Review

Angioscopy 2017; 3: 9–18

What Does the Yellow Color of Angioscopy Mean? Why Yellow Plaque Is Always Vulnerable?

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Angioscopy is the only imaging modality that can directly evaluate the color of plaques. Therefore, nothing is more important to angioscopy than color. Plaque is classified into yellow plaque and white plaque according to their color. Yellow plaque has been considered to be vulnerable and high risk for the acute coronary syndromes, especially high-intense yellow plaque. Beta carotene is lipotorophic binding to lipid and coexisting with lipids in human atherosclerotic lesions and produces the yellow color of atherosclerotic plaque. Yellow plaque has several kinds of histopathology, such as a thin fibrous cap with lipid core, superficial or diffuse lipid deposition (cholesterol and cholesterol ester) with or without macrophage-foam cells and calcified plate. Therefore, all yellow plaques might not be vulnerable. Some pharmacological intervention and trans-catheter therapy decreased the intensity of yellow color. As angioscopic interpretation of color is usually subjective, objective computerized colorimetric evaluation is desirable.

Key words: angioscopy, yellow plaque, vulnerable plaque, calcification, neoatherosclerosis

Introduction

Angioscopy provides a full-color, three-dimensional perspective image of intracoronary artery surface morphology,[1,2] and direct visualization of the coronary lumen is applicable for macroscopic diagnosis intra vascular structures including atherosclerotic plaque based on color and morphology. Especially, the capability of assessing the true color of the coronary artery is not found in any other cardiovascular imaging techniques. Color discrimination in angioscopy makes it relatively easy to distinguish between yellow and white plaque.[3–9] Angioscopy can also distinguish thrombus according to color[10] (Fig. 1). But, angioscopic interpretation of color is usually subjective. An objective computerized colorimetric evaluation is desirable.

In this review article, meaning of yellow color (yellow plaque), semi quantitative, and quantitative yellow color evaluation are described.

1. Yellow plaque and white plaque in clinical setting

Many studies including our previous study[11–13] showed that yellow plaque is more common in patients with acute coronary syndromes such as acute myocardial infarction or unstable angina, conversely, white plaques were seen in patients with stable coronary syndromes such as stable angina or old myocardial infarction. Yellow plaque is likely to be vulnerable and white plaque is seemed to be stable.

2. The origin of yellow color

Angioscopy is the only imaging modality that can directly evaluate the color of plaques. Therefore, nothing is more important to angioscopy than color. Carotenoids have long been known to contribute to the yellow color of human deposit fat, adrenal cortex, and atheromatous plaques.[14] Beta carotene, a kind of carotenoid, accumulates in atherosclerotic plaque in atherosclerotic rabbit model and human atherosclerotic plaque. Beta carotene is lipotrophic binding to lipid and coexisting with lipids in human atherosclerotic lesions and produces the yellow color of atherosclerotic plaque.[15–18]

3. Comparison of plaque color and pathological findings

1) Lipid pool (necrotic core) beneath thin fibrous cap

A relatively large number of human coronary segments harvested at autopsy were examined to compare between plaque color and the thickness of fibrous cap (lipid pool beneath the fi-

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(Received 2016.07.19; Accepted 2016.12.13)
doi.org/10.15791/angioscopy.re.16.0013

