

## Neoatherosclerosis: a novel player in late stent failure

Evidence derived from histopathologic and intravascular imaging studies has suggested a key role for neoatherosclerosis as a substrate for the occurrence of late events after both drug-eluting stent and bare-metal stent implantation. In particular, the development of neoatherosclerosis has been associated with occurrence of late in-stent restenosis and stent thrombosis. In this review, we describe pathogenetic mechanisms responsible for neoatherosclerosis and recent evidences deriving from histopathologic and intravascular imaging studies. Finally, we discuss possible approaches for risk stratification and therapeutic strategies.

**Keywords:** drug-eluting stent • in-stent restenosis • late events • neoatherosclerosis • stent thrombosis

Neoatherosclerosis is a newly formed atherosclerotic change within the neointima following bare-metal stent (BMS) or drug-eluting stent (DES) implantation. Of importance, recent studies suggested an important role for neoatherosclerosis in late events after both DES and BMS implantation. In particular, the development of neoatherosclerosis has been associated with occurrence of late in-stent restenosis (ISR) and stent thrombosis (ST). In this review, we describe pathogenetic mechanisms responsible for neoatherosclerosis and evidence derived from histopathologic and intravascular imaging studies (Table 1). Finally, we discuss possible approaches for risk stratification and therapeutic strategies.

### Mechanisms of neoatherosclerosis

Neoatherosclerosis is characterized by infiltration and accumulation of clusters of foamy macrophages within the neointima, following both BMS and DES implantation, due to the inability to maintain a fully functional luminal surface within the stented segment. Of importance, recent studies demonstrated a key role of neoatherosclerosis for late stent failure [1–3].

The mechanisms responsible for the development of neoatherosclerotic lesions are multiple (Figure 1) [4,5]. First of all, endothelial dysfunction following stent implantation has been shown to be involved. In normal conditions, the endothelium provides a protection against excessive infiltration of circulating lipids, making the development of the atherosclerotic lesion very slow. Conversely, endothelial cells within the DES stented segment show poorly formed intercellular junctions, reduced expression of antithrombotic molecules and decreased nitric oxide production [6,7].

Endothelial dysfunction may be the consequence of a chronic local inflammatory activation induced by stent polymer or metal [4,5]. Moreover, the local shear stress resulting from flow disturbances may play a role in endothelial dysfunction [8,9]. The activation of endothelial cells results in an increased expression of ICAM-1 and VCAM-1, which attract circulating monocytes into the subendothelial space.

Impaired barrier of endothelium within the stented segment, inflammatory activation and stent-induced shear stress may produce an increased permeability, resulting in an

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Study	Imaging type	Stent type	Enrolled patients (n)	Follow-up	Main findings	Ref.
Yokoyama <i>et al.</i>	Angioscopy	BMS	26	Phase I: 6–12 months Phase II: 4 years	↑ yellow plaque (4% at the Phase I follow-up, 15% at the Phase II follow-up) ↑ stenosis	[17]
Ueda <i>et al.</i>	Angioscopy	BMS	38	Phase I: 1–4 weeks; Phase II: 2–5 months	↑ neointima and ↓ thrombus from the Phase I follow-up to the Phase II follow-up	[18]
Higo <i>et al.</i>	Angioscopy	DES	57	10 months	Sirolimus DES promoted the formation of yellow neointima	[19]
Takano <i>et al.</i>	OCT	BMS	41	Phase I: <6 months Phase II: ≥5 years	↑ lipid-laden intima (from 0% at Phase I follow-up to 67% at the Phase II follow-up) ↑ intimal disruption (from 0% at Phase I follow-up to 38% at Phase II follow-up); ↑ luminal thrombus (from 5% at Phase I follow-up to 52% at Phase II follow-up)	[3]
Kang <i>et al.</i>	OCT	DES	50	32.2 months (median)	52% of overall lesions had at least once TCFA-containing neointima; 58% had at least one in-stent neointimal rupture; 58% had intraluminal thrombi	[25]

BMS: Bare-metal stent; DES: Drug-eluting stent; OCT: Optical coherence tomography; TCFA: Thin-cap fibroatheroma.

accelerated infiltration and accumulation of lipoproteins and inflammatory cells within the subendothelial space [8–10]. Moreover, lipoproteins in the subendothelial space undergo oxidative modifications, which lead to production of chemoattractant and inflammatory mediators such as MCP-1 and VCAM-1, which are involved in the further recruitment and attachment of monocytes [11].

