

Continuous development of neoatherosclerosis beyond a decade after drug-eluting stent implantation



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Coronary stents are widely used for the treatment of patients with coronary artery disease. Drug-eluting stents (DES) have reduced the rate of late restenosis compared with bare metal stents (BMS). However, late and very late stent thrombosis have become a major concern in DES. Pathological findings from patients who died of very late DES thrombosis have demonstrated that incomplete re-endothelialisation, late acquired stent malapposition, and atherosclerosis within neointima (known as neoatherosclerosis) are important underlying substrates of very late DES thrombosis¹. Rupture of neoatherosclerosis is the most common mechanism of very late DES thrombosis. Neoatherosclerosis in DES occurs earlier compared with BMS and develops continuously.

Present study

In the current issue of EuroIntervention, Usui et al report the prevalence of inadequate vascular responses in sirolimus-eluting stents more than 10 years after implantation by using optical coherence tomography (OCT)².

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The authors demonstrated that the prevalence of neoatherosclerosis was significantly higher in sirolimus-eluting stents more than 10 years after implantation compared with sirolimus-eluting stents five to 10 years after implantation, though the prevalence of uncovered and/or malapposed stents tended to be lower in sirolimus-eluting stents more than 10 years after implantation². These results suggest a potentially increased risk of sirolimus-eluting stent failure due to continuous development of neoatherosclerosis beyond 10 years after implantation.

Neoatherosclerosis in DES

Pathohistologically, neoatherosclerosis is characterised by the accumulation of lipid-rich foamy macrophages within the neointima of stented coronary segments. Unlike native coronary disease, necrotic core formation in neoatherosclerosis occurs from macrophage apoptosis in the absence of pathologic intimal thickening and lipid pools. The neoatherosclerosis in DES is observed at six months after implantation, though that in BMS is seen at two years after implantation¹. There are two possible mechanisms responsible for

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the development of neoatherosclerosis in DES. One mechanism is incomplete re-endothelialisation induced by the drug from DES. Poor cell-to-cell junctions lead to impairment of endothelial barrier function, which allows lipoproteins and macrophages to infiltrate the neointima. The other mechanism is chronic inflammation promoted by the polymer of DES. Accumulation of macrophages, lymphocytes, and giant cells around the DES struts contribute to the development of neoatherosclerosis. These mechanisms responsible for the development of neoatherosclerosis have been confirmed by pathological studies of DES months to years after implantation. However, there has been no pathological study investigating neoatherosclerosis beyond a decade after DES implantation. It remains unclear whether incomplete re-endothelialisation and chronic inflammation have a lasting influence on the neoatherosclerosis in the extremely late phase after DES implantation.

Stent architecture (e.g., stent strut thickness) and components (e.g., metal, polymer, and drug) influence the development of neoatherosclerosis. The first-generation DES had the disadvantages of thick metallic struts (140 μm for the CYPHER[®] sirolimus-eluting stent [Cordis, Johnson & Johnson, Miami, FL, USA], and 132 μm for the TAXUS[™] paclitaxel-eluting stent [Boston Scientific Corp., Marlborough, MA, USA]) and poorly biocompatible permanent polymers. The second-/third-generation DES are equipped with thinner (<100 μm) cobalt-chromium or platinum-chromium stent struts, more biocompatible permanent polymers or biodegradable polymers, and lower drug loads with predominant use of limus agents. These features of second-/third-generation DES reduce vascular inflammation and improve the re-endothelialisation of stents. Nevertheless, recent pathological studies showed that the prevalence of neoatherosclerosis was not different between the first-generation DES and the second-/third-generation DES¹. Therefore, neoatherosclerosis remains a major drawback even in the second-/third-generation DES.

Intravascular imaging allows us to examine neointimal tissue characteristics and detect in-stent neoatherosclerosis in living patients (**Figure 1**). An angiography study showed that yellow

neointima suggestive of lipid-rich tissue or necrotic core was detected in 95% of DES at 10 months after implantation, though it was observed in 58% of BMS at four years after implantation³. A virtual histology intravascular ultrasound study demonstrated that necrotic core and dense calcium within neointima of DES increased with time (mean follow-up time: 11 \pm 8 months, range 4 to 33)⁴. A near-infrared spectroscopy study revealed that this technology was capable of identifying lipid-rich neointima in early (median follow-up time: 7 months, interquartile range 3 to 10) DES restenosis⁵. An OCT study disclosed that thin-cap fibroatheroma, which is recognised as a precursor lesion of plaque rupture, developed in the neointima of DES at 20 months after implantation⁶. These intravascular imaging studies consistently suggest that DES accelerate neoatherosclerosis.

Neoatherosclerosis identified by intravascular imaging is associated with very late stent thrombosis. A retrospective OCT study showed that rupture of neointima with advanced neoatherosclerosis was seen in 63% of very late DES thrombosis⁷. Furthermore, a prospective angiography study named DESNOTE (Detect the Event of very late Stent failure from the drug-eluting stent NOT well covered by neointima determined by angiography) demonstrated that yellow neointima identified at one year after DES implantation was an independent predictor of very late (mean follow-up time: 4 \pm 2 years) stent thrombosis⁸. Thus, the assessment of neoatherosclerosis by using intravascular imaging might be helpful for risk stratification of subsequent very late DES thrombosis.