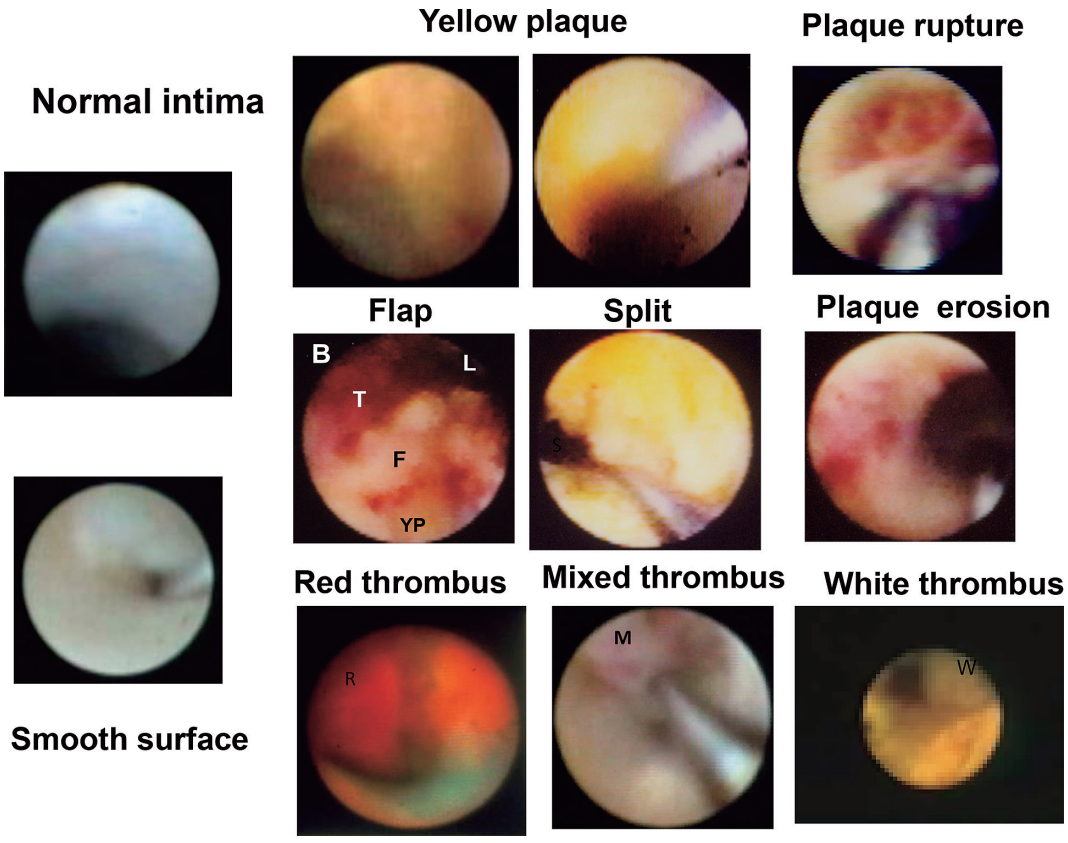

Fig. 1 Angioscopic examples of plaque and thrombus.
According to the color, plaque is classified into yellow and white. Thrombus is classified mainly into red and white. According to the shape, Plaque is classified into complex (rupture, erosion, flap, split) and smooth. Thrombus is classified into protrusion and mural according to shape.
T: thrombus, F: flap, L: lumen, YP: yellow plaque, R: red thrombus, M: mixed thrombus, W: white thrombus

brous cap). Yellow plaque has a thin fibrous cap (Fig. 2). On the other hand, white plaque has a thick fibrous cap (Fig. 3). The thickness of fibrous cap was significantly thinner in the yellow plaque group than in the white plaque group[19–20] (Fig. 4).

The lipid core (pool) area was not significant between two groups, but the lipid core (pool) size relative to plaque size was significantly higher in the yellow plaque group than in the white plaque group. Yellow plaque reflects thin fibrous cap rather than the size of the lipid pool (Fig. 5).

2) Superficial or diffuse lipid deposition (cholesterol and cholesterol ester) with or without macrophage-foam cells

Superficial or diffuse lipid deposition in intima or a large quantity of macrophrge-foam cells on the luminal surface is diagnosed as yellow plaque by angioscopy[21] (Fig. 6). In this lipid deposition, tiny calcium particle, macrophage-foam cells or degenerated collagen fiber may glisten yellow plaque (glistening yellow plaque.[22,23] High yellow color intensity region may not necessarily represent thin-cap fibroatheroma.

3) Dense calcified plates

Not all dense calcified plates reveal yellow color. But 70% of dense calcified plaques look yellow color although different plaque color grades are found[21] (Fig. 7). The precise reason for why a yellow-colored plaque is created from the deposition of calcium on the luminal surface is unclear. Arterial calcium may contain yellow-colored carotenoid.

4) White plaque

White plaques were histologically composed of dense collagen fiber (fibrous), or thick fibrous (Fig. 4)

4. Semi-quantitative and Quantitative evaluation of angioscopy

All yellow plaques are not a vulnerable, because ACS occurred in a few patients with yellow plaque.[24–25] To detect vulnerable plaque, differentiation of yellow plaque should be needed more accurately and more reliably.

Postmortem pathological analysis revealed that the main cause (70%) of case of acute coronary syndrome is plaque rupture fol-

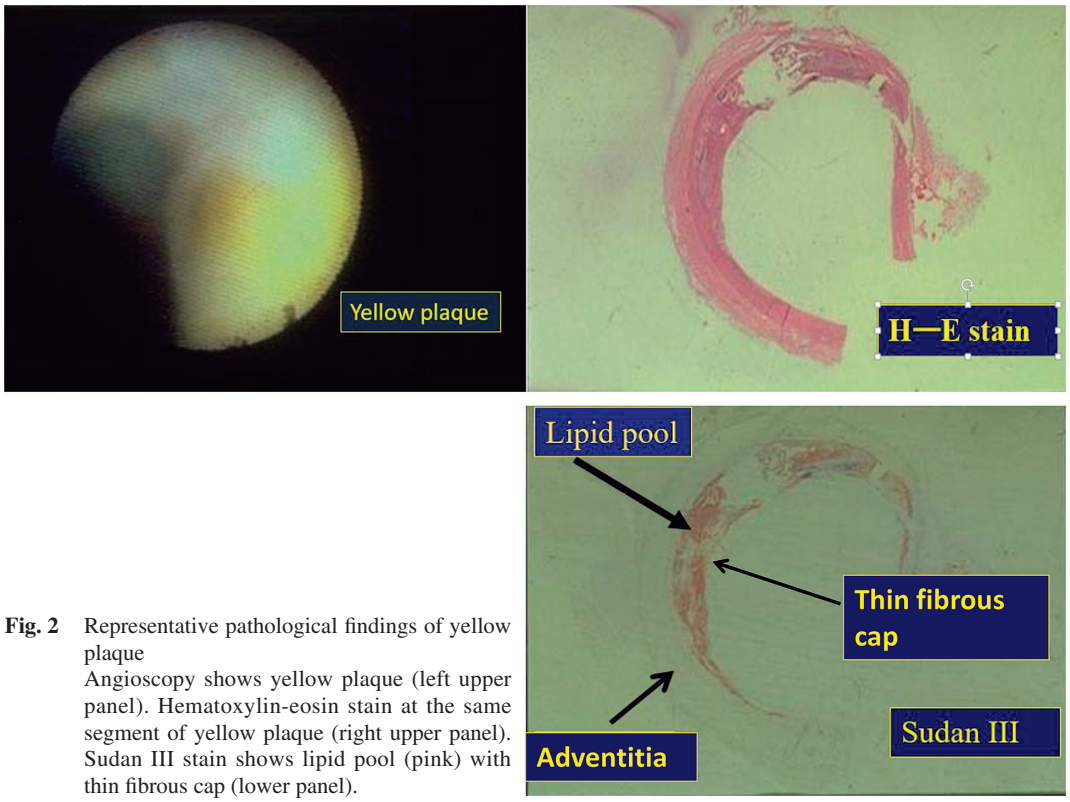

Fig. 2 Representative pathological findings of yellow plaque
Angioscopy shows yellow plaque (left upper panel). Hematoxylin-eosin stain at the same segment of yellow plaque (right upper panel). Sudan III stain shows lipid pool (pink) with thin fibrous cap (lower panel).

