

Chapter 17

Neoatherosclerosis

Hideo Kawakami and Hiroshi Matusoka

Abstract Today, neoatherosclerosis as atherogenic plaque formation process after stent implantation is widely recognized, but was unknown only a decade ago. In the bare-metal stent era, the neointimal proliferation in chronic phase following percutaneous coronary intervention appeared thick and white, without thrombi. Yellow neointima within the stent segment, now called “neoatherosclerosis,” was firstly observed after implantation of drug-eluting stent involving sirolimus-eluting stent. Surprisingly, about half of the stents had yellow neointima 1 year after its implantation. In those days, it was understood that formation of yellow neointima is specific to sirolimus-eluting stent. However, yellow neointima developed in a few patients underwent implantation of other drug-eluting stents and bare-metal stents. Neoatherosclerosis can be detected by angiography and other imaging modalities such as intravascular ultrasound, optical coherence tomography, and computed tomography. Different mechanisms depending on the type of stents may be involved in neoatherosclerosis. Following drug-eluting stent implantation, incomplete or delayed reendothelialization may contribute to the atherogenesis because of an inefficient barrier against the excessive uptake of circulating lipids. Regarding bare-metal stents, neoatherosclerosis may be similar to the development of atherosclerosis in native coronary arteries. Considering these proposed mechanisms of in-stent neoatherosclerosis, statin therapy may be effective for preventing neoatherosclerosis.

Keywords Drug-eluting stent • Bare-metal stent • Yellow neointima • Delayed endothelialization • Statin

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17.1 Introduction

Today, neoatherosclerosis after stent implantation is widely recognized as an atherogenic plaque formation [1], but the word was unheard-of a decade ago. In the bare-metal stent (BMS) era, 6-month follow-up angiography after percutaneous coronary intervention (PCI) revealed that thick, smooth, and white neointima without thrombi fully covered the stent struts; the struts were invisible even in a case of acute coronary syndrome (ACS) that has complex yellow plaque and thrombi in the culprit lesion [2, 3]. Therefore, this phenomenon was understood to be plaque sealing and stabilization and was believed to continue indefinitely (Fig. 17.1). Afterward, Yokoyama S et al. reported that neoatherosclerosis occurred several years after BMS implantation [4]. With the introduction of the first-generation drug-eluting stent (DES), the same effect of plaque stabilization was expected. However, contrary to the expectation, plaque healing after implantation of sirolimus-eluting stent (SES) was completely different from that of BMS [5, 6]. Within the segment of SES, uncovered struts, thrombi, and yellow plaque under the struts were observed. Remarkably, thin, but yellow neointima covered part of the struts [7]. Yellow neointima had not been reported prior to the DES era, and the phenomenon was unfamiliar. The yellow neointima was regarded as atherosclerotic plaque according to a previous ex vivo study [8]. Later, pathological analysis confirmed that the yellow neointima was consistent with atherosclerosis [1]. In this chapter, we describe the typical neoatherosclerosis on the basis of angioscopic findings.

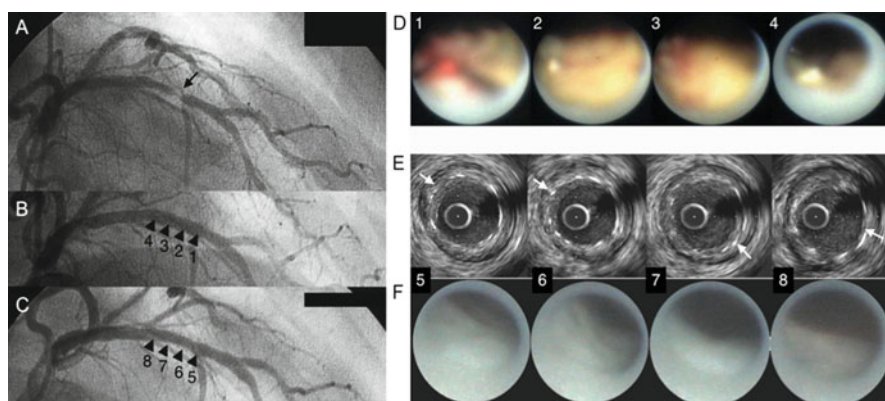


Fig. 17.1 Neointima formation after BMS implantation. This image shows a case of unstable angina in a 58-year-old-man. The *black, numbered arrowheads* in panel **B** and **C** correspond with the images in panels **D**, **E**, and **F**. (**A**) Coronary angiography before percutaneous coronary intervention (PCI). Significant (90 % of the diameter) stenosis is observed at midportion of the left descending artery (*black arrow* in **A**). (**B**) Immediately after PCI. The patient received a bare-metal stent (BMS) implant. (**C**) 8 months after PCI, no in-stent restenosis is apparent. (**D**) Angioscopic images immediately after PCI. The plaque behind the BMS was dense yellow with a red thrombus. (**E**) Intravascular ultrasound images 8 months after PCI. Thick neointima is seen covering the stent struts using intravascular ultrasound. (**F**) Angioscopic images 8 months after PCI. The stent struts, behind the white, thick, neointima, are not evident and the thrombus was none

17.2 First-Generation Drug-Eluting Stents

Conventional PCI including BMS deployment had an Achilles' heel; in-stent restenosis (ISR) occurred in more than 20 % of the cases [9, 10]. To overcome this Achilles' heel, a new concept of coronary stents, DESs were developed such as SES and paclitaxel-eluting stents (PES). Since their introduction, these two types of DESs have been broadly used, and the Achilles' heel associated with ISR was almost completely solved because of low frequency of the DES-ISR below 10 % [11, 12]. However, an unanticipated new problem emerged following DES use: late and very late stent thrombosis with high mortality rate [13]. Several mechanisms of the stent thrombosis have been considered to be responsible, including delayed neointimal formation [14], hypersensitivity reaction to the stent polymer [15], and neoatherosclerosis [1]. In the BMS era, 6-month follow-up angiography revealed that thick, smooth, and white neointima fully covered the stent struts and there were no thrombi within the BMS segment; the struts could not be seen, even after ACS that has complex yellow plaque and massive thrombi in its culprit lesion [2, 3]. Thus, this phenomenon was understood to be the effect of plaque stabilization, sealing, or whitening (*bihaku* in Japanese) [3]. Following the introduction of the first-generation DESs, similar effect of DESs on plaque stabilization was expected; however, contrary to the expectation, plaque healing of first-generation DESs was completely different from the BMS [16]. In 2006, we firstly reported the formation of yellow neointima 3 months after SES implantation [7]. In the study, we clearly demonstrated that the frequency of yellow plaque increased from 29 % immediately after stenting to 86 % of the follow-up (Fig. 17.2). Figure 17.3 shows that the white plaque had changed to yellow neointima, and we concluded that this phenomenon represented plaque destabilization by SES implantation. It was also speculated that the mechanisms of plaque destabilization involved thinning of fibrous cap as apoptosis due to a pharmacological effect of sirolimus [17] or polymer-induced inflammation of the plaque [15]. In those days, the phenomenon was not considered to be neoatherosclerosis. To investigate when yellow neointima appeared, we performed angiographic observation at different follow-up periods. Surprisingly, a quarter of the patients had yellow neointima within 4 months and about half had that within 8 months (Fig. 17.4). Why the frequencies of yellow neointimal formation was different between the first and second reports? It was speculated that diversity of baseline patients and lesion characteristics made the differences. First report included ACS cases, whereas second report excluded ACS cases. Atherogenesis progressed in short term following SES implantation. Up to now, there is no data regarding the long-term prognosis of yellow neointima of SES. In comparison between SES and PES, yellow-plaque grade was higher in SES than in PES, as Fig. 17.5 shows [18]. This result suggested higher atherogenic potential of SES compared to PES. A recent pathological study has clarified the mechanisms of neoatherosclerosis after stent implantation (See Sect. 17.6) [1].