In addition to endothelial dysfunction, macrophage and vascular smooth muscle cell death appear to play a role in the pathogenesis of neoatherosclerosis. Indeed, release of lipids deriving from macrophage death may contribute to the pool of free cholesterol and cholesterol esters, thereby forming a necrotic core [12]. Finally, vascular smooth muscle cell death and degradation may result in increased levels of free cholesterol and cholesterol esters, which may further attract macrophages [13].

#### Evidence derived from histopathologic studies

Different histopathological studies have shown an important role for chronic inflammation and/or endothelial dysfunction in the pathogenesis of neoatherosclerosis, following both DES and BMS implanta-

tion, suggesting that neoatherosclerosis may be an important player for late ISR and late ST (LST).

Inoue *et al.* [14] reported histopathologic findings of autopsied samples in 19 patients with noncardiac death after implantation of Palmaz–Schatz coronary stents, suggesting the possibility that peristrut inflammation evoked by a foreign body reaction to the metal corrosion might accelerate new indolent atherosclerotic changes within the stents. Conversely, Hasegawa *et al.* [15], analyzing 14 BMS restenotic lesions developed beyond 5 years, demonstrated that restenotic tissues retrieved by directional coronary atherectomy were composed of newly developed atherosclerosis facing the underlying intima, regardless of the presence of peristrut inflammation. Furthermore, four samples from the cases presented with acute coronary syndrome showed typical histological morphologies that are similar to vulnerable plaque in native coronary arteries.

However, some studies have pointed out the differences that exist between DES and BMS neoatherosclerosis. Nakazawa *et al.* [1] reviewed autopsy cases from the CVPATH stent registry and compared 66 sirolimus-eluting stent (SES) lesions with 77 BMS lesions. This study showed that neoatherosclerosis

occurred in both BMS and DES, but the incidence of this phenomenon is greater in DES ( $n = 64$ ; 31%) than BMS ( $n = 31$ ; 16%) lesions ( $p < 0.001$ ). Moreover, a significant difference in the timing of neoatherosclerosis development was found among BMS and DES. Indeed, atherosclerotic change occurred in shorter implant durations for DES than for BMS (DES: median 420 days; BMS: median 2160 days). In addition, the earliest necrotic core formation began at 9 months, whereas in BMS it occurred at 5 years.

These findings were confirmed more recently in another study from the same group [2]. Regarding DES, data are mostly available for SES and paclitaxel-eluting stent (PES), suggesting a trend for a more rapid neoatherosclerotic changes in SES than in PES. The cumulative incidence up to 6 years are: SES 38% versus PES 24% versus BMS 10%, indicating that differences of drugs or polymers may influence on neointimal tissues. A recent human autopsy analysis by Otsuka *et al.* evaluated the occurrence and characteristics of neoatherosclerosis after SES, PES or everolimus-eluting stent (EES) implantation, showing that EES had greater strut coverage with less inflammation, less fibrin deposition, and less LST and very late ST (VLST) compared with SES and PES [16]. Nevertheless, the observed frequencies of neoatherosclerosis-related adverse pathological events were comparable in these devices, indicating that careful long-term follow-up remains important even after EES placement.

Taken together, these data suggest that mechanisms of failure after BMS and DES implantation are quite different. Indeed, BMS patients tend to develop ISR early, due to neointima hyperplasia. On the contrary, DES patients tend to develop less neointima in the early period, explaining the benefit in the occurrence of target lesion revascularization (TLR) after 1-year follow-up compared with BMS. However, DES patients tend to develop neoatherosclerosis later, probably explaining the late catch-up phenomenon and the occurrence of VLST.