Final remarks

In addition to the drug and polymer of DES, traditional clinical risk factors for native atherosclerosis influence the development of neoatherosclerosis in a very late phase after DES implantation. Previous OCT studies showed that current smoking, chronic kidney disease, lack of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade use, and absence of statin therapy were associated with neoatherosclerosis in a very late phase after DES implantation⁹. According to the results of the study by

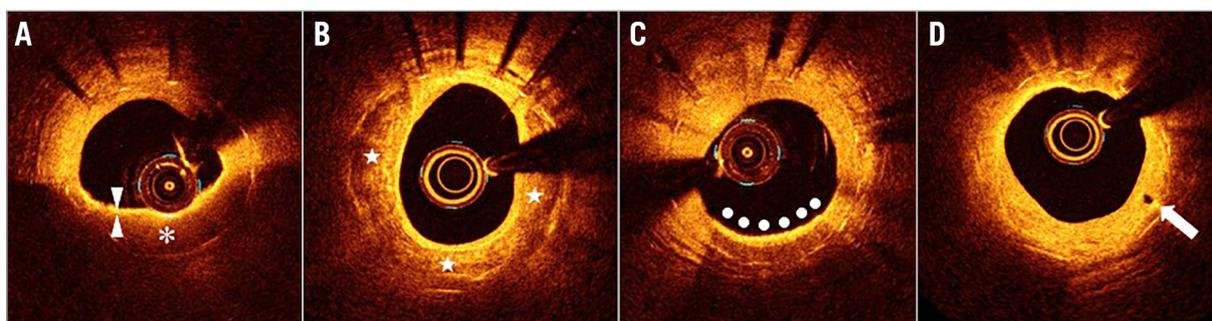


Figure 1. Optical coherence tomography findings of neoatherosclerosis. A) Lipid (asterisk) is characterised by a signal-poor region with a poorly delineated border. Fibrous cap (arrowheads) is characterised by a signal-rich tissue layer overlying a signal-poor region. B) Calcium (stars) is characterised by a signal-poor and heterogeneous region with a sharply delineated border. C) Accumulations of macrophages (bullets) are seen as confluent or punctate signal-rich regions that shadow underlying tissue. D) Neovascularisation (arrow) appears as a signal-poor void that is sharply delineated.

Usui et al², comprehensive risk factor control and optimal medical therapy seem to be necessary for the long period of beyond a decade to prevent very late stent failure in patients treated with DES.

Conflict of interest statement

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References

1. Otsuka F, Byrne RA, Yahagi K, Mori H, Ladich E, Fowler DR, Kutys R, Xhepa E, Kastrati A, Virmani R, Joner M. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36:2147-59.
2. Usui E, Yonetsu T, Kanaji Y, Hoshino M, Yamaguchi M, Hada M, Hamaya R, Kanno Y, Murai T, Lee T, Hirao K, Kakuta T. Prevalence of neoatherosclerosis in sirolimus-eluting stents in a very late phase after implantation. *EuroIntervention*. 2018;14:e1316-23.
3. Higo T, Ueda Y, Oyabu J, Okada K, Nishio M, Hirata A, Kashiwase K, Ogasawara N, Hirotsu S, Kodama K. Atherosclerotic and thrombotic neointima formed over sirolimus drug-eluting stent: an angioscopic study. *JACC Cardiovasc Imaging*. 2009;2:616-24.
4. Kang SJ, Mintz GS, Park DW, Lee SW, Kim YH, Lee CW, Han KH, Kim JJ, Park SW, Park SJ. Tissue characterization of in-stent neointima using intravascular ultrasound radiofrequency data analysis. *Am J Cardiol*. 2010;106:1561-5.
5. Roleder T, Karimi Galougahi K, Chin CY, Bhatti NK, Brilakis E, Nazif TM, Kirtane AJ, Karpalotis D, Wojakowski W, Leon MB, Mintz GS, Maehara A, Stone GW, Ali ZA. Utility of near-infrared spectroscopy for detection of thin-cap neoatherosclerosis. *Eur Heart J Cardiovasc Imaging*. 2017;18:663-9.
6. Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation*. 2011;123:2954-63.
7. Kang SJ, Lee CW, Song H, Ahn JM, Kim WJ, Lee JY, Park DW, Lee SW, Kim YH, Mintz GS, Park SW, Park SJ. OCT analysis in patients with very late stent thrombosis. *JACC Cardiovasc Imaging*. 2013;6:695-703.
8. Ueda Y, Matsuo K, Nishimoto Y, Sugihara R, Hirata A, Nemoto T, Okada M, Murakami A, Kashiwase K, Kodama K. In-Stent Yellow Plaque at 1 Year After Implantation Is Associated With Future Event of Very Late Stent Failure: The DESNOTE Study (Detect the Event of Very late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy). *JACC Cardiovasc Interv*. 2015;8:814-21.
9. Yonetsu T, Kato K, Kim SJ, Xing L, Jia H, McNulty I, Lee H, Zhang S, Uemura S, Jang Y, Kang SJ, Park SJ, Lee S