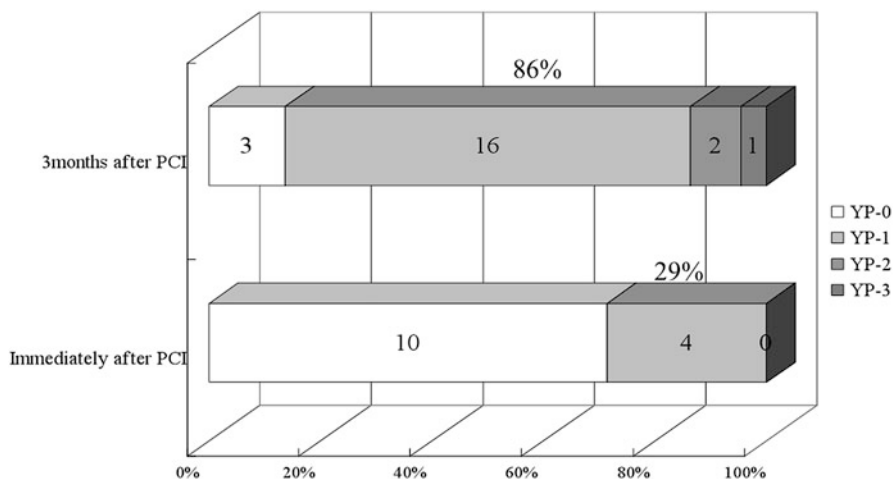


Fig. 17.2 Yellow color present at stented site, 3 months after sirolimus-eluting stent (SES) implantation. The yellow-colored grade markedly increased 3 months after SES implantation. By angiography, progression of atherosclerosis was demonstrated with a yellow-colored density because of thinner formation of fibrous cap. Progression of atherosclerotic plaque was assessed by a yellow-colored grade. Grade 0 was white, grade I was light yellow, grade II was normal yellow, grade III was bright yellow. YP-0, yellow-plaque grade 0; YP-1, yellow-plaque grade 1; YP-2, yellow-plaque grade 2; YP-3, yellow-plaque grade 3

17.2.1 Sirolimus-Eluting Stent (SES)

Since SES had launched into the market, this stent rose an epoch-making change in the field of PCI. In the RAVEL (RANdomized study with the sirolimus-eluting VELOCITY balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) [11] and SIRIUS (a U.S. multicenter, randomized double-blind study of the sirolimus-eluting stent in de novo native coronary lesions) [12] studies showed infrequent ISR after SES implantation. Afterward, unconsidered complication in the DES era occurred, that is, late and very late stent thrombosis [13]. The Bern-Rotterdam study [19] and j-Cypher Registry [20] demonstrated that cumulative incidence of very late stent thrombosis was gradually increasing throughout several years after PCI using SES. Several mechanisms of the phenomenon were considered, and one of them is neoatherosclerosis [21]. Figure 17.6 demonstrates representative case of neoatherosclerosis after SES implantation. In this case, the newly formed yellow plaque with a red thrombus was observed 5 months after stenting. Furthermore, 403 days after PCI, the yellow neointima still remained, and it changed thicker and denser than previous observation. From the angioscopic findings, SES-induced neoatherosclerosis might be progressive. Figure 17.7 shows a case of very late stent thrombosis associated with yellow intima. A 43-year-old man, with a history of stable angina pectoris, underwent elective PCI procedure of SES implantation into the left circumflex artery. Immediately after the

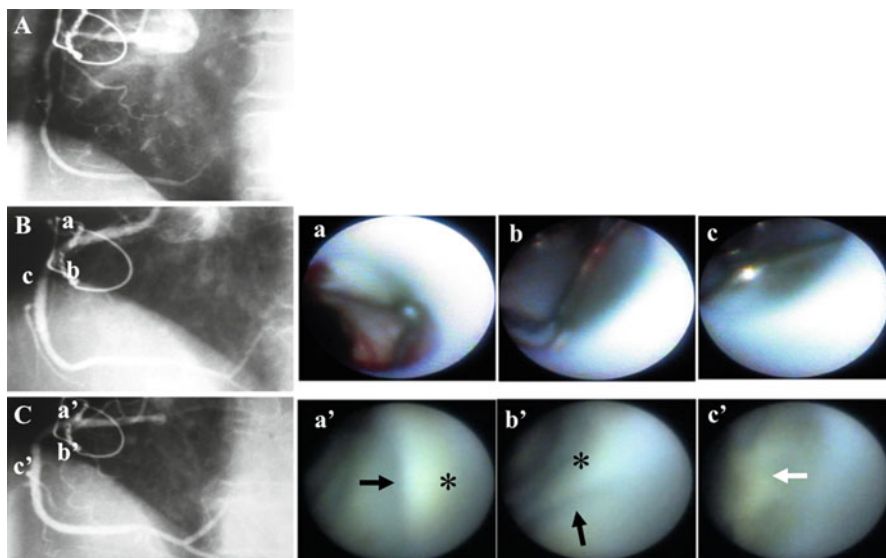


Fig. 17.3 Yellow neointima formation, 3 months after percutaneous coronary intervention (PCI) in a 70-year-old female with an old myocardial infarction. **(A)** Coronary angiography before stent implantation; 99 % diameter stenosis is evident at proximal right coronary artery. **(B)** *Left panel* shows coronary angiography immediately after stent implantation. Narrowing site was opened by sirolimus-eluting stent. *Small letters in left panel* correspond with the images of angioscopy. Angioscopic images (*right panels*) immediately after PCI (*a, b, c*). The stent struts are clearly seen, with sharp light reflection. Red thrombi are evident under the stent strut (*a*) and the plaque was white. **(C)** Ninety-seven days after stent implantation, in-stent restenosis is not evident at the stented site. *Small letters in left panel* correspond with the images of angioscopy. By angioscopy, the stent struts are visible, without light reflection (*black arrow* in *b', c'*). The plaque color has changed from white to yellow (* in *a' b'*), and the white thrombus, covering the stent strut (*white arrow* in *c'*), is evident. (*a, a'*: proximal lesion of the stent; *b, b'*: midportion of the stent; *c, c'*: distal lesion of the stent)

PCI, the plaque under the stent was completely white. One year later, the color at the segment of SES changed to yellow. Very late stent thrombosis originated from the SES segment occurred 9 years later. Angioscopic observation found an intense yellow plaque with red thrombi at the culprit lesion. In this case, the cause of very late stent thrombosis was considered to be rupture of the neoatherosclerosis. Thus, yellow neointimal formation after SES implantation may be a possible risk factor of very late stent thrombosis.