## Evidence deriving from intravascular imaging

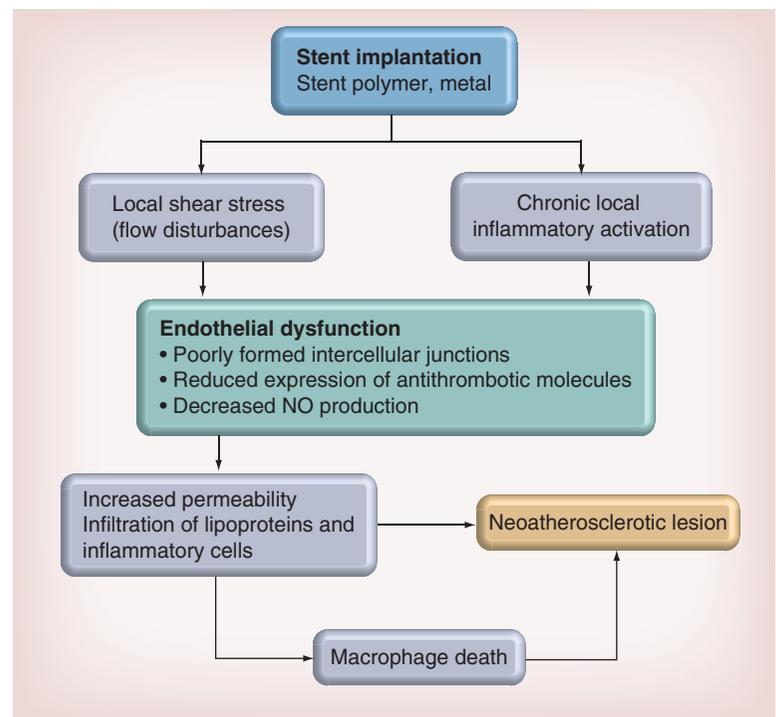
### Angioscopy

In a serial angioscopic study (at baseline, at 6–12 months and after 4 years) following 26 BMS implantations, Yokoyama *et al.* investigated the neointimal changes derived from vessel healing response, showing the occurrence of new atherosclerotic lesions, represented as yellow plaque [17]. Although there are no available data regarding the correlation between angioscopic and histologic findings, yellow neointima observed at the angioscopy most likely corresponds

to foamy macrophages infiltrating into fibrous cap and/or underlying lipid accumulation. Of note, the intensity of yellow likely signifies thickness of fibrous cap and amount of necrotic core. In this study, an increase in the incidence of yellow plaque, from three cases (4%) at the first follow-up to 15 cases (58%) at the second follow-up, was shown. This increase was accompanied by a rise of the late luminal narrowing, defined as an increase in percentage diameter stenosis between the first and second follow-up, that was significantly greater in segments with yellow plaque than in those without yellow plaque (18.4 vs 3.6%;  $p = 0.011$ ). This finding indicated that atherosclerotic degeneration inside BMS may contribute to the late luminal narrowing.

Another serial angioscopic examination by Ueda *et al.* [18] demonstrated that BMSs at 1–4 weeks after implantation were not completely covered by neointima, whereas they were often (45%) accompanied by thrombus. Nevertheless, at 2–5 months, BMS were completely covered by neointima, while thrombus was detected only in 13% of patients. This reduction in the incidence of the thrombus is due to the fact that the neointima over BMS usually covers both stent and yellow plaques under stent completely, and thrombus was no longer detected on the white and smooth neointima even if thrombus was detected on the yellow plaque.

Regarding the DES, Higo *et al.* [19] demonstrated that sirolimus DESs promoted the forma-



**Figure 1. Pathogenic mechanisms of neoatherosclerosis.** NO: Nitric oxide.

tion of atherosclerotic yellow neointima in the stent-implanted lesion at 10-month follow-up. Thrombus was detected more often on the yellow area than on the white area and was never detected where a stent was buried under white neointima. These data suggest that the increased potential risk of LST in DES lesions may be due to the newly formed yellow neointima and cholesterol-laden plaque.

Finally, it is also possible that the angioscopic yellow neointima with advanced atherosclerotic degeneration ruptures and leads to further neointimal progression as well as to late thrombotic events [20].

#### Virtual histology-intravascular ultrasound

Virtual histology-intravascular ultrasound (VH-IVUS) involves spectral analysis for frequency and intensity of back-scattered ultrasound data to construct tissue maps of coronary plaques [21]. Although it is difficult for intravascular ultrasound (IVUS) to determine neointimal tissue because of the signal interference from metal struts, there are several reports attempting discrimination of neointimal tissues by IVUS. Kang *et al.* [22] reported findings from 70 DES-ISR and 47 BMS-ISR lesions with intimal hyperplasia in >50% of the stent area by VH-IVUS. The mean follow-up time was 43.5 months for BMS lesions and 11.1 months for DES lesions, and this study showed that both BMS- and DES-treated lesions develop an in-stent necrotic core and dense calcium, suggesting the development of in-stent neoatherosclerosis, especially in lesions with longer implant duration.