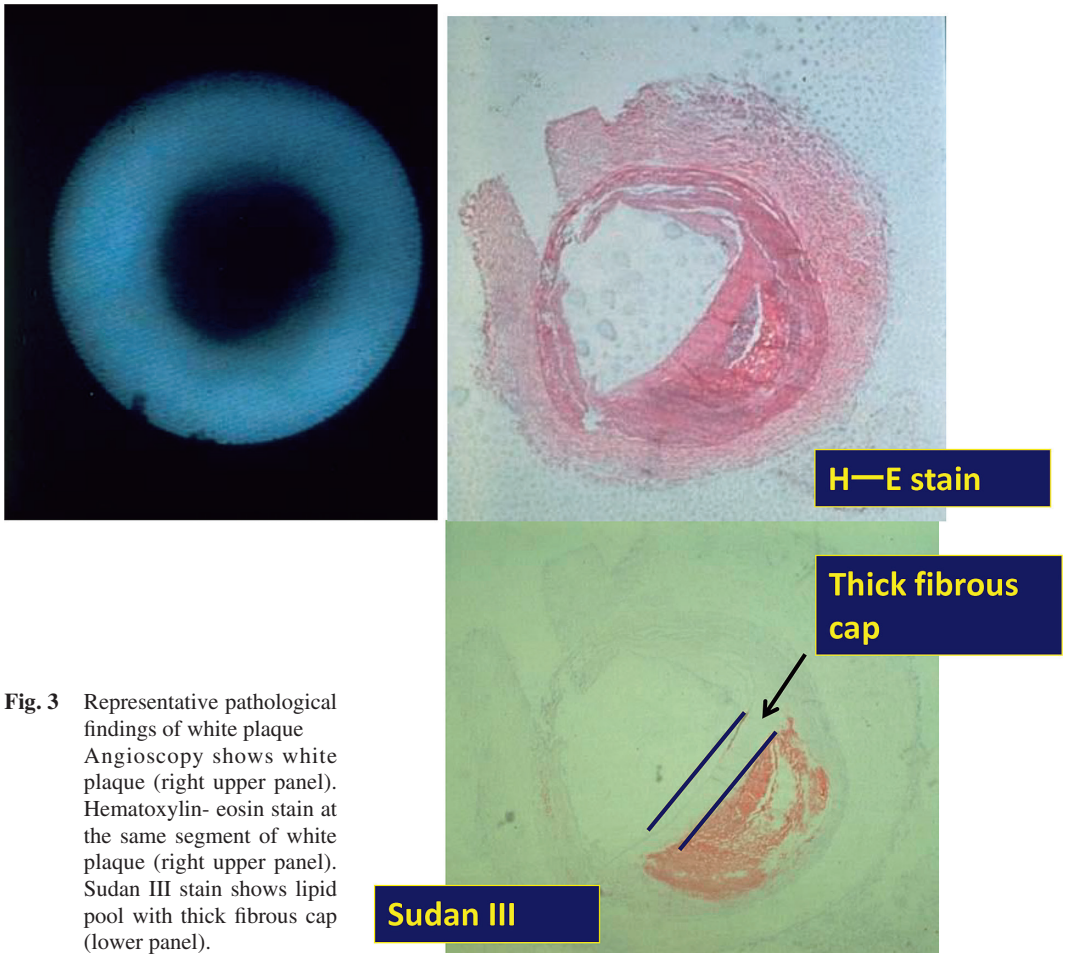

Fig. 3 Representative pathological findings of white plaque
Angioscopy shows white plaque (right upper panel). Hematoxylin- eosin stain at the same segment of white plaque (right upper panel). Sudan III stain shows lipid pool with thick fibrous cap (lower panel).

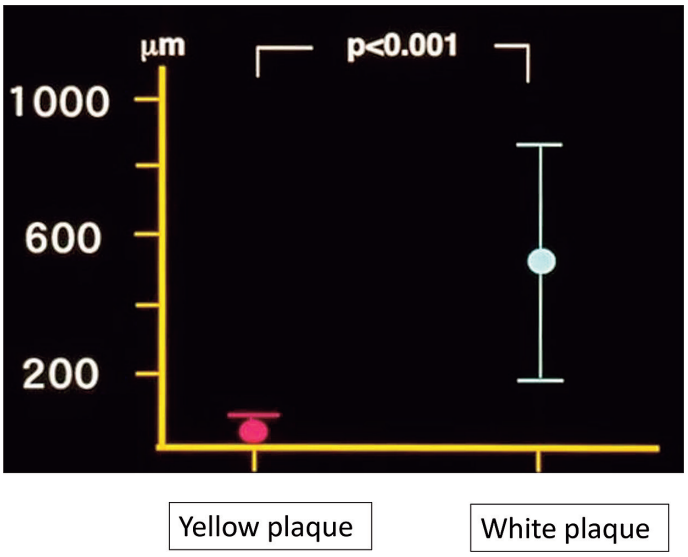

Fig. 4 Comparison of the thickness of the fibrous cap between yellow plaque group and white plaque group. The thickness of the fibrous cap is significantly thinner in the yellow plaque group than in the white plaque group.[19)]

