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STATE-OF-THE-ART PAPER

In-Stent Neoatherosclerosis

A Final Common Pathway of Late Stent Failure

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Percutaneous coronary intervention with stenting is the most widely performed procedure for the treatment of symptomatic coronary disease, and drug-eluting stents (DES) have minimized the limitations of bare-metal stents (BMS). Nevertheless, there remain serious concerns about late complications such as in-stent restenosis and late stent thrombosis. Although in-stent restenosis of BMS was considered as a stable condition with an early peak of intimal hyperplasia, followed by a regression period beyond 1 year, recent studies have reported that one-third of patients with in-stent restenosis of BMS presented with acute coronary syndrome that is not regarded as clinically benign. Furthermore, both clinical and histologic studies of DES have demonstrated evidence of continuous neointimal growth during long-term follow-up, which is designated as "late catch-up" phenomenon. Here, we present emerging evidence of de novo neoatherosclerosis based on histology, angioscopy, and intravascular images that provide a new insight for the mechanism of late stent failure. In-stent neoatherosclerosis is an important substrate for late stent failure for both BMS and DES, especially in the extended phase. In light of the rapid progression in DES, early detection of neoatherosclerosis may be beneficial to improving long-term outcome of patients with DES implants. (J Am Coll Cardiol 2012;59:2051–7) © 2012 by the American College of Cardiology Foundation

Percutaneous coronary intervention with stenting is the most widely performed procedure for the treatment of symptomatic coronary disease (1), and drug-eluting stents (DES) have minimized the limitations of bare-metal stents (BMS). Nevertheless, there remain serious concerns about late complications such as in-stent restenosis (ISR) and late stent thrombosis (LST) (2–4). Although ISR of BMS was considered as a stable condition with an early peak of intimal hyperplasia, followed by a regression period beyond 1 year (5–8), recent studies have reported that one-third of patients with ISR of BMS presented with acute coronary syndrome that is not regarded as clinically benign (4). Furthermore, both clinical and histologic studies of DES have demonstrated evidence of continuous neointimal growth during long-term follow-up, which is designated as "late catch-up" phenomenon (9,10). Here, we present emerging evidence of de novo neoatherosclerosis based on histology, angioscopy, and intravascular images that provide a new insight for the mechanism of late stent failure.

Late Restenosis With Evolving Neointima

Traditionally, intimal hyperplasia after BMS implantation has been considered stable, with an early peak between 6 months and 1 year and a late quiescent period thereafter (5–7). Kimura et al. (5) reported an early peak of intimal growth, followed by intimal regression with luminal enlargement in a clinical study with 3-year follow-up by angiography. A histopathologic study of coronary lesions treated by percutaneous transluminal coronary angioplasty postulated maturation of smooth muscle cells and modification of extracellular matrix as the possible mechanisms of late neointimal regression (8). This concept has been confirmed by a detailed histologic study of autopsy hearts with BMS implantation in which it was elucidated that alteration of proteoglycan contents together with conversion of type III to type I collagen occur over time, eventually leading to complete neointimal healing at 2-year follow-up (11). However, a further longer-term follow-up study demonstrated a triphasic luminal response after BMS placement characterized by an early restenosis, an intermediate regression, and a late luminal re-narrowing likely related to neoatherosclerosis beyond 4 years (12).

In the DES era, late neointimal growth developed within DES was documented in several animal studies. In a porcine model study, long-term inhibition of neointimal hyperplasia after polymer-based sirolimus-eluting stents (SES) was not maintained, partly because of drug absence and/or persistent

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Abbreviations and Acronyms

BMS = bare-metal stent(s)

DES = drug-eluting stent(s)

ISR = in-stent restenosis

IVUS = intravascular ultrasonography

LST = late stent thrombosis

OCT = optical coherence tomography

PES = paclitaxel-eluting stent(s)

SES = sirolimus-eluting stent(s)

TCFA = thin-cap fibroatheroma

VH = virtual histology

inflammatory stimuli and subsequent cellular proliferation (13). Similarly, another animal study using polymer-coated paclitaxel-eluting stents (PES) also reported late neointimal growth with delayed healing and local toxicity due to high-dose paclitaxel (14). Furthermore, intravascular ultrasound (IVUS) substudy of the ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial) in humans illustrated suppression of intimal growth at 6 months and subsequent late catch-up at 2-year follow-up after high-dose nonpolymeric PES implantation (15). More recently, the late catch-up in patients with SES placement was indicated by the higher rate of late target lesion revascularization (16). In a serial IVUS study (post-stenting, 6-month, and 2-year IVUS follow-up), intimal hyperplasia continued to increase beyond 6 months after SES and PES implantation in spite of the early attenuation of intimal growth and late luminal narrowing over time (17). The previous observations consistently supported a later occurrence of DES ISR that might be explained by delayed healing and persistent inflammatory process (18,19).