17.2.2 Paclitaxel-Eluting Stent (PES)

PES, another type of the first-generation DES, showed a different vascular healing response than from SES. The primary characteristic of this stent type was the increased numbers of residual thrombi on the stent during in the chronic phase

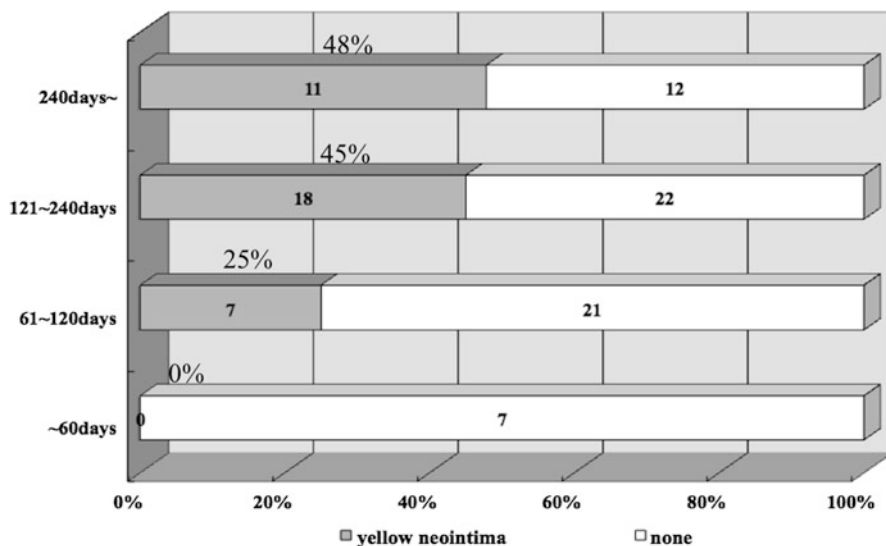


Fig. 17.4 Frequency of yellow neointima at the stent implant site after sirolimus-eluting stent implantation. There were no yellow neointima formations within 2 months. After then, the rate of yellow neointima formation gradually increased over time, after percutaneous coronary intervention

[22]. Figure 17.8 shows a case of good vascular healing after PES implantation. All of the PES struts are covered with white neointima without thrombus formation. On the other hand, yellow neointima infrequently developed as Fig. 17.9 shows. This patient suffered from angina pectoris due to BMS-ISR. He underwent PES implantation at the ISR lesion to avoid recurrent restenosis. Angioscopy demonstrated absolutely white neointima before PES implantation. One year after PES implantation, the stent segment was patent and had minimum neointimal growth on angiography. However, the newly formed neointima with yellow color was found by angioscopic observation.

17.3 Second-Generation Drug-Eluting Stents

Considering the disadvantages of the first-generation DESs, drug pharmacokinetics and drug-carrying polymers improved for the next generation of DESs. In the fast-release zotarolimus-eluting stent (E-ZES), at least 90 % of the drug releases within two weeks of its implantation. Thus, the drug release of E-ZES is earlier than the first-generation DESs. Approach of everolimus-eluting stent (EES) is different from the first-generation DES, and the DES has more biocompatible polymer. Although problems caused by stent polymer of the first-generation DESs are almost solved, some of them may remain. Figure 17.10 shows the presence of a yellow plaque in

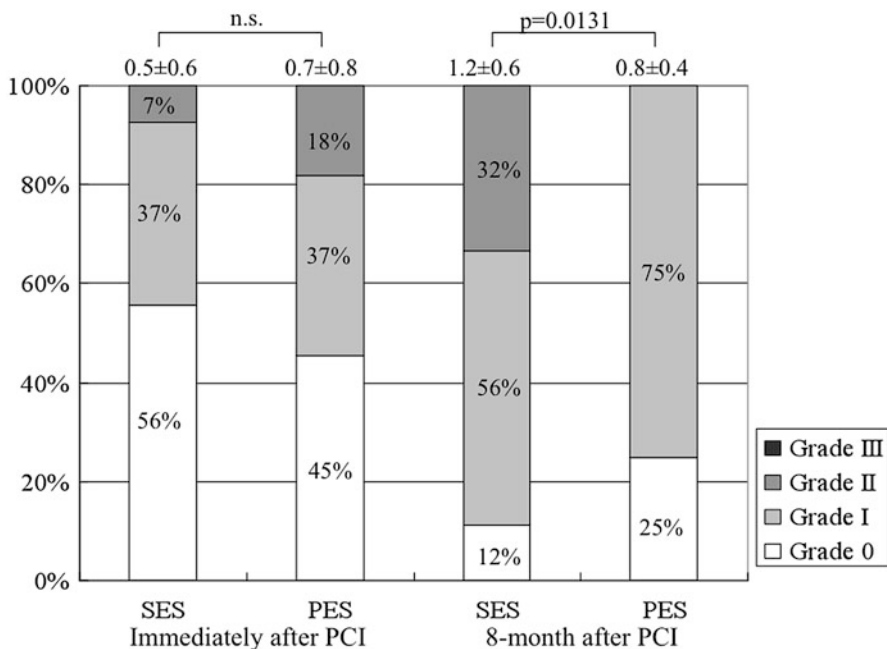


Fig. 17.5 The grades of yellow plaque immediately, and 8 months, after percutaneous coronary intervention (PCI) using first-generation drug-eluting stents. Immediately after PCI, there is no difference between the two groups, with regard to the yellow grade; 8 months after PCI, the yellow-plaque grade was significantly higher in the sirolimus-eluting stent group than in paclitaxel-eluting stent group

the segments of E-ZES and EES one year after their implantation in patients with ACS and non-ACS. The grade of yellow plaque was significantly higher in the EES group, among ACS patients, than ACS and non-ACS in E-ZES groups and non-ACS in EES group. The exact reasons for the presence of the yellow plaque are unclear. Residual yellow plaque underneath the struts may be observed through the thin neointima, or atherogenic yellow neointima may appear as well as the first-generation DESs. Whether or not, such stent segment seems to be angiographically vulnerable lesion [23].