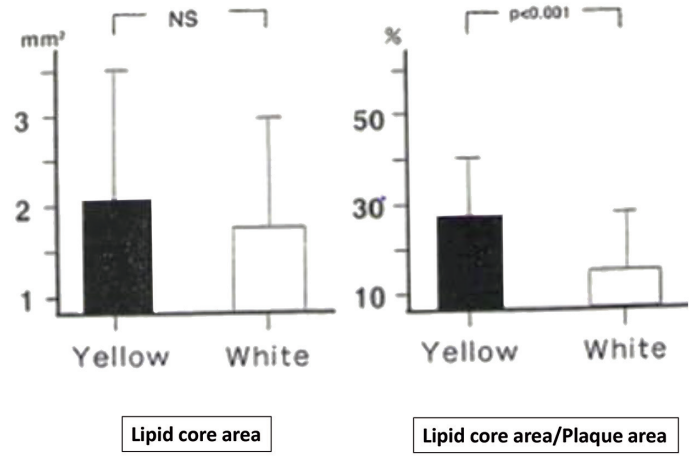

Fig. 5 Comparison of the stenosis and the plaque area between yellow and white plaque groups
The lipid core (pool) area was not significant between two groups, but the lipid core (pool) size relative to plaque size was significantly higher in the yellow plaque group than in the white plaque group.[19)]

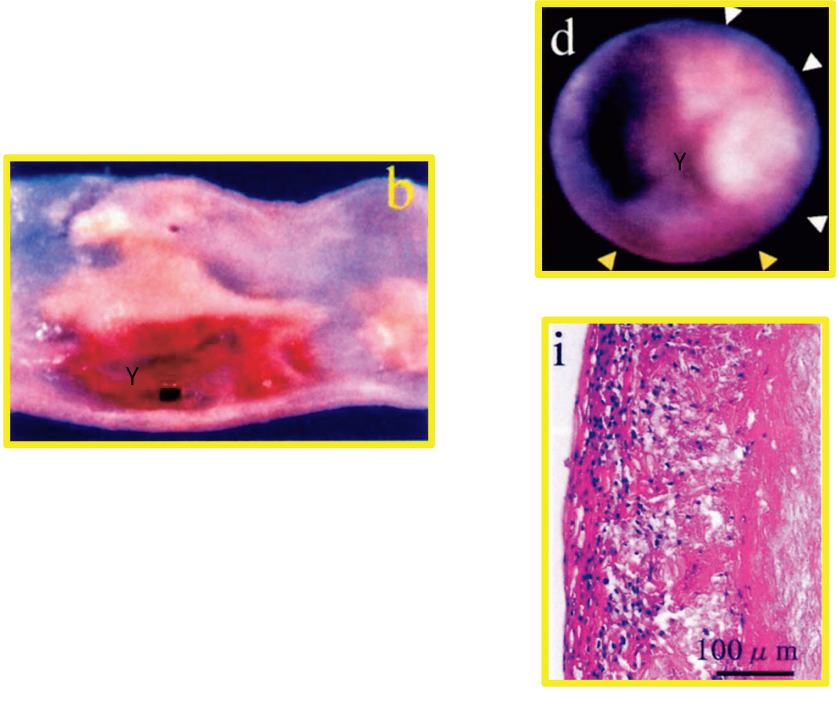

Fig. 6 Diffuse lipid deposition with macrophage-foam cell.
Yellow plaque (Y) exists in the artery (left panel). Angioscopy revealed yellow plaque (right upper panel). A large amount of inflammation cells such as probably macropharge with diffuse lipid deposition are seen (right lower panel)