Histologic Evidence of De Novo Neoatherosclerosis

Early histopathologic studies revealed that neointimal components after DES implantation were similar to those in BMS lesions in that the neointima was mainly composed of proliferative smooth muscle cells with proteoglycans-rich extracellular matrix (11,20,21). Nevertheless, there is emerging evidence suggesting that chronic inflammation and/or incompetent endothelial function induce late de novo neoatherosclerosis inside both BMS and DES, which may be an important mechanism of the late phase ISR or thrombosis. Inoue et al. (22) reported histology 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 (22). Conversely, Hasegawa et al. (23) analyzed 14 BMS lesions with new restenosis that developed beyond 5 years and demonstrated that restenotic tissues retrieved by directional coronary atherectomy were composed of newly developed atherosclerosis facing the “previously” healed underlying intima regardless of the presence of peristrut inflammation (Online Table) (23). It is also intriguing that 4 samples from the cases presented with acute coronary syndrome exhibited typical histologic morphologies that resemble vulnerable plaque in native coronary arteries.

Nakazawa et al. (24) reviewed autopsy cases from the CVPath (Gaithersburg, Maryland) stent registry and compared 66 SES lesions with 77 BMS lesions where neoatherosclerotic change, including the presence of lipid-laden foamy macrophages, was more frequently identified in the SES lesions than in the BMS lesions (35% vs. 10%, $p < 0.001$). Interestingly, a significant difference in the timing of neoatherosclerosis development was noted; the earliest atherosclerotic change with foamy macrophage infiltration began at 4 months after SES implantation, whereas the same change in BMS lesions occurred beyond 2 years and remained a rare finding until 4 years (Fig. 1). In addition, the earliest necrotic core formation began at 9 months, whereas in BMS it occurred at 5 years. Recently, we reviewed histology findings in 299 autopsy cases (197 BMS and 209 DES lesions) (25). The incidence of neoatherosclerosis was greater in DES lesions (31%) than in BMS lesions (16%), and the median stent duration with neoatherosclerosis was shorter in DES compared with BMS (420 days [361 to 683 days] vs. 2,160 days [1,800 to 2,880 days]). Unstable lesions like the thin-cap fibroatheromas (TCFA) or intimal rupture had shorter implant duration for DES (1.5 ± 0.4 years) compared with BMS (6.1 ± 1.5 years). These results represent that neoatherosclerosis in DES is more frequent and occurs earlier than in BMS, likely from different pathogenesis (Fig. 2).

Further, there is a question about the difference in the induction of neoatherosclerosis among various DES. Currently, the data are mostly available only in SES and PES, for which the trend toward more rapid neoatherosclerotic changes is observed in SES than in PES, although the frequency of neoatherosclerosis in both DES is higher than BMS (cumulative incidence up to 6 years: SES 38% vs. PES 24% vs. BMS 10%), indicating that differences of drugs or polymers may influence on neointimal tissues. The effects of new generation or developing DES have yet to be investigated.

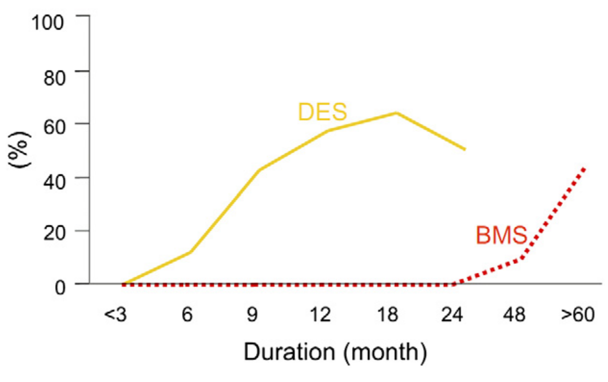

Figure 1 **Different Time Points of the Neoatherosclerosis**

Percentage of patients with atherosclerotic change in drug-eluting stent (DES) versus bare-metal stent (BMS) in relation to duration of implant at autopsy is depicted (24). Note the atherosclerotic change in sirolimus-eluting stents is seen in >40% of cases by 9 months; in the BMS, the atherosclerotic change does not begin to appear until 2 years, and remains a rare finding until 4 years.