17.3.1 Fast-Release Zotarolimus-Eluting Stent (E-ZES)

In E-ZES, 90 % of the drug is released within 2 weeks after the implantation. Therefore, vascular healing response of E-ZES is earlier than other DESs and mimics that of BMS. In E-ZES, rather thicker neointima covers the stent struts compared with first-generation DESs [24]. Formation of yellow neointima was rare one year after E-ZES implantation. Figure 17.11 shows typical angioscopic images

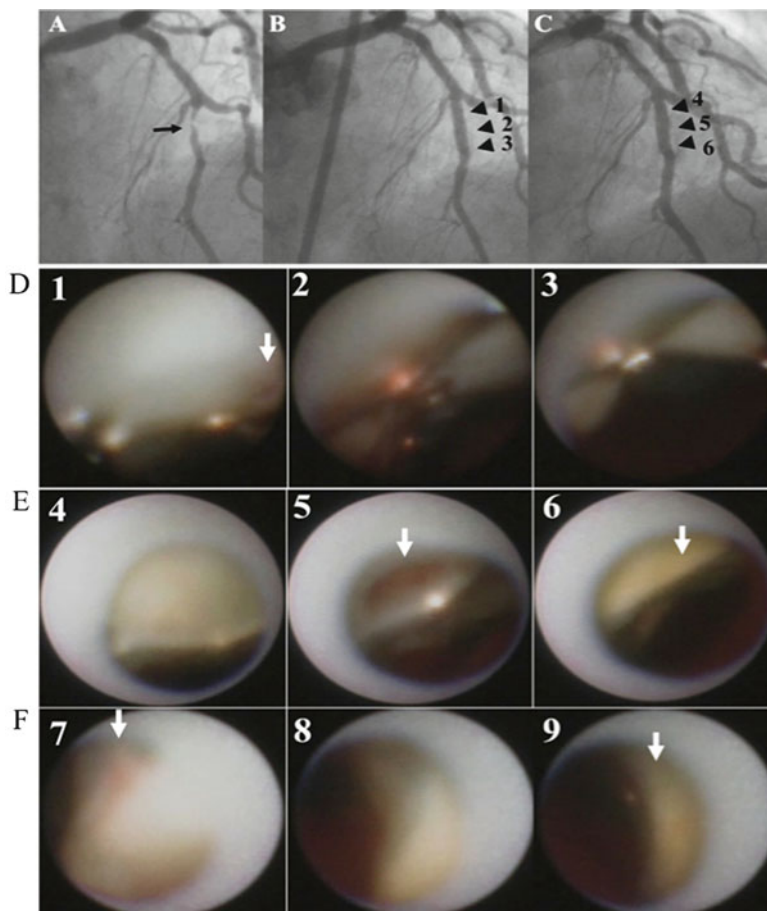


Fig. 17.6 Yellow neointima formation after sirolimus-eluting stent implantation. Angiograms and angioscopic images of a 73-year-old female, with old myocardial infarction. The black, numbered arrowheads in panels B and C correspond to the images in panels D and E. (A) In the pre-percutaneous coronary intervention (PCI) angiogram, 90 % diameter stenosis can be seen in midsegment of left anterior descending artery. (black arrow in A). (B) In the angiogram taken immediately after PCI, the newly implanted sirolimus-eluting stent is evident. (C) The angiogram taken 162 days after PCI shows no in-stent restenosis of the stented site. (D) The angioscopic images taken immediately after PCI show the presence of white plaque, with a small red thrombus (white arrow in D1). (E) The angioscopic images taken 162 days after PCI show the presence of a red thrombus near the stent struts (white arrow in E5). Yellow neointima is seen covering the stent struts (white arrow in E6). (F) The angioscopic images taken 403 days after PCI show that the red thrombus (white arrow in F7) is still evident. Yellow neointima is seen covering the stent struts. The yellow neointima is thicker and denser than before

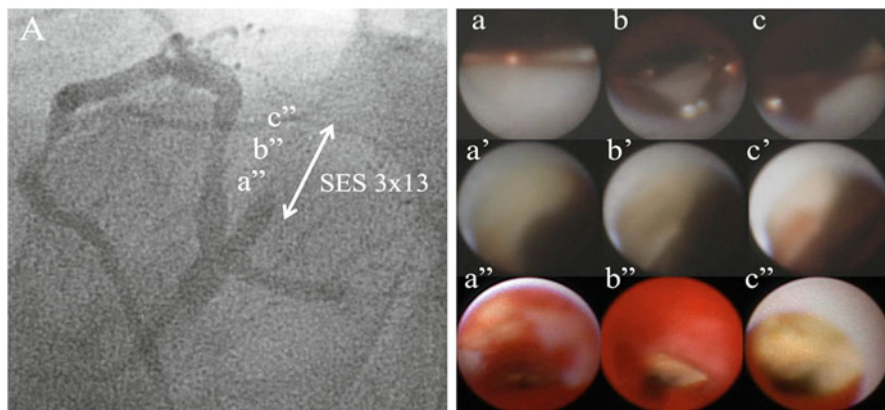


Fig. 17.7 A case of very late stent thrombosis. A 43-year-old man with stable angina pectoris received a sirolimus-eluting stent (SES), electively, in the left circumflex artery. (A) Left coronary angiogram (spider view). *a, b, c* Angioscopic images immediately after percutaneous coronary intervention (PCI). The plaque color under the stent is completely white. *a', b', c'* Angioscopic images one year after PCI. The neointima color at the SES implant site is yellow with red thrombus (*c'*). *a'', b'', c''* Angioscopic images at the site of the very late stent thrombosis. Angioscopy reveals dense, yellow, plaque with massive red thrombi

of E-ZES implantation for ACS patient. There was a light yellow plaque in the acute phase and in the chronic phase. The stent struts were invisible, and they were completely covered with thick and white neointima at follow-up. E-ZES may have sufficient effects of plaque sealing as well as BMS.

17.3.2 Everolimus-Eluting Stent (EES)

Several sorts of DESs are now available; EES is thought to be the most balanced DESs in reduction of ISR and stent thrombosis. Recent reports have demonstrated that incidence of very late stent thrombosis was significantly lower than first-generation DESs [25]. In addition, possibility of discontinuation of dual antiplatelet therapy within three months is suggested [26]. In EES, the atherogenic potential of neointima seemed to be decreased due to its biocompatible polymer. These conclusions were based on meta-analysis and retrospective analysis. However, there are some cases showing that EESs do not initiate favorable healing, but formed yellow intima. Figure 17.12 clearly demonstrates the presence of yellow neointima after stenting of EES. The patient underwent hybrid stenting at the proximal of the right coronary artery using E-ZES and EES distal to the E-ZES. One year later, thick and white neointima covered the E-ZES, while yellow neointima was found at the EES segment by angioscopy suggesting difference of healing response between the two DESs and neoatherosclerosis of EES.