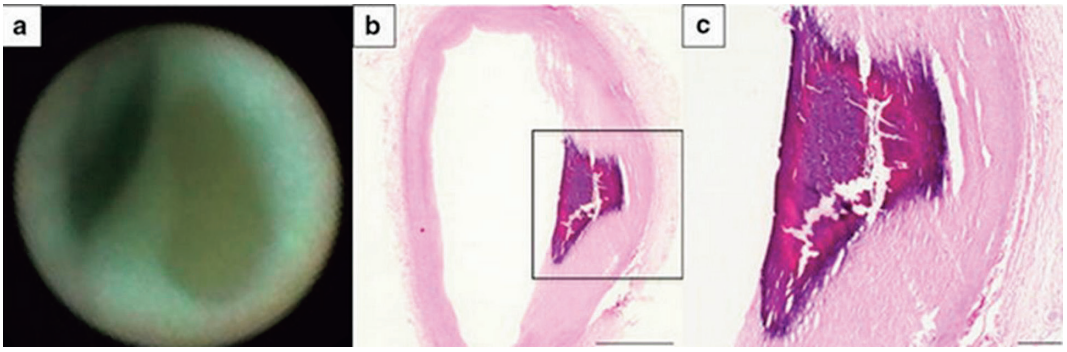

Fig. 7 Yellow color calcification.
a: Angioscopy shows a dark yellow plaque and borderline is sharp.
b: A corresponding histology of a dense calcified plate identified at the superficial part of the plaque (Hematoxylin-eosin stein)
c: Magnified image of a showed calcium deposition. The border between the fibrous tissue and calcification is clear. There is no lipid deposition on the luminal surface.[21)]
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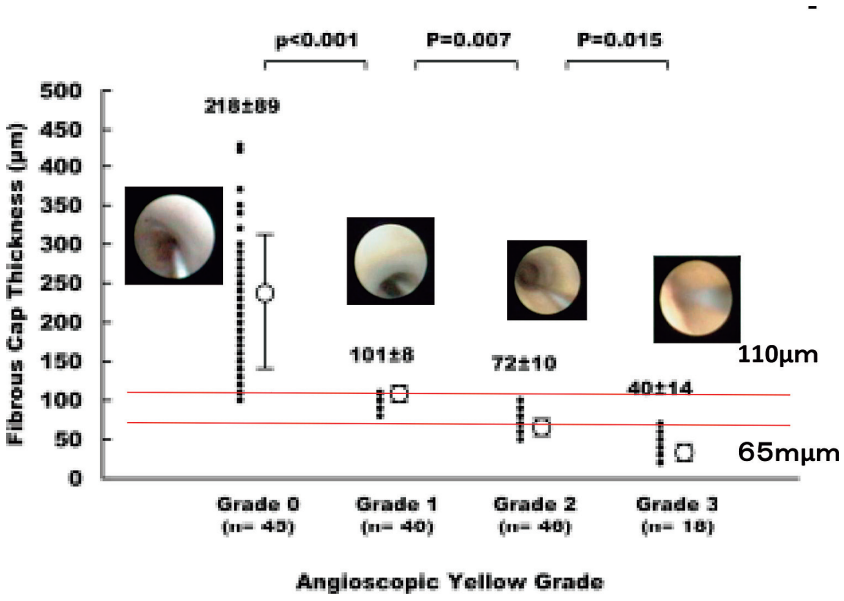

Fig. 8 The relationship between the angioscopic yellow grade and the fibrous cap thickness measured by optical coherence tomography (OCT).
Yellow grade of the plaque is conversely correlated with its fibrous cap thickness. Pathological thin-cap fibroatheroma is identified with intense yellow plaque on coronary angioscopy.[29)]
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lowing thrombus formation[26)]; a plaque that is prone to rupture is characterized by having an abundant necrotic core (lipid pool) beneath a thin fibrous cap. The fibrous cap thickness must be a very important determinant of plaque rupture. Inference and measurement of plaque thickness are important for the detection of vulnerable plaque.

1) Semi-quantitative evaluation

The degree of the yellow color is various and its grading or scoring system is proposed and often used for semi-quantitative analysis as follows: grade 1 = light yellow, grade 2 = medium yellow, grade 3 = dark or intense yellow and grade 0 = white (no yellow).[27,28)]

Optic coherence tomography (OCT) studies revealed that yellow grade is conversely correlated with fibrous cap thickness[29,30)] (Fig. 8). Thickness of fibrous cap covering lipidic content is a determinant of the plaque color. This finding agrees with digitized images analyzed by converting the Red, Green, Blue (RGB) color model[31)] (Fig. 9). An inverse correlation was observed between Yellow intensity (percent yellow saturation and thickness of fibrous cap (Fig. 10). These data suggest that intense yellow plaque is a lipidic plaque with thin fibrous cap {thin-cap fibroatheroma (TCFA)}. In contrast, white plaque is a lipidic atheroma with a thick fibrous cap or completely fibrous plaque without lipid, as mentioned previously.

Yellow plaque with higher intense yellow is likely to coexist with high incidence of thrombus. Some pharmacological intervention with statin decreased yellow color grade[27,32,33)] (Fig. 11). The mechanism of the reduction of yellow grade is speculated that statin increases collagen fiber in the fibrous cap of which

