

Chapter 18

Angioscopic Evaluation of In-Stent Restenosis

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Abstract Although drug-eluting stents (DESs) have greatly reduced the incidence of in-stent restenosis (ISR), the management of patients with ISR remains an important clinical problem. The use of DESs can reduce one of the main factors for ISR, neointimal hyperplasia, but recent data have revealed that neoatherosclerosis may also play an important role in ISR, especially in DES cases. ISR shows two patterns: early ISR (<1 year) especially for bare-metal stents (BMSs) and late ISR (≥ 1 year) especially for DESs. Angioscopy is the only image modality that can directly visualize the coronary artery lumen. In the early ISR phase, if white plaques on the stent and complete neointimal coverage are found by angioscopy, the neointimal condition is considered stable, but clinicians should carefully evaluate whether the neointimal condition can cause myocardial ischemia at this phase. In the late ISR phase, if yellow plaques in the stent segments are found angioscopically, the potential for neoatherosclerosis in ISR tissue should be considered. Angioscopy can provide original and important information about the neointima at early and late phases of ISR.

Keywords In-stent restenosis • Neoatherosclerosis • Yellow plaque • Thrombus • Bare meal stent drug-eluting stent

18.1 Introduction

The major clinical problem in the use of balloon angioplasty is the occurrence of restenosis, which has been observed in approximately 30–40 % of patients [1]. Restenosis is characterized by the following three major factors: (1) acute elastic recoil, (2) chronic elastic recoil (negative remodeling), and (3) neointimal proliferation. To resolve the elastic recoil problem, bare-metal stents (BMSs) were

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developed [2]. BMS implantation resulted in a decline of the restenosis rate to 20–30 % [3], but the use of a BMS does not resolve another of the major factors for restenosis: neointimal proliferation.

Drug-eluting stents (DESs) were developed to address neointimal proliferation. Drugs that inhibit neointimal proliferation, with a stent as a local delivery platform, have been found to be a highly promising method for preventing in-stent restenosis (ISR). The use of DESs has achieved markedly reduced ISR, at approximately 12 % [4], but ISR remains a major clinical problem even in the DES era because a completely effective strategy for preventing ISR has not yet been established [5, 6]. In addition, a recent pathological study showed that neoatherosclerosis represents a common substrate in patients with late stent failure, including late ISR [7].

Early ISR (<1 year) was found to be greatly reduced with the use of DESs, but DES cases also demonstrated evidence of continuous neointimal growth during long-term follow-up, which was designated the “late catch-up phenomenon,” including late ISR [8]. Therefore, at present, both early and late ISR should be considered when we evaluate ISR lesions.

18.2 Angioscopic Evaluation for Early ISR (<1 Year)

Angioscopy can only visualize the surface of the coronary artery lumen; it cannot evaluate the cross-sectional components of in-stent tissue characteristics, as can intravascular ultrasound (IVUS) and optical coherence tomography (OCT). However, angioscopy is the only imaging modality that can directly evaluate the color of plaques and the existence of thrombi on the surface of the coronary artery lumen. Intimal hyperplasia after BMS implantation was found to peak early, between 6 months and 1 year, followed by intimal regression with luminal enlargement [9]. These phenomena are supported by histological research [10].

A serial angioscopy study demonstrated luminal changes in early restenosis phase after BMS stent implantation. The BMSs <1 month after implantation were often not completely covered by neointima and were accompanied by a thrombus, but BMSs at approximately 6 months were completely covered by white neointima [11]. The neointima over a BMS usually completely covers the stent, yellow plaques under the stent, and any thrombus [11–13].

In cases of early ISR (which frequently occurs after BMS implantation), angioscopy can provide images of the complete neointima coverage (Fig. 18.1). Compared to early ISR after BMS implantation, DES tended to show focal pattern, often affecting the stent edges, that may be occurred by geographic-miss phenomenon or strut fractures [14]. The clinical impact using angioscopy for these cases is usually weak. IVUS or OCT may be more useful to evaluate early ISR cases, especially for clinical decision-making regarding the strategy for intervention therapy. However, several studies of the clinical impact of angioscopy at 6–8 months after implantation among patients with a DES have been informative. For example, Awata et al. reported that angioscopic findings at approximately 8 months' follow-

Fig. 18.1 A case of early in-stent restenosis who received bare-metal stent. Angioscopy revealed complete coverage with white plaque