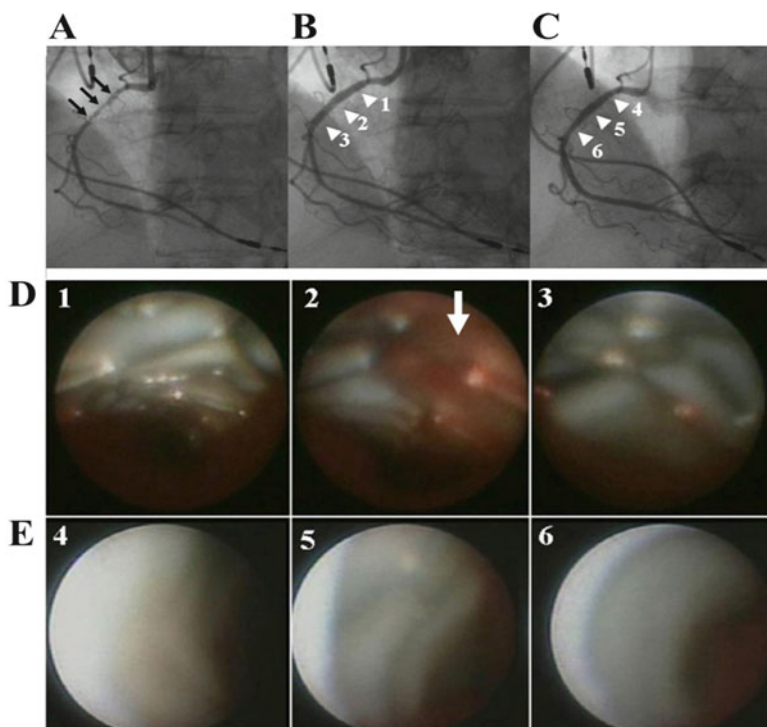


Fig. 17.8 A case involving paclitaxel-eluting stent (PES) implantation. (A) Before percutaneous coronary intervention (PCI), severe stenosis is evident at the proximal right coronary artery. (B) The PES is shown after implantation. (C) One year after implantation, there is no evidence of in-stent restenosis. (D) Angioscopic images immediately after PCI show a white plaque with a red thrombus (*white arrow* in *D-2*). (E) Angioscopic images one year after PCI show the white neointima, fully covering the stent struts; neoatherosclerosis is not evident

17.3.3 Other Second-Generation Drug-Eluting Stents

Slow-release zotarolimus-eluting stent (R-ZES) and biolimus A9-eluting stents (BES) are the other second-generation DESs. At the present, we have no enough data on vascular healing response regarding these two new stents. According to recent papers, BES has an abluminal bioabsorbable polymer and R-ZES has a highly biocompatible polymer. In fact, Awata M et al. [27] clearly demonstrated by angioscopy that BES induced better healing having more homogeneous neointima as compared with SES implantation; however, atherogenic potential has been uncertain.

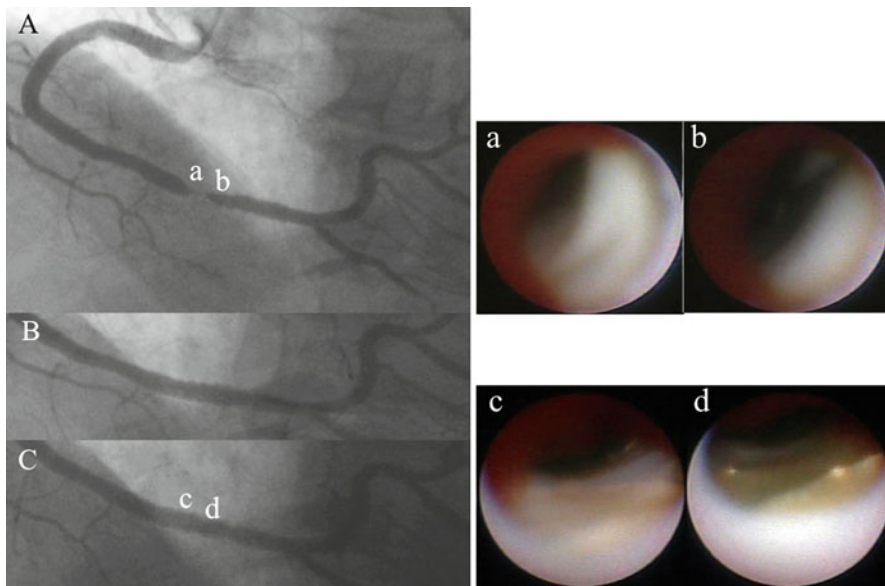


Fig. 17.9 A case of paclitaxel-eluting stent (PES) implantation after bare-metal stent in-stent restenosis. **(A)** Before percutaneous coronary intervention (PCI), severe restenosis is evident in distal right coronary artery. **(B)** The PES is implanted. **(C)** One year later, there is no evidence of in-stent restenosis. *a, b* Angioscopic images before PCI show white neointima, which is thought to be proliferation of smooth muscle. *c, d* Angioscopic images one year after PCI show the presence of yellow neointima; neoatherosclerosis occurred

17.4 Bare-Metal Stent (BMS)

As mentioned in the previous chapter, BMS segments escaped from ISR were considered favorable healing continue within a couple of years because the segments are covered with thick and white neointima and that completely seals vulnerable plaque under the stents in chronic phase. According to an angioscopic follow-up examination in long-term period, the neointima becomes thinner and transparent 3 years after BMS implantation [28]. Recent analyses show that very late stent thrombosis originated from BMS segment occurs as well as DESs. The mechanism of very late stent thrombosis is rupture of atheromatous lesion within the BMS segment [1]. Figure 17.13 shows angioscopic images of a patient with unstable angina. The patient underwent BMS implantation in the left circumflex artery 9 years before the onset. Angioscopic observation revealed the presence of dense yellow plaque and white thrombi. These findings indicated that neoatherosclerosis of BMS and following its disruption caused ACS. In such cases, at least optimal medical therapy seems to be important after stent implantation.

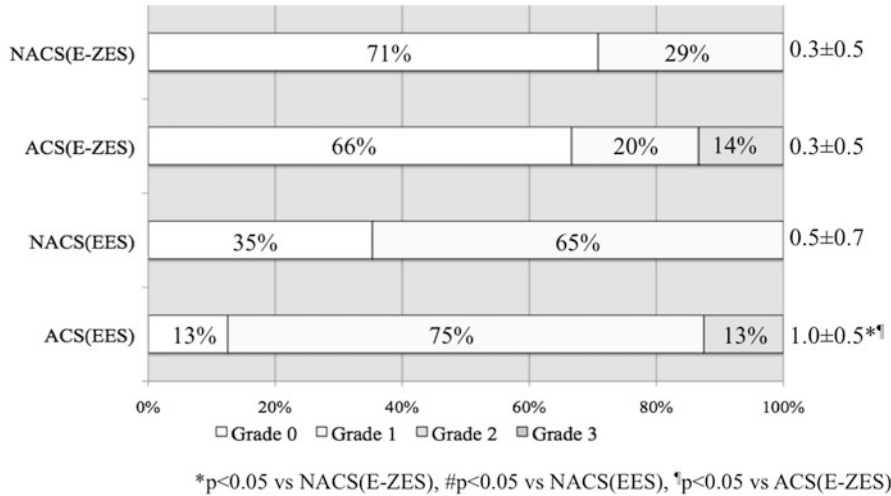


Fig. 17.10 Yellow-plaque grades after the implantation of second-generation drug-eluting stents. The existence of residual or newly formed yellow plaque is lower in the fast-release zotarolimus-eluting stent group compared with the everolimus-eluting stent group, especially among ACS patients. NACS, non-acute coronary syndrome; ACS, acute coronary syndrome

17.5 Other Imaging Modalities for Detection of Neoatherosclerosis

Angioscopy has played an important role in validation of neoatherosclerosis after stent implantation. However, other modalities can also detect the neoatherosclerosis. In this section, several cases of neoatherosclerosis detected by intravascular ultrasound (IVUS), optical coherence tomography (OCT), and computed tomography (CT) will be presented.