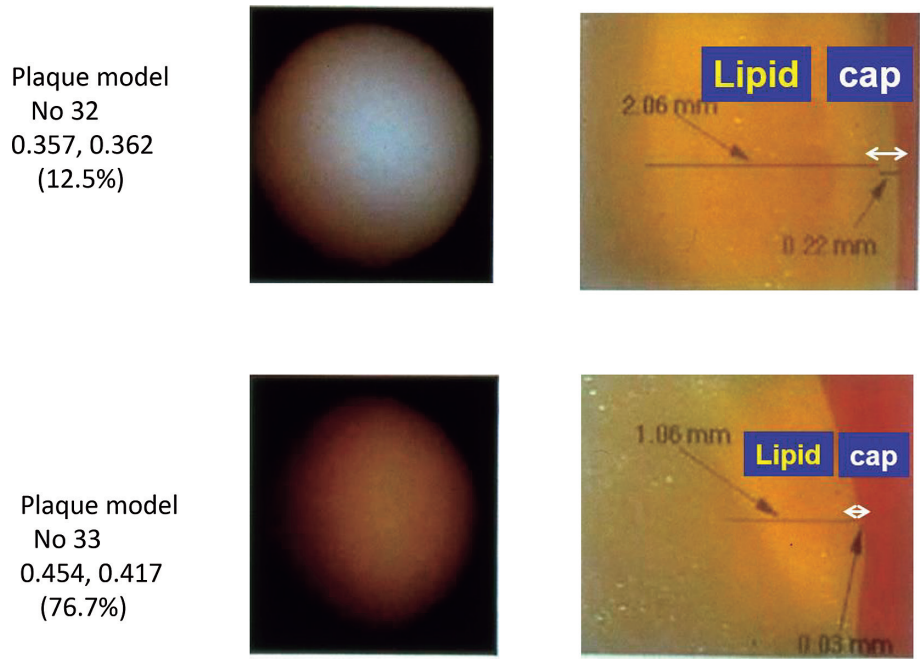

Fig. 9 Angioscopic images of plaque model and histology.
Angioscopic image with low yellow saturation (12.5%) and corresponding cross section of plaque with relatively thick cap thickness (220 μm) (Top). Angioscopic image with high yellow saturation (76.7%) and corresponding histology with thin cap thickness (30 μm).[31)]
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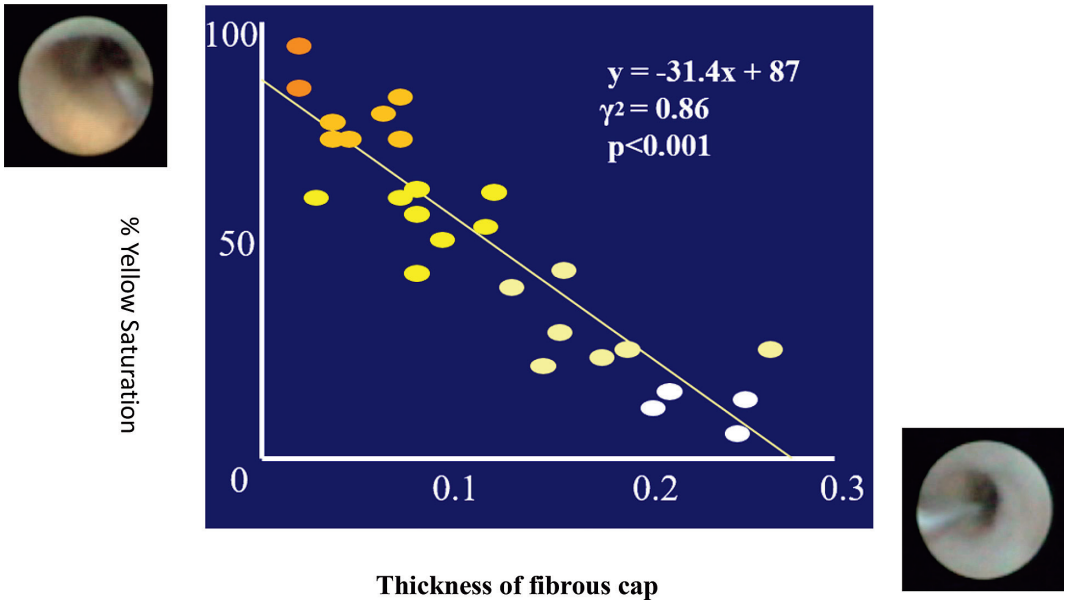

Fig. 10 Relationship between the percent yellow saturation and cap thickness in the lipid -rich plaque model.
The percent yellow saturation had a strong inverse linear correlation with cap thickness.[31)]
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thickness closely affect plaque color and decreases lipidic tissue of the plaque. Coronary intervention such as stenting, also decreases yellow plaque grade[34–37)]. The yellow grade of plaque color in ruptured segment was higher than that of non-ruptured segment immediately after stenting and at 1–month follow up. Plaque color eventually became equivalent white at six month[38)] (Fig. 12). Stent is covered with matured thick fibrocellular neointima. Surprisingly, white neointima changes into yellow plaque over an extended period of time (Fig. 13). This change is called neoatherosclerosis. This phenomenon occurs in not only bare metal stent but also drug eluting stent.[39,40)]