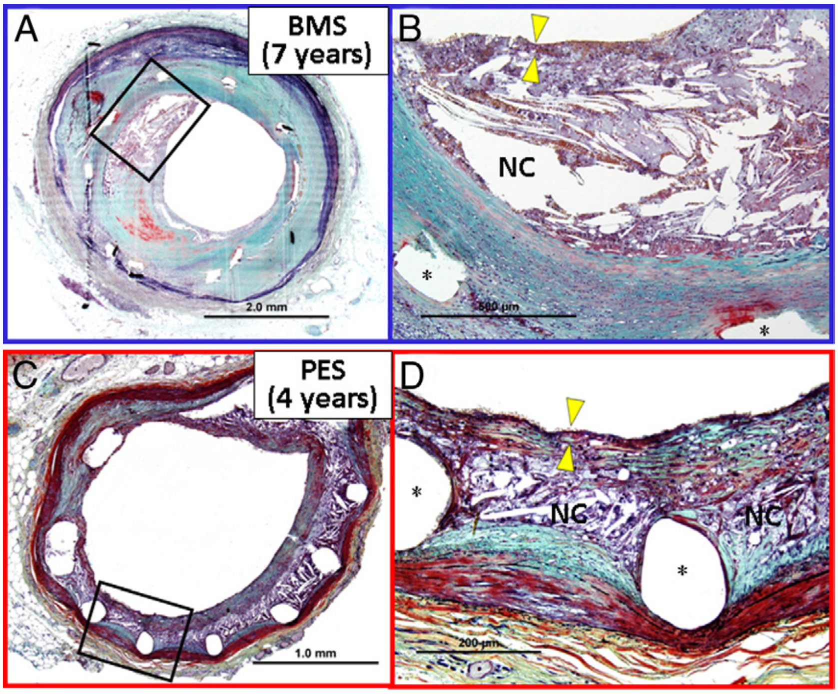

Figure 2 Histological Findings of Neoatherosclerosis

(A) Cross-sectional histology of bare-metal stent (BMS) implanted in the coronary artery for 7 years antemortem (Movat, ×20). **(B)** High-power image of the **box in A** (×100). A large necrotic core (NC) containing cholesterol crystals is identified within the neointima. The fibrous cap overlying the NC is infiltrated by numerous foamy macrophages and is markedly thinned (**yellow arrowheads** point to thinnest portion), which resembles vulnerable plaque encountered in native coronary arteries. The **asterisks** represent metal struts. **(C)** Cross-sectional histology of paclitaxel-eluting stent (PES) implanted in the coronary artery for 4 years antemortem (Movat, ×40). **(D)** High-power image of the **box in C** (×200). A relatively small NC containing cholesterol crystals is formed around metal struts **(asterisk)**. The fibrous cap is infiltrated by numerous foamy macrophages and is markedly thinned (**yellow arrowheads** point to thinnest portion).

Angioscopic Evidence of De Novo Neoatherosclerosis

A serial angioscopic study (at baseline, 6 to 12 months, and ≥4 years) after 26 BMS implantations illustrated the neointimal changes that varied from early healing response to atherosclerotic transformation represented as yellow plaque (26). There was a remarkable increase in the incidence of yellow plaque: from 3 cases (4%) at the first follow-up to 15 cases (58%) at the second follow-up. Late luminal narrowing, defined as an increase in percent diameter stenosis between the first and second follow-up, was significantly greater in segments with yellow plaque than in those without yellow plaque (18.4% vs. 3.6%, $p = 0.011$), which indicated that atherosclerotic degeneration inside BMS may contribute to the late luminal narrowing. By serial angioscopic examinations, Ueda et al. (27) demonstrated that BMS at 1 to 4 weeks after implantation were not yet completely covered by neointima and were often (45%) accompanied by thrombus. However, BMS at 2 to 5 months were completely covered by neointima and thrombus was detected only slightly in 13% of patients. Neointima over BMS usually covers both stent and yellow plaques under stent completely; and therefore, thrombus was no longer detected on the white and smooth neointima even if thrombus was detected on the yellow plaque (27). Referring to DES, an angioscopic study by Higo et al. (28) demonstrated that SES promote the formation of lipid-rich, atherosclerotic yellow neointima at 10 months, with intramural thrombi being more frequently detected in newly formed yellow neointima (Fig. 3).