17.5.1 Intravascular Ultrasound (IVUS)

IVUS was the first modality used to observe the intravascular structure in living patients [29]. IVUS has played an important role in the assessment of vessel structure including atherosclerosis. Furthermore, recent IVUS techniques have also permitted tissue characterization of the vessel wall [30, 31]. In-stent neoatheroma may be also analyzed by recent IVUS images. However, the resolution of IVUS is 100 μm, and it has limitation of detecting thin neointima. IVUS analysis is suitable for detection of thick neointima and ISR lesions. Figure 17.14 shows an ISR lesion of SES in midportion of right coronary artery. Angioscopy revealed that the neointimal tissue was a yellow, so-called neoatherosclerosis. Integrated backscatter

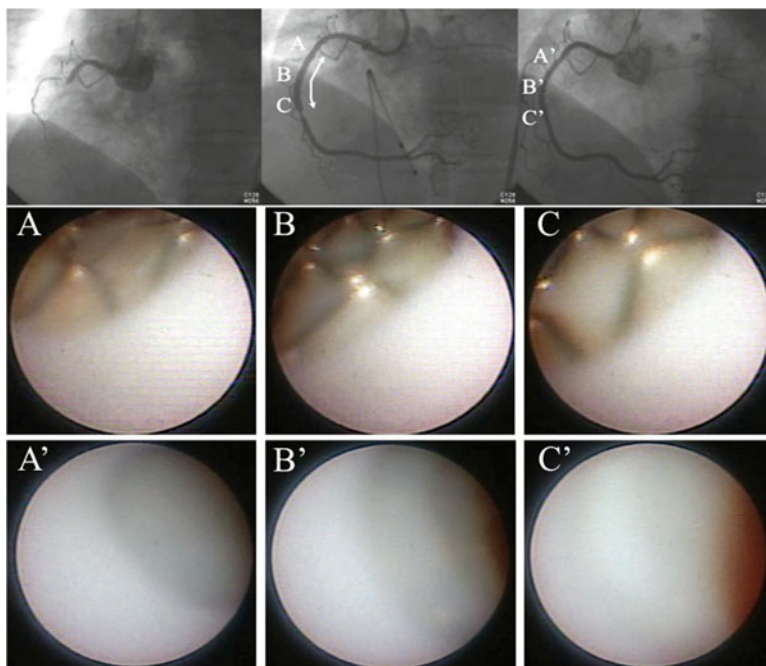


Fig. 17.11 An acute coronary syndrome patient showing typical angioscopic images after fast-release zotarolimus-eluting stent (E-ZES) implantation. *Upper left panel* Right coronary angiogram before percutaneous coronary intervention (PCI). *Upper middle panel* Right coronary angiogram immediately after PCI. *Upper right panel* Right coronary angiogram one year after PCI. There is no in-stent restenosis evident after the PCI. (A, B, C) An E-ZES is shown in the proximal right coronary artery with light yellow plaque during the acute phase. (A', B', C') One year later, the stent struts are not visible due to the thick, white neointima

IVUS clearly indicated the presence of lipid-rich tissue in the ISR lesion. The lesion was treated by BMS, for the expectation of sealing effect of the BMS. Our attempt was successful; thick and white neointima covered the ISR lesion without recurrence of restenosis at follow-up study [32]. Thus, integrated backscatter IVUS is also useful for characterization of neointimal tissue in thick ISR lesion.

17.5.2 *Optical Coherence Tomography (OCT)*

OCT is a recent intravascular imaging technique and its resolution is about 10 μm , enabling detection of the thin fibrous cap of atheroma and thin neointima of DESs segment [33]. Thus, OCT became gold standard for assessment of in-stent neointima [34]. In addition, OCT provides accurate tissue characteristics, such as lipid pool, calcification, and thrombi [35]. Furthermore, OCT can detect

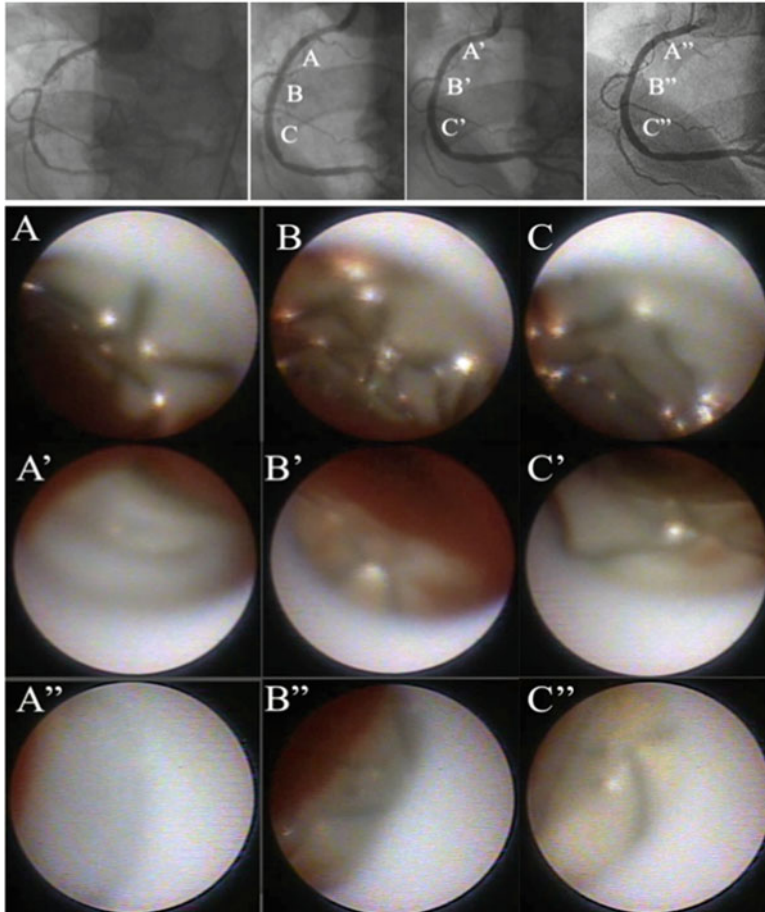


Fig. 17.12 A patient with hybrid stenting involving an everolimus-eluting stent (EES) in segment 2 and a fast-release zotarolimus-eluting stent (E-ZES) in segment 1. The *upper panel* from the *left* shows coronary angiograms before percutaneous coronary intervention (PCI), immediately after PCI, 3 months after PCI, and 1 year after PCI. There is no in-stent restenosis evident after the PCI. (A) Immediately after PCI, at E-ZES implantation site. (B) Immediately after PCI, at Overlapping site. (C) Immediately after PCI, at EES implantation site. The two stents are implanted on the white plaque. (A') Three months after PCI, at the E-ZES site. The stent struts are covered with thick, white neointima. (B') Three months after PCI, at the overlapping site. The stent struts are covered with thin neointima. (C') Three months after PCI, at the EES site. The stent struts are covered with a thin neointima. (A'') One year after PCI, at the E-ZES site. The stent struts are covered with a thick, white neointima. (B'') One year after PCI, at the overlapping site. The stent struts are covered with thin neointima. (C'') One year after PCI, at the EES site. The stent struts are covered with thin neointima. The neointima color appears to be yellowish