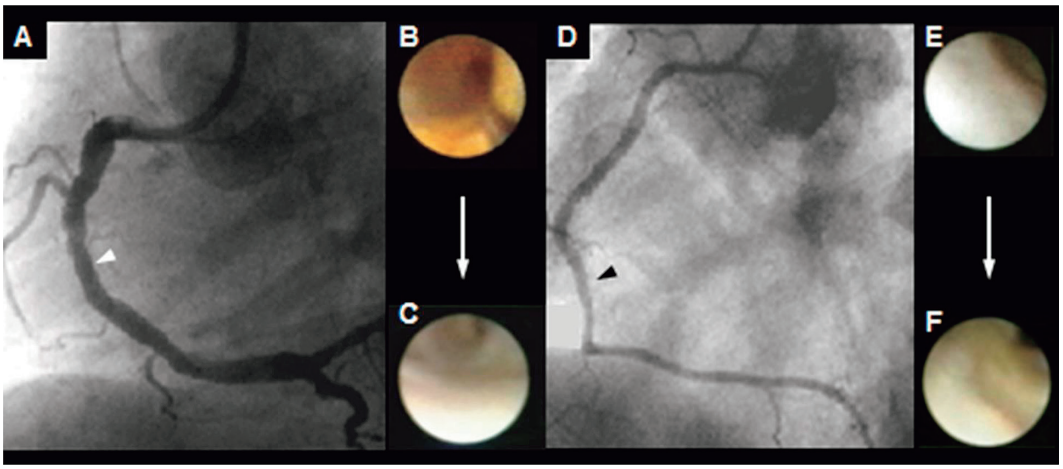

Fig. 11 Pharmacological intervention by lipid lowering drug
Representative angiographic and angioscopic findings of statin therapy (left panels; A to C) and diet therapy (right panels; (D to F) are shown. A: Angiography showed no severe stenosis in the right coronary artery (RCA). B: Angioscopy found 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 diet therapy, the previous white plaque appeared light yellow, and its surface had irregularity.[27)]
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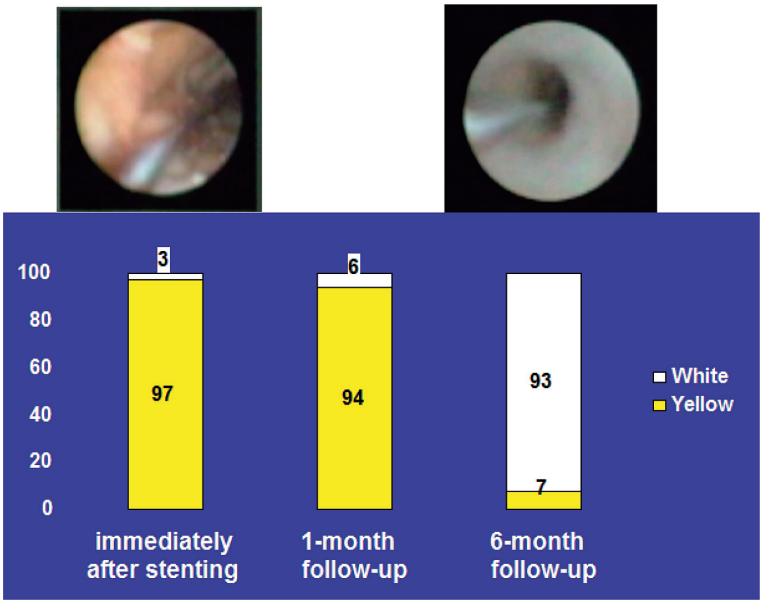

Fig. 12 The color of yellow plaque changes after bare metal stent implantation in patients with acute myocardial infarction.
Yellow plaque color is observed immediately after bare metal stenting and at 1 month after follow-up. Yellow color plaque (left) became white (right) at 6 months.[34)]
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2) Quantitative evaluation

The angioscopic interpretation of color was usually subjective, even though semi-quantitative analysis, tempered by substantial observer disagreement in the visual assessment of angioscopic color. A computerized calorimetric analysis system for processing in angioscopic images was assembled, and the digitized images were analyzed by converting the RGB color model values stored in the computer to the chromaticity coordinate x and y on the American Standard Chromaticity Diagram. Yellow saturation derived from hue, saturation, lightness (HSL) color space was used to represent yellow color intensity. Using an experimental model that was constructed by injecting a yellow beta-carotene – lipid emulsion subendothelially into normal bovine aorta, and the nature of yellow color was validated (Fig. 9). Inverse relationship between yellow color saturation and the cap thickness of fibroatheromas is shown[31)] in Fig. 10.