Although there are no available data to date regarding the angioscopic findings and histologic correlation in intimal tissue, angioscopic yellow neointima most likely corresponds to foamy macrophages infiltrating into fibrous cap and/or underlying lipid accumulation; the intensity of yellow likely signifies thickness of fibrous cap and amount of necrotic core. Ultimately, 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 (29).

Grayscale IVUS and VH-IVUS Findings of In-Stent Neoatherosclerosis

Virtual histology (VH) intravascular ultrasonography (IVUS) involves spectral analysis for frequency and intensity of the signals to construct tissue maps by classifying plaque into 4 components (fibrous = green; fibrofatty = light green; necrotic core = red; and dense calcium = white) (30).

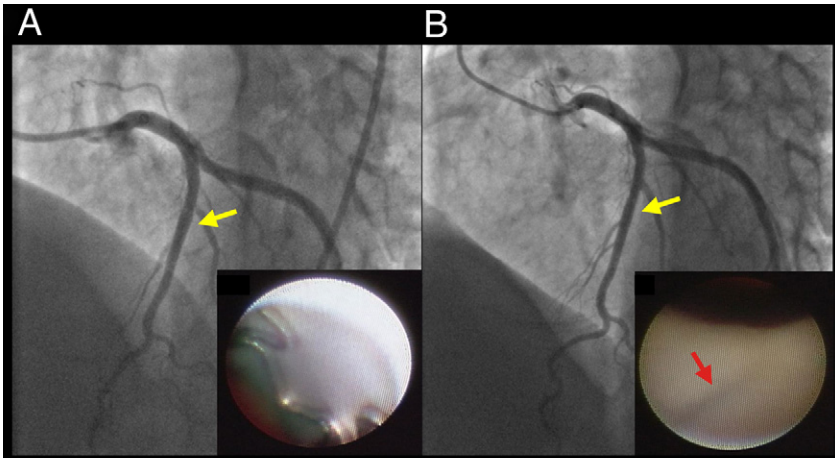

Figure 3 **Representative Case of Yellow Neointima Formation Over DES**

A 44-year-old man with stable effort angina received percutaneous coronary intervention with a Cypher drug-eluting stent (DES) in the proximal left anterior descending coronary artery **(yellow arrows)**. Angiographic and angioscopic images immediately after stenting **(A)** and at 12-month follow-up **(B)** are presented. Stent was covered by yellow neointima (grade 2, **red arrow**) at 12 months.

Although it is difficult for IVUS to determine or classify neointimal tissue because of the signal interference from metal struts, there are several reports attempting discrimination of neointimal tissues by IVUS. A case report described calcified neointima on grayscale IVUS 8 years after BMS deployment (31), and other reports demonstrated plaque rupture and a flaplike dissection inside a restenotic stent (32,33). In addition, VH-IVUS has recently been reported to identify neointimal hyperplasia with unstable morphology that mimics a TCFA as in native arteries.

Kang et al. (34) reported findings from 70 DES-ISR and 47 BMS-ISR lesions with intimal hyperplasia >50% of the stent area by VH-IVUS (34). The region of interest was placed between the luminal border and the inner border of the struts, and tissue composition was represented as percentages of intimal area (Fig. 4). The mean follow-up time was 43.5 months for BMS lesions and 11.1 months for DES lesions. In both DES and BMS groups, necrotic core and dense calcium suggesting in-stent neoatherosclerosis were greater especially in the lesions with longer implant duration.

Even though VH-IVUS is histologically validated in the assessment of the compositions of naïve atherosclerotic plaques with high accuracy (94% for necrotic core and 99% for dense calcium), it is yet to be validated for use with in-stent tissues (35). Factoring in the complexity of the in-stent tissues, the methodology needs to be revisited for the evaluation of neointimal characteristics.