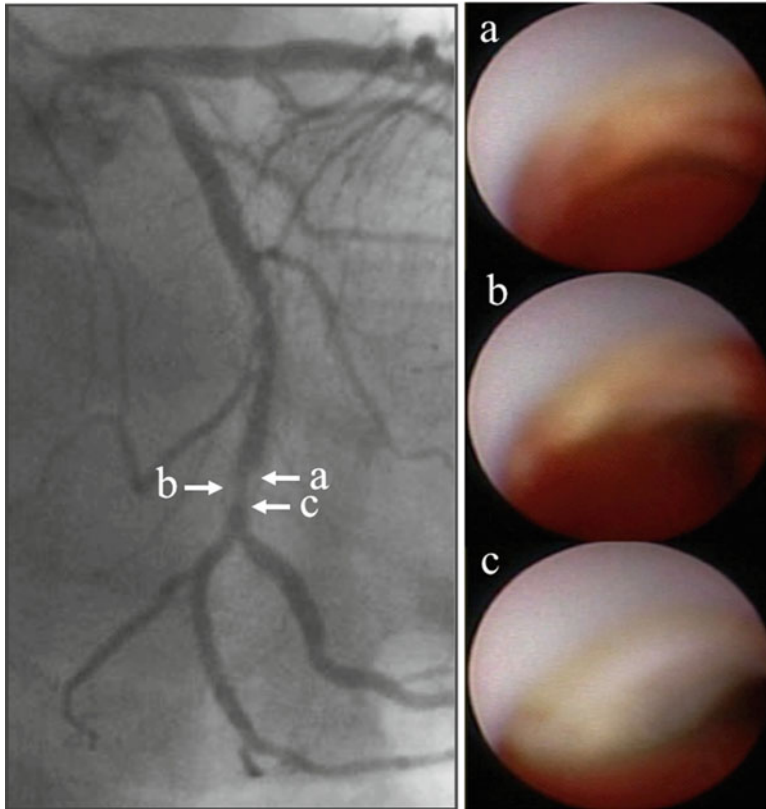


Fig. 17.13 Bare-metal stent (BMS) neoatherosclerosis. The *left panel* shows the results of a coronary angiogram. Severe stenosis is evident in the distal left circumflex artery. This patient received a BMS in segment 13, 9 years earlier. (*a, b, c*) Angioscopy reveals dense, yellow plaque, with white thrombi

macrophage recruitment in the plaque indicative of inflammation [36]. Figure 17.15 shows angioscopically yellow neointima of SES segment. In this segment, lipid-rich neointima and macrophage infiltration were found by OCT [37].

17.5.3 Computed Tomography (CT)

A recent trend for the diagnosis of coronary artery disease is initially performed CT angiography [38]. CT angiography is valuable for understanding plaque characteristics in a noninvasive way [39]. CT may be valuable for detecting ISR after stenting. Figure 17.16 shows a case of ISR occurred 5 years after SES implantation. Not only

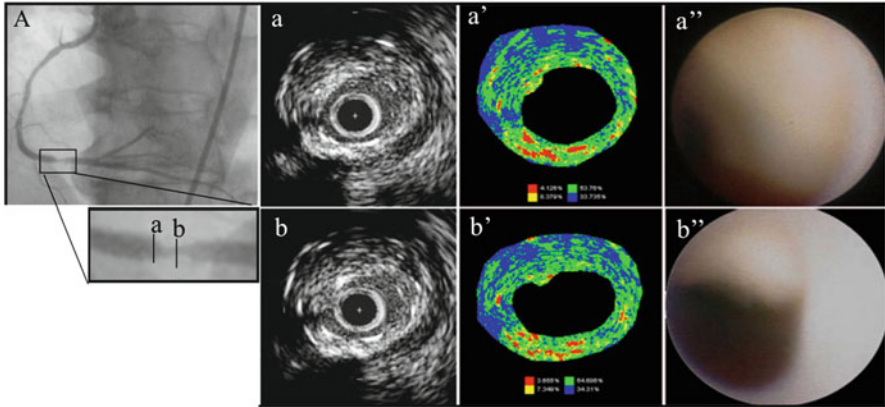


Fig. 17.14 A case of in-stent restenosis after the implantation of a sirolimus-eluting stent. (A) Coronary angiogram showing severe stenosis in distal right coronary artery. (a, b) Gray scale intravascular ultrasound images showing thick neointima developing in the stent. (a', b') Integrated backscatter-intravascular ultrasound images showing a *blue color* predominating in the thick neointima, indicating a lipid-rich neointima. (a'', b'') Angioscopy revealing yellow neointima (lipid-rich plaque)

coronary angiography but also CT clearly detects the ISR lesion. Angioscopic color of the ISR lesion was yellow. In quantitative CT analysis of the lesion, CT value was 24 HU, indicating lipid-dominant tissue. Also, CT may be useful for the analysis of tissue components in ISR lesion.

17.6 Mechanisms of In-Stent Neoatherosclerosis

Nakazawa et al.[1] reported that in-stent neoatherosclerosis occurs in both BMSs and DESs. However, neoatherosclerosis of DESs is observed more frequently and at earlier time points (median, 420 days) compared with BMSs (median, 2,160 days). Moreover, neoatherosclerosis associated with DESs is associated with unstable symptoms within 2 years after their implantation, whereas similar features occur at a late phase (average time to implant, 6 years) following BMS implantation. These results indicate that different mechanisms are responsible for neoatherosclerosis between DES and BMS. Following DES implantation, incomplete endothelialization, and the inability to maintain a fully functional, endothelialized luminal surface within the stented segment appears to induce permeability of inflammatory cells and/or lipid and subsequent neoatherosclerosis. Normal endothelium commonly works as an efficient barrier against the excessive uptake of circulating lipid regardless of the segment of DESs and BMSs. The incomplete or delayed endothelial regrowth in DESs may contribute to atherogenesis due to the inefficient barrier