Moreover, Sánchez-Recalde *et al.* performed an IVUS study during primary angioplasty in five patients with very late BMS thrombosis and carried out a histological analysis of the material removed by manual thrombectomy [23]. The mean (standard deviation) time from the index procedure was 7 ( $\pm 4$ ) years and at IVUS analysis they found calcified atherosclerosis with in-stent plaque rupture, complex plaque in the distal segment of the stent, in-stent neointimal proliferation associated with underexpansion and severe in-stent proliferation.

#### Optical coherence tomography

Optical coherence tomography (OCT) is a near-infrared light-based imaging modality with very high resolution. As a consequence of its high resolution (10–20  $\mu\text{m}$ ), OCT has been shown to better evaluate the vascular responses after stent implantation [24]. Habara *et al.* [24], through the use of OCT, have evaluated the progression of in-stent atherosclerotic lesion >5 years after BMS implantation and found a high incidence (90.7%) of possible neoatherosclerotic change, defined as heterogeneous OCT appear-

ance with low-intensity areas, whereas lesions <1 year after BMS implantation showed only 17.9% incidence of neoatherosclerosis. In-stent intimal growth was accompanied by neointimal disruption, which had analogous morphology of ruptured fibroatheroma in a native coronary artery and occurred more frequently in >5-year lesions (18.6%) than in <1-year lesions (0%).

Takano *et al.* [3] evaluated neointimal OCT characteristics of BMS in early (<6 months) and extended late phases ( $\geq 5$  years). In the early phase there was no sign of lipid-laden intima, evidenced by the presence of a homogeneous OCT appearance. Conversely, lipid-laden intima, intimal disruption and luminal thrombus formation were more frequently observed in the late phase, when compared with the early phase (67 vs 0%, 38 vs 0%, and 52 vs 5%, respectively; all  $p < 0.05$ ). These findings suggest that neointima within BMS often undergoes a neoatherosclerotic process during an extended follow-up period and this process, promoting further luminal narrowing, may play a role in the development of in-ST.

By an OCT analysis in 50 patients with DES-ISR (median follow-up period: 32.2 months), Kang *et al.* showed that the 52% of overall lesions had at least one TCFA-containing neointima, 58% had in-stent neointimal rupture and 58% showed intraluminal thrombi [25]. Although Gonzalo *et al.* previously reported various OCT patterns of restenotic tissue after stenting (84% were various DES), the median follow-up time was only 12 months, too short to manifest the entire spectrum of neoatherosclerosis as suggested in this study [26]. In contrast to patients with stable angina, patients presenting with unstable angina showed a thinner fibrous cap and an increasing number of unstable OCT findings, including TCFA-containing neointima, neointima rupture and thrombus. Compared with DES <20 months post-implantation (the best cutoff to predict TCFA-containing neointima), DES  $\geq 20$  months postimplantation had a higher incidence of TCFA-containing neointima (69 vs 33%;  $p = 0.012$ ) and red thrombi (27 vs 0%;  $p = 0.007$ ). These findings suggest that in-stent neoatherosclerosis assessed by OCT may be an important mechanism of DES restenosis, especially late after implantation.

#### Risk stratification & therapeutic approach

In the past, inflammatory activation has been shown to be associated to clinical recurrence of thrombotic events arising from native coronary artery atherosclerotic lesions [27]. At the same time, inflammatory biomarkers have been shown to predict clinical outcome in patients undergoing stent implantation.

Indeed, in order to stratify the risk of angiographic and clinical outcomes after stent implantation, several inflammatory biomarkers have been investigated. CRP represents the most extensively studied biomarker in patients undergoing percutaneous coronary intervention (PCI). CRP is a sensitive marker of systemic inflammation [28–30] and, in particular, has been shown to be an important marker of poststenting inflammation [31]. Indeed, CRP levels increase after PCI in a time-dependent manner, peaking at 48 h, and the magnitude of CRP change after the procedure has been shown to predict ISR in patients undergoing BMS deployment [32]. Inflammatory biomarkers, however, cannot specifically predict ISR because they may also predict progression and destabilization of atherosclerosis in native coronary arteries. However, some angiographic studies have shown that both baseline and postprocedural CRP levels may allow the identification of patients at higher risk of restenosis after BMS [33–35].