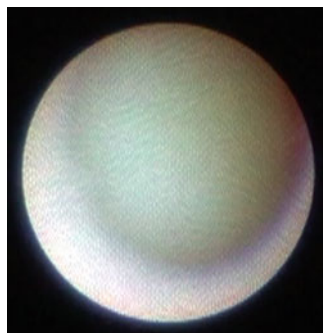


Fig. 18.2 Red thrombus (arrows) around stent struts

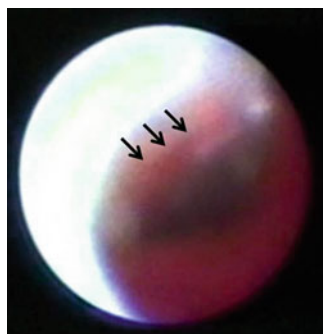
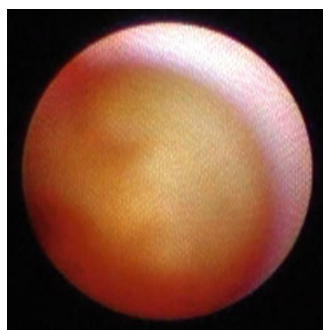


Fig. 18.3 A case of late in-stent restenosis who received drug-eluting stent. New formation of yellow plaque on stent was found by an angioscopy



up showed a lower grade of neointimal coverage and a higher incidence of the presence of a subclinical thrombus (Fig. 18.2) and yellow plaque (Fig. 18.3) in DES cases (sirolimus-eluting stents) compared to BMS cases [15]. In this study, serial angioscopy showed only persistent yellow plaques underneath the stent struts, and there were no new formation of yellow plaques which were considered as neoatherosclerosis.

However, these angioscopic findings (including the existence of angioscopic [subclinical] thrombi) had no direct link to major cardiac events including thrombotic clinical events and ISR. We have also shown that the lower minimum grade and more heterogeneous properties of neointimal coverage and thrombi in DES

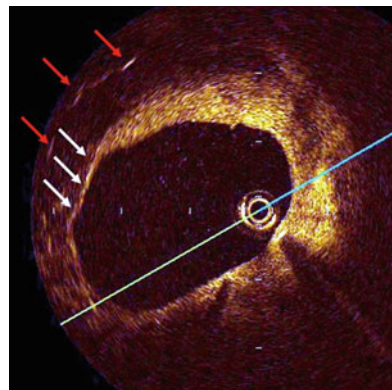
cases compared to BMS cases at 8 months' angioscopic evaluation did not correlate with cardiac events (including ISR) over a period of 3 years [16]. Other studies demonstrated that yellow plaques (which can be visualized only by angiography) may be correlated with advanced atherosclerotic degeneration ruptures and may lead to neointimal progression including ISR in both BMS and DES cases [12, 17]. We thus believe that the angioscopic findings, especially those of yellow plaque, at an 8-month follow-up can be used as a marker to predict future cardiac events, including ISR.

18.3 Angioscopic Evaluation for Late ISR (≥ 1 Year)

Neoatherosclerosis is an important indicator of late ISR in both BMS and DES cases [18]. In DES cases, neoatherosclerosis occurred in $>40\%$ of the patients by 9 months after implantation, whereas in BMS cases, it did not begin to appear until 2 years and remained a rare finding until 4 years [19]. Moreover, it was reported that DESs promoted the new formation of yellow neointima at 10 months after implantation [16] and that neoatherosclerosis occurred earlier in DES compared to BMS [18, 20, 21]. Thus, it is even more important to evaluate neoatherosclerosis in DES than in BMS.

Several OCT studies revealed that its findings of neoatherosclerosis involved the presence of neointimal disruption, lipid-laden neointima, lipid pools, thin-cap fibroatheromas (TCFAs) and macrophage accumulation [22, 23]. It was also shown that TCFA findings (Fig. 18.4) by OCT were well correlated with angioscopic yellow plaques, supported by a virtual histology-IVUS study [24] and a histological study [25]. Angioscopic evaluations may be useful to evaluate and predict late ISR correlated with neoatherosclerosis. If yellow plaque is detected in the late phase (≥ 1 year) after BMS or DES implantation, clinicians should pay close attention to the possibility of neoatherosclerosis, which may lead to late ISR.

Fig. 18.4 *White arrows:* thin-cap fibroatheromas (TCFA) in in-stent tissue detected by optical coherence tomography (OCT). *Red arrows:* the stent strut



18.4 Summary

Angioscopy is the only modality that directly visualizes the surface of the coronary artery lumen. In the early ISR phase, angioscopic findings of complete coverage by white neointima are well correlated with stable condition after stent implantation. However, if a patient shows ischemic findings due to narrowing of the coronary lumen, repeated intervention therapy should be performed. In the late ISR phase, angioscopic findings of yellow plaque may be correlated with neoatherosclerosis. When yellow plaque is angioscopically identified in this phase, careful follow-up should be conducted to examine the multifaceted and elusive condition causing both ISR and stent thrombosis.

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