OCT Findings of In-Stent Neoatherosclerosis

Optical coherence tomography (OCT) is a near-infrared light-based imaging modality with ultrahigh resolution. Due to the excellent resolution (10 to 20 μm), OCT has demonstrated its potential capacity to accurately characterize or evaluate the vascular responses after stent implantation, albeit histological validation has not been performed as yet.

Habara et al. (35) examined the restenotic lesions >5 years after BMS implantation and found a high incidence (90.7%) of possible neoatherosclerotic change, defined as heterogeneous OCT appearance with low-intensity areas, whereas lesions <1 year after BMS implantation showed only 17.9% incidence of neoatherosclerosis. Neointimal disruption, which has analogous morphology of ruptured fibroatheroma in a native coronary artery, occurred more frequently in >5-year lesions (18.6%) than in <1-year lesions (0%).

Gonzalo et al. (36) also reported various OCT patterns of restenotic tissue after stenting (84% were various DES); however, the median follow-up time was only 12 months, too short a time to observe the entire spectrum of neoatherosclerosis. In contrast, Takano et al. (37) demonstrated neointimal OCT characteristics of BMS in early (<6 months) and extended late phases (≥5 years). Neointima exhibited a homogeneous OCT appearance, and there was a lack of lipid-laden intima in the early phase. 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 $p < 0.05$). Thus, it is reasonable to postulate that neointima within BMS often undergoes a neoatherosclerotic process during an extended follow-up period. Notably, the neoatherosclerotic process may promote further luminal narrowing and may play a possible role in the development of an unstable substrate in the late phase BMS.

Recent OCT analysis in 50 patients with DES-ISR (median follow-up period 32.2 months) demonstrated that

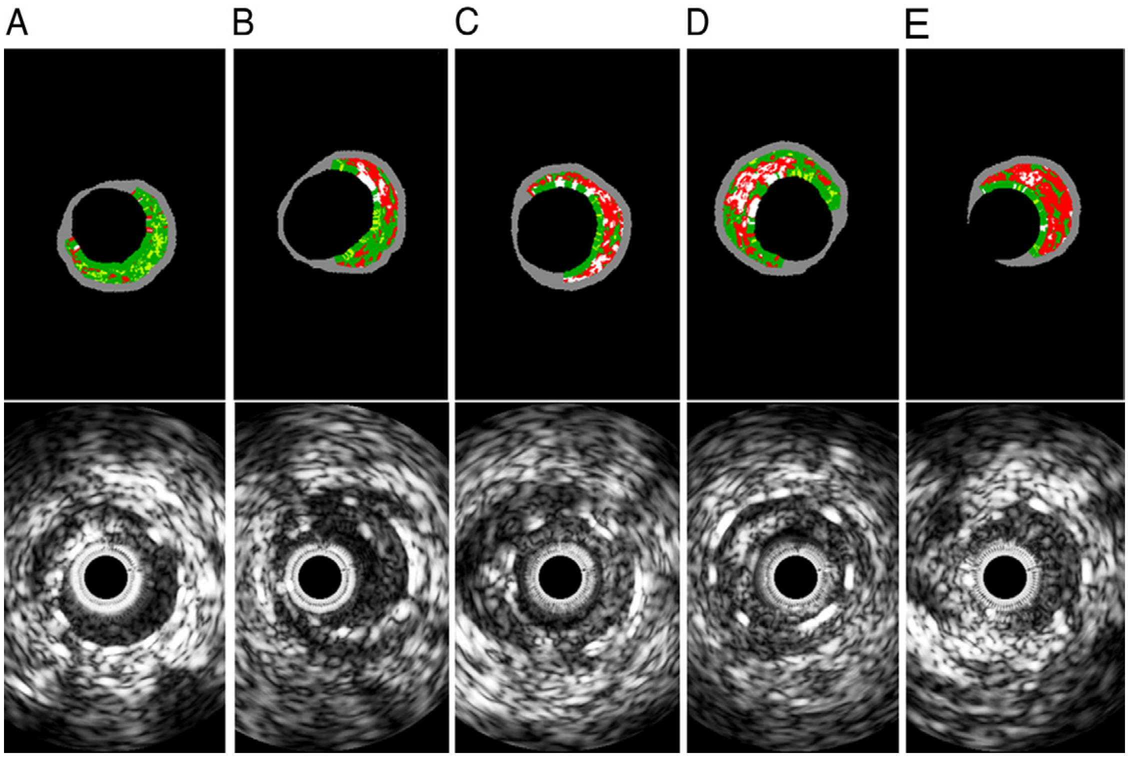

Figure 4 **Examples of Virtual Histology Intravascular Ultrasonography Composition of Neointima at Maximal Percent Intimal Hyperplasia Sites**