Moreover, different studies evaluated the association between CRP with angiographic and clinical end points after DES deployment showing that baseline CRP levels have been associated with hard clinical end points [36,37]. Indeed, Park *et al.* demonstrated that higher baseline CRP levels were associated with an increased risk of death, myocardial infarction (MI) and ST, but there was no association with target vessel revascularization [38]. These data suggest that the predictive value of inflammatory activation, as assessed by CRP levels, seems to shift from restenosis as observed in the BMS era to thrombotic events in the DES era. However, a small study by Niccoli *et al.* has recently investigated the association between baseline CRP levels and restenosis pattern after DES implantation [39]. Interestingly, preprocedural CRP serum levels were an independent predictor of a diffuse pattern of restenosis (odds ratio: 2.5; 95% CI: 1.4–4.3;  $p = 0.001$ ).

To assess the risk prediction after DES implantation, in addition to CRP, other inflammatory biomarkers have also been evaluated. Several studies evaluated serum levels of matrix metalloproteinases (MMPs), which are involved in extracellular matrix degradation and vascular smooth muscle cells migration, and may play a role in the pathogenesis of ISR. Katsaros *et al.* showed that baseline MMP-9 and postprocedural (after 24 h) MMP-9 and MMP-2 levels were significantly higher in patients with ISR at 6–8-month angiographic follow-up, as compared with patients without ISR [40]. Also, plasma levels of PAI-1, before and 24 h after PCI, were associated with the occurrence of angiographic ISR [41] and, finally, Speidl *et al.* found that serum levels of C3a, before and 24 h after PCI, as well as baseline C5a levels, were significantly higher in

patients developing ISR at 6–8-month angiographic follow-up [42].

Despite these findings, more studies are needed in order to confirm the association between inflammatory activation assessed by inflammatory biomarkers and the development of neoatherosclerosis. Indeed, as shown in native coronary artery atherosclerotic lesions, the association between inflammatory biomarkers and the risk of ISR and/or ST after stent implantation may reflect the development of neoatherosclerosis. As a consequence, by combining intravascular imaging and inflammatory biomarker assessment, we can better stratify patients undergoing stent implantation to low or high risk of developing neoatherosclerosis. Moreover, a targeted therapy may be considered. Indeed, as PCI-related inflammation is associated with a higher risk of adverse cardiovascular events, periprocedural myocardial necrosis and ISR, several therapies targeting the local or systemic inflammatory response after stent implantation have been investigated. Statins have important anti-inflammatory effects and their efficacy following stent deployment has been documented in many clinical studies [43–49]. In the BMS era, administration of statins has been suggested as a treatment to improve clinical and angiographic outcome, and patients treated with statins, either before or at the time of PCI, had a smaller increase in CRP level after the procedure and a reduced incidence of clinical events and repeat TVR at 6-month follow-up compared with control patients. Moreover, angiographic analysis established a reduction in the occurrence of ISR after BMS implantation, in patients receiving statin therapy [50,51]. Furthermore, the anti-inflammatory effect of statins might contribute to reduce myocardial necrosis owing to microembolization during coronary intervention [52].

Also, a therapy with steroids could reduce the inflammatory burden in the PCI context. In fact, the IMPRESS study in 83 patients undergoing BMS implantation with high CRP levels after the procedure (CRP > 0.5 mg/dl at 72 h) treated with oral systemic steroid therapy showed a reduction of clinical events at 12 months (28% absolute reduction) and a reduced rate of angiographic restenosis at 6 months (7 vs 33%). This beneficial effect of steroid on ISR occurrence was dose dependent as both clinical and angiographic outcomes worsened when the dose of prednisone was decreased by nearly 50% [53,54].

