesion without significant stenosis [32, 45, 46]. In such case, pharmacological therapy is chosen even though plaque seems to be vulnerable, because the lesion has no indication of invasive intervention. Therefore, angioscopy targets on the plaque with vulnerable features for the analysis of pharmacological intervention.

The first angioscopic study of pharmacological intervention was reported in 2003 [27]. Administration of atorvastatin for 12 months significantly reduces the above yellow score (or grade) of the non-culprit plaque from 2.03 to 1.13. The change in yellow score has good correlation with the change in LDL-C level. Complexity (or disrupted) score (defined as 0 = smooth surface or 1 = irregular surface, and 0 = without thrombus or 1 = with thrombus) also decreases from 0.23 to 0.10. In the comparison group receiving diet therapy, both scores change from 1.67 to 1.99 and from 0.31 to 0.44, respectively (Fig. 19.3). The score gain of the comparison group suggests gradual progression of atherosclerosis during natural history. Other investigators later concluded resemble alternation of the plaque character [47, 48]. Another class of antihyperlipidemic drug, bezafibrate, for 6-month administration invites similar vascular response to statin [49].

The mechanisms of reduction of the yellow grade are speculated that stain increases collagen fiber in the fibrous cap of which thickness closely affects plaque color and decreases lipidic tissue of the plaque [50]. Actually, thickening of the fibrous cap due to statin therapy is confirmed by the measurement of OCT [51]. As numbers of examinations using gray-scale IVUS show, stain decreases plaque volume and acts on quantitative regression of atheroma [52–55]. However, gray-scale IVUS has inability to approve loss of lipid content. Instead, integrated backscatter IVUS, virtual histology IVUS, and NIRS verify lipid-core reduction after intervention of statin [56–58]. Decline of the complexity score means trend toward plaque healing. Therefore, statin can advance healing process of the

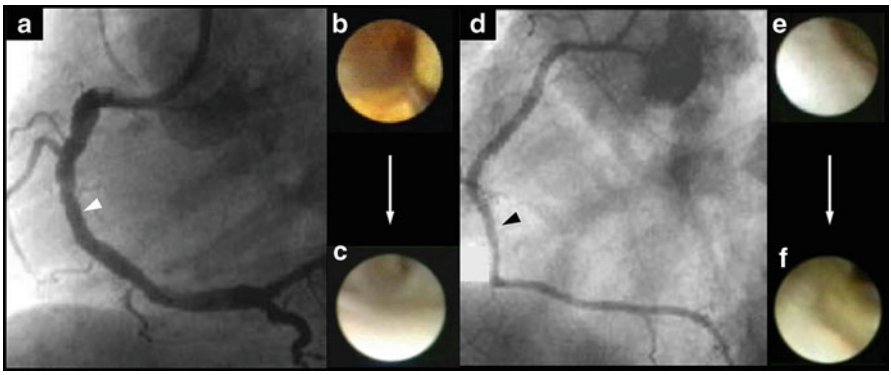

Fig. 19.3 Serial changes in plaque color. Representative angiographic and angioscopic findings of statin therapy (*left panels*; **a** to **c**) and diet therapy (*right panels*; **d** to **f**) are shown. (**a**) Angiography showed no severe stenosis in the right coronary artery (RCA). (**b**) Angioscopy found intense yellow plaque hidden in mild stenosis in the mid RCA (white arrowhead in panel **a**). (**c**) Yellow grade of the plaque markedly regressed 12 months later of aggressive lipid-lowering therapy with atorvastatin. (**d**) There was no significant stenosis in the RCA. (**e**) Almost white plaque with smooth surface was seen in normal segment the mid RCA (*black arrowhead* in panel **d**). (**f**) After 12 months of diet therapy, the previous white plaque appeared light yellow, and its surface had irregularity

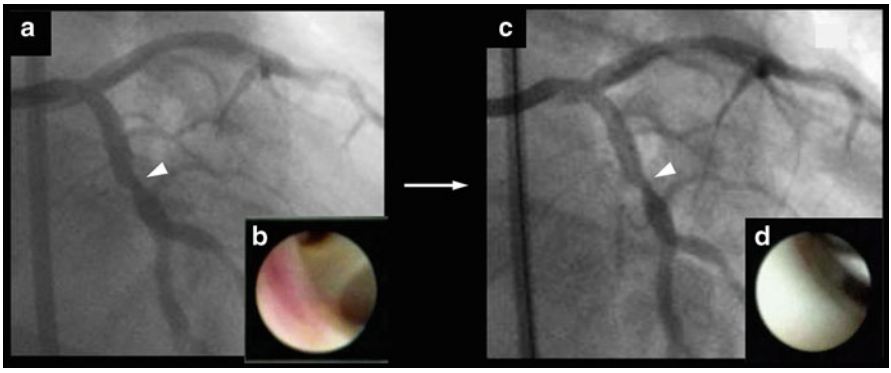

Fig. 19.4 Plaque healing caused by statin. Angiographic and angioscopic findings of plaque healing are shown. (**a**) Moderate stenosis was seen in the left circumflex artery (*white arrowhead*). (**b**) Disrupted plaque covered by pinkish thrombus was found at the lesion corresponding to angiographic moderate stenosis. (**c**) Angiographic change in lumen stenosis was slight after 12 months of atorvastatin treatment (*white arrowhead*). (**d**) Thrombotic plaque disappeared and the lumen surface was replaced by white intima. Statin completely healed up disrupted plaque

disrupted plaque (Fig. 19.4) [46]. The above angioscopic serial changes in plaque features indicate that statin dynamically changes quality of the plaque and results in plaque stabilization.

Although volumetric analysis by use of gray-scale IVUS shows both of amlodipine (antihypertensive drug) and pioglitazone (hypoglycemic drug) inhibit increase

in the coronary-plaque volume [59, 60], there is no angioscopic evidence for plaque changes by these drugs. Lipidic yellow plaque is found not only in native coronary artery but also on proliferated neointima in the stent segment [61–63]. Appearance of the yellow plaque inside metallic stent is named neoatherosclerosis [64], and the lesion has possibility of the origin in acute thrombotic occlusion as well as the yellow plaque in native vessel [65]. Efficiency of pharmacological intervention for the lesion of neoatherosclerosis has been unknown.

19.6 Summary

Aggressive lipid-lowering therapy with strong statin leads regression of yellow grade and improvement of complexity of the plaque. It is understood that the angioscopic changes in plaque morphology represent qualitative transition of the plaque from vulnerable to stable. A number of new medicines inhibiting atherosclerosis have been developed and part of them are now available for the treatment and management of cardiovascular disease. Accumulation of new findings in the field of pharmacological intervention is heartily expected in the future.

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