(A) Six-month follow-up of paclitaxel-eluting stent [percent necrotic core [%NC] 10%, percent dense calcium [%DC] 2%); **(B)** 9-month follow-up of paclitaxel-eluting stent (%NC 28%, %DC 8%); **(C)** 22-month follow-up of paclitaxel-eluting stent (%NC 39%, %DC 20%); **(D)** 48-month follow-up of bare-metal stent (%NC 40%, %DC 25%); and **(E)** 57-month follow-up of bare-metal stent (%NC 57%, %DC 15%).

the 52% of overall lesions had at least 1 TCFA-containing neointima, 58% had in-stent neointimal rupture, and 58% showed intraluminal thrombi (38). Patients presenting with unstable (vs. stable) angina showed a thinner fibrous cap and an increasing number of unstable OCT findings, including TCFA-containing neointima, neointima rupture, and thrombus (Fig. 5). Compared with DES $<$20 months post-implantation (the best cut-off to predict TCFA-containing neointima), DES $\geq$20 months post-implantation 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.

In-Stent Neoatherosclerosis as Common Mechanism of Late Restenosis and Stent Thrombosis

To date, several pathologic or procedural risk factors have been elucidated as indicators of LST: delayed arterial healing with incomplete endothelialization, chronic inflammation and hypersensitivity reactions, late malapposition related to positive remodeling, ostial and/or bifurcation stenting, and strut penetration into a necrotic core (10,39–41). Besides these factors, the extensive data as reviewed in the preceding text support the importance of in-stent neoatherosclerosis as a mechanism of LST after either BMS or DES implantation. A recent histopathology study conducted by Nakazawa et al. (25) confirmed presence of neoatherosclerosis in both BMS and DES, with shorter implant duration for the latter. Although uncovered struts as a marker of incomplete endothelialization remain the primary cause of DES thrombosis, advanced neoatherosclerosis with neointimal rupture is also suggested as another contributing factor to very late thrombotic events (25).

This new paradigm appears to be rational as it is consistent with recent clinical data. Angioscopic data by Higo et al. (28) reported that SES promoted the formation of lipid-rich, atherosclerotic yellow neointima at 10 months, and intramural thrombi were more prevalent in newly formed yellow neointima. Further, Lee et al. (42) demonstrated that in-stent neointimal rupture was identified by IVUS in 44% of DES lesions (mean follow-up of 33 months) and 100% of BMS lesions (mean follow-up of 108 months), indicating that neoatherosclerotic progression with intimal rupture was 1 of the mechanisms of very late stent thrombosis. Although there seem to be different biological mechanisms underlying the development of stent