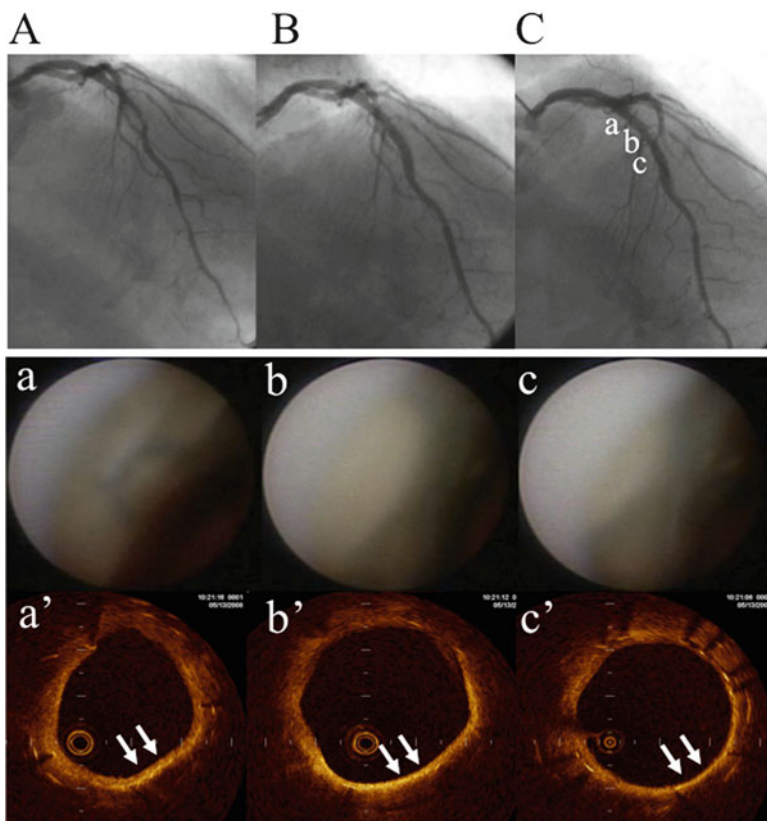


Fig. 17.15 A case of in-stent yellow neointima after sirolimus-eluting stent implantation. (A) Coronary angiogram before percutaneous coronary intervention (PCI) showing severe stenosis in segment 7. (B) Coronary angiogram immediately after PCI. (C) Coronary angiogram 1 year after PCI. Angioscopic images show yellow neointima (*a, b, c*). Using optical coherence tomography, high intensity neointima, without backscatter (*white arrows*), is shown to cover the stent struts, indicating lipid-rich neointima

effect. In the segment of BMSs with complete endothelialization, neoatherosclerosis may occur in a manner similar to the development of atherosclerosis in native coronary arteries. Regarding the potential mechanisms of atherosclerotic transformation inside the BMS segment, so far few interpretations have arisen. One is that stainless steel of the BMS evokes a remarkable foreign-body inflammatory reaction to the metal, and peri-stent chronic inflammatory cells may accelerate new atherosclerotic changes [40].

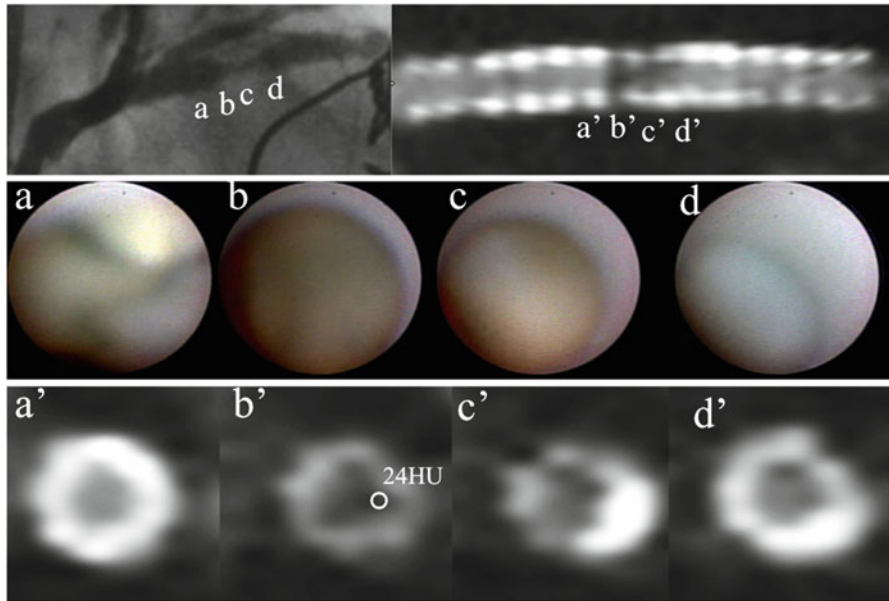


Fig. 17.16 A case of in-stent restenosis after sirolimus-eluting stent implantation. *Upper left panel:* A coronary angiogram shows severe stenosis in proximal left descending coronary artery. *Upper right panel:* A computed tomography (CT) coronary angiogram shows a low-intensity plaque in the proximal left descending coronary artery. Angioscopic images show yellow plaque at the site of severe stenosis (*b, c*). CT analysis reveals that the CT value of the in-stent restenosis site was 24 Hounsfield Unit, indicating lipid-rich plaque

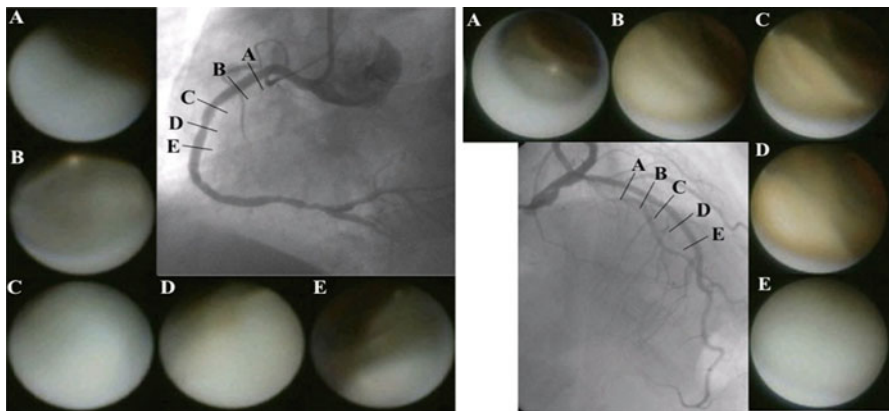


Fig. 17.17 Effect of statin therapy. The right panel shows angioscopic images, after SES implantation, in conjunction with statin therapy (LDL-C concentration, 76 mg/dL). There was no yellow neointima, 1 year after PCI. The *left panel* shows angioscopic images after SES implantation in the absence of statin therapy (LDL-C concentration, 147 mg/dL); yellow neointima formation was evident 1 year after PCI

17.7 Prevention of In-Stent Neoatherosclerosis

Considering the mechanisms of in-stent neoatherosclerosis, statin therapy may prevent neoatherosclerosis. Kanai et al. reported [41] the development of yellow plaque under implanted SES. In aggressive lowering of low-density lipoprotein-cholesterol (LDL-C) group, angioscopic grade of yellow plaque, within the SES segment, was significantly decreased from 9 to 14 months of follow-ups compared to baseline. They concluded that the adequate lowering of LDL-C using a statin might prevent the biochemical action and development of atherosclerosis associated with SES implantation. Figure 17.17 shows presence and absence of neoatherosclerosis after SES implantation in different levels of LDL-C. With statin treatment, white neointima is present one year after PCI. Without statin, yellow neointima formation occurred within one year after PCI. These observations indicated that optimal medical therapy, using statins, may prevent neoatherosclerosis after implantation of either DESs or BMSs.

17.8 Conclusion

In this chapter, we have explained the new concept of “neoatherosclerosis” on the basis of angioscopic images. Today, neoatherosclerosis after stent implantation is prevalently accepted, and angiography plays an important role in the discovery of this phenomenon. Since seeing is believing, continuing to clarify changes of the coronary lumen by angiography may be required.

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