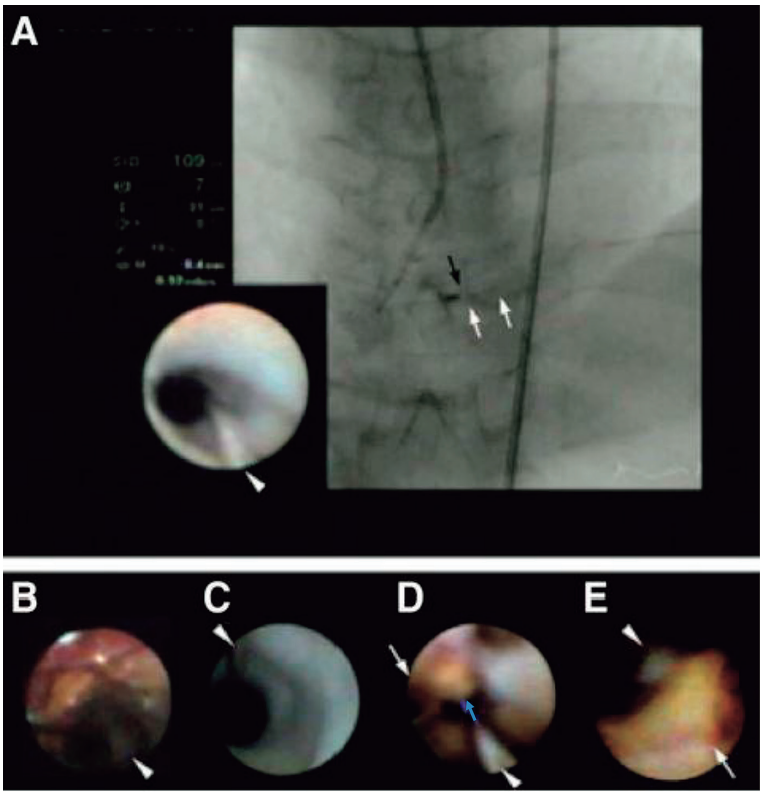

Fig. 13 Neoatherosclerosis after bare metal stent
A) Composite image of fluoroscopy and angioscopy shows the precise positions ofangioscopic images (black arrow) and implanted BMS (white arrows). B) Immediately after BMS implantation, yellow plaque and red thrombus crushed out by the stent struts are seen. They are located outside the stent struts. C) At the first follow-up, nontransparent white neointima completely covers over the stent struts. The stent struts are invisible, and the lumen surface is smooth. D) At the second follow-up, irregular yellow plaque (blue arrow) is obviously protruding from the surrounding white intima into the lumen, and the plaque is accompanied with red thrombus (white arrow). The stent struts are invisible. E) A yellow plaque is seen around the visible struts (white arrow) at the second follow-up. The plaque is clearly protruding from the struts. In this case, yellow plaque and visible struts simultaneously exist in the BMS segment. A white arrowhead indicates a guide wire.[39]
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Yellow saturation may not ideally represent yellow color intensity because of its nonlinear nature. In addition, detailed process of optimization against the effect of variable unique to angioscopy was not examined. $L^*a^*b^*$ color space (Fig. 14) is widely used to describe color differences because of its linear nature.[41] That is uniform color space, which is intended to the color difference perceived as an equal dimension may correspond to an equal distance. In their system, a yellow color intensity and brightness can be represented as simply the b^* value (yellow color intensity 0 to 100) and L^* value (brightness of the color – 100 to 100). Their system can consistently measure yellow plaque color independent of such conditions as light intensity, the distance from the lens of angioscope to the objective, and the angle of the angioscope to the region of interest, after proper adjustments for brightness (L^* value is within 40–80). The inverse linear correlation between b^* value and the fibrous cap thickness covering lipid core. Furthermore, a plaque of b^* value >23 contains atheroma that has a fibrous cap thickness <100 μ m, using ex vivo human tissue samples[41] (Fig. 15). Thus, the intensive yellow color (b^* value >23) reflects a vulnerable plaque. This system based on $L^*a^*b^*$ color space has been applied to clinical use. The plaques of b^* value >23 are more frequently observed in the culprit lesions of acute coronary syndrome (ACS) than in the culprit lesions of stable angina pectoris[42] and are strongly correlated with the thin cap fibroatheroma determined by Virtual Histology-IVUS.[43] The plaques of b^* value >23 are associated with elevated malondialdehyde-modified low-density lipoprotein levels[44], which has been reported to be detected in the plasma of patients with ACS.

Another quantitative color analysis was developed using lightness chroma hue (LCH) color space[45].

Disclosure Statement

The authors have disclosed no conflicts of interest.

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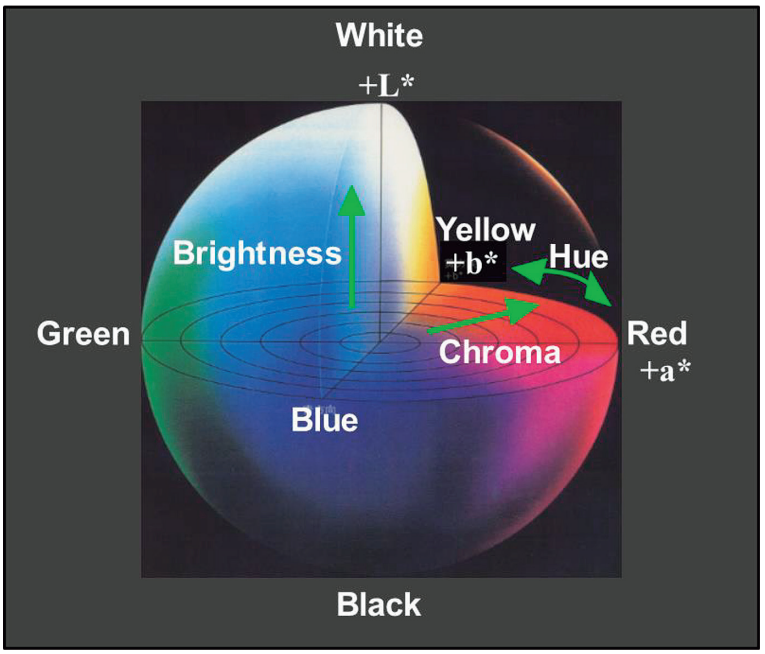

Fig. 14 $L^*a^*b^*$ color space
In this system, a yellow color intensity and brightness can be represented as simply the b^* value (yellow color intensity) and L^* value (brightness of the color).

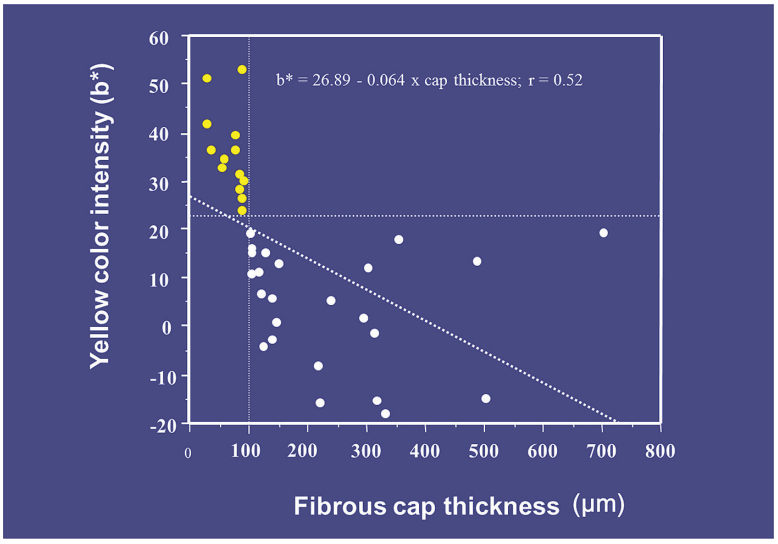

Fig. 15 The inverse correlation between yellow color intensity and fibrous
cap thickness
yellow color intensity is high (b^*>23; represent by yellow circles) in all location with the fibrous cap thickness <100 μm.[41]
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