Pioglitazone, clinically used to treat Type 2 diabetes, acts as a ligand for peroxisome proliferator-activated receptors (PPARs), in particular the subtype PPAR- $\gamma$ , which is expressed by endothelial cells, monocytes/macrophages and smooth muscle cells in the atherosclerotic plaque, and it is known to regulate anti-inflammatory responses [55–59]. In patients with Type 2 diabetes undergoing BMS implantation, 6-month treat-

ment with pioglitazone at 30 mg/day has been demonstrated to reduce neointimal formation and ISR, as measured by intravascular ultrasound imaging [60], and the TLR rate at 6 months was significantly lower in the pioglitazone group than in the control group (12.5 vs 29.8%;  $p = 0.04$ ). By contrast, the incidence of death and MI did not differ between the two groups. However, MACEs (major adverse cardiac events: death, MI and TLR) were significantly lower in the pioglitazone group than in the control group (13 vs 31%, respectively;  $p = 0.02$ ).

Also antithrombotic therapies (e.g., clopidogrel and Gp IIb/IIIa inhibitors) demonstrated anti-inflammatory activity [61] and in the CURE trial, clopidogrel in combination with aspirin reduced the cumulative occurrence of cardiovascular death, MI or the need for urgent TVR in patients presenting with acute coronary syndromes and undergoing PCI, compared with aspirin alone [62–64]. Drugs targeting the Gp IIb/IIIa receptor (e.g., abciximab and eptifibatide) inhibit platelet aggregation and thrombus formation at the injured coronary plaque, reducing the risk of acute ischemic events by up to 50% in patients undergoing PCI [65,66]. In particular, they may also reduce the inflammatory response following PCI. Abciximab demonstrated a potent and direct anti-inflammatory effect, binding to Gp IIb/IIIa

or vitronectin (avb3), and reduced interaction between platelets and leukocytes, leukocyte adherence and transmigration across endothelial cells [67–70].

### Conclusion & future perspective

Recent studies suggested that neoatherosclerosis represents an important substrate for late ISR and ST after both DES and BMS implantation [4–5,16–19]. Intravascular imaging techniques have been shown to reliably identify and characterize neoatherosclerosis. However, prevention of neoatherosclerosis and its consequences may represent an important target to improve the long-term outcome of patients undergoing stent implantation. Future studies combining biomarkers and intravascular imaging are needed in order to stratify the risk of late stent failure and to target therapy.

### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Executive summary

- Recent studies suggested an important role for neoatherosclerosis in late events after both drug-eluting stent (DES) and bare-metal stent (BMS) implantation. In particular, the development of neoatherosclerosis has been associated with occurrence of late in-stent restenosis (ISR) and stent thrombosis (ST).
- Neoatherosclerosis is characterized by infiltration and accumulation of clusters of foamy macrophages within the neointima, following both BMS and DES implantation, due to the inability to maintain a fully functional luminal surface within the stented segment.
- Different histopathological studies have shown an important role for chronic inflammation and/or endothelial dysfunction in the pathogenesis of neoatherosclerosis, following both DES and BMS implantation.
- A significant difference in the timing of neoatherosclerosis development was found among BMS and DES. Indeed, atherosclerotic change occurred in shorter implant durations for DES than for BMS.
- Optical coherence tomography and intravascular ultrasound studies confirmed an important role of neoatherosclerosis for late events after DES or BMS implantation.
- Yellow neointima observed at the angiography most likely corresponds to foamy macrophages infiltrating into fibrous cap and/or underlying lipid accumulation. Thrombus was detected more often on the yellow area than on the white area and was never detected where a stent was buried under white neointima. These data suggest that the increased potential risk of late ST in DES lesions may be due to the newly formed yellow neointima and cholesterol-laden plaque.
- Inflammatory biomarkers have been shown to predict clinical outcome in patients undergoing both DES and BMS implantation. As in native coronary artery atherosclerotic lesions, the association between inflammatory biomarkers and the risk of ISR and/or ST after stent implantation may reflect the development of neoatherosclerosis. However, further studies are needed in order to confirm this hypothesis.
- As percutaneous coronary intervention-related inflammation is associated with a higher risk of adverse cardiovascular events, periprocedural myocardial necrosis and ISR, several therapies targeting the local or systemic inflammatory response after stent implantation may be useful to reduce the occurrence of neoatherosclerosis. However, further studies are needed in order to confirm this hypothesis.
- Future studies combining biomarkers and intravascular imaging are needed in order to stratify the risk of late stent failure and to target therapy.

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