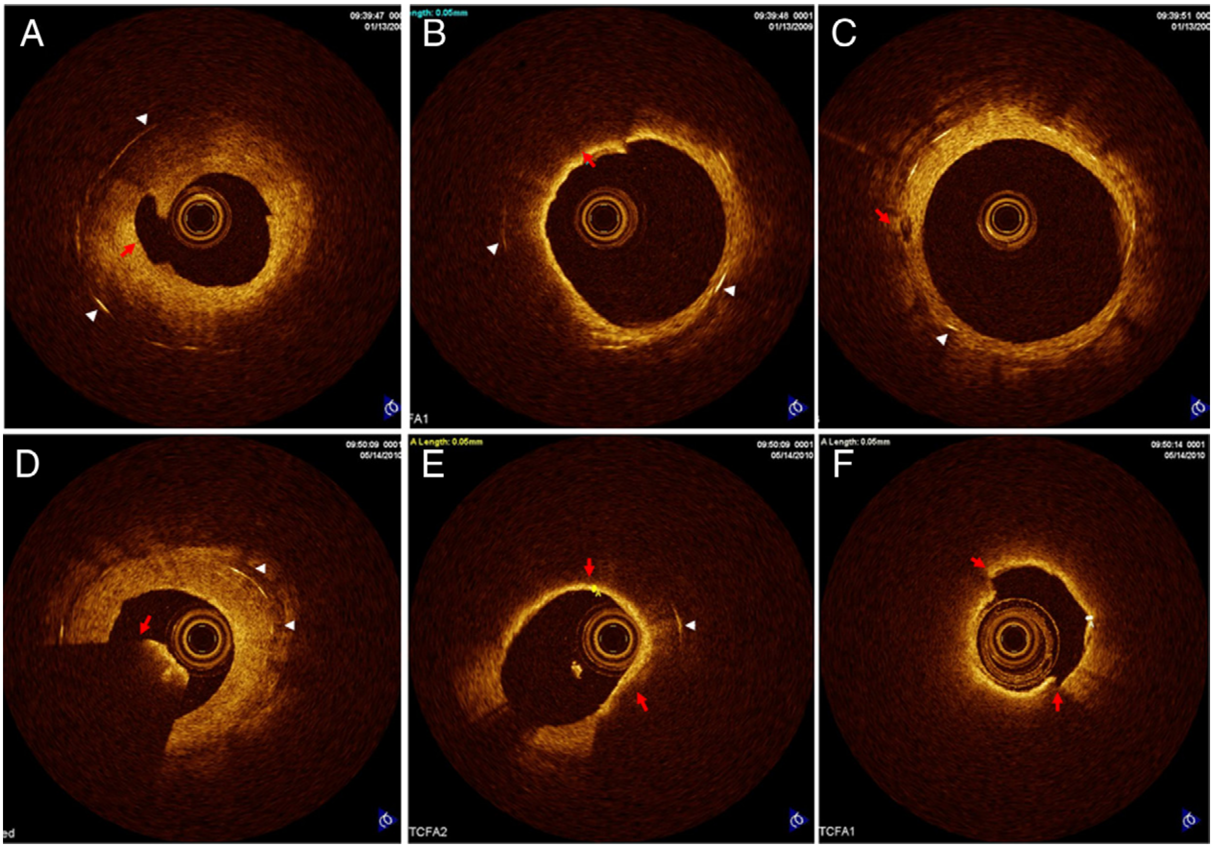

Figure 5 **OCT Findings of Neointima Inside DES**

All **white arrows** indicate stent struts. Optical coherence tomography (OCT) findings for a 71-year-old woman who had undergone drug-eluting stent (DES) implantation at mid-right coronary artery 65 months earlier and who presented with stable angina: **(A)** intimal rupture **(red arrow)**; **(B)** thin-cap fibroatheroma (TCFA)-containing neointima surrounded by signal-poor, lipidic area **(red arrow)**; and **(C)** Fibrotic neointima with microvessels **(red arrow)**. Findings at OCT for a 70-year-old man who had undergone DES implantation at mid-left anterior descending artery 60 months earlier and who presented with unstable angina: **(D)** intraluminal red thrombus with fast attenuation **(red arrow)**; **(E)** TCFA-containing neointima **(red arrows)** with lipidic tissue; and **(F)** intimal rupture **(red arrows)** surrounded by TCFA-containing neointima. The minimal thickness of fibrous cap was measured at 60 μm.

thrombosis depending upon stent type, it is clear that neoatherosclerosis plays a role as an important indicator of LST as well as restenosis in both BMS and DES, but more importantly in DES, as it occurs much earlier (25). The shorter interval from implantation to very late stent thrombosis in DES than in BMS was consistent with the shorter time period needed to develop neoatherosclerotic intima with rupture (41).

The precise mechanisms of neoatherosclerotic development in DES remain unknown to date, although incomplete endothelial coverage or defective function and alteration of extracellular matrix as an enhancer of atherosclerosis are suggested through the increased lipid insudation with monocyte/macrophage activation. The lack of knowledge regarding the relative roles of progressive intimal hyperplasia, endothelialization, and in-stent atheroma formation, along with the presence of risk factors, warrants further investigation on this topic.

Conclusions

Emerging evidence suggests in-stent neoatherosclerosis as an important substrate for both ISR and LST, especially in the extended phase. In light of the rapid progression in DES, early detection of neoatherosclerosis may be beneficial to improving long-term outcome of patients with DES implants. Although angioscopy and multimodal images have consistently supported de novo atherosclerotic changes of neointima for both BMS and DES, the methodologies should be more validated to clarify the clinical implications.

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Key Words: neoatherosclerosis ▪ restenosis ▪ stent thrombosis.

APPENDIX

For a supplemental table, please see the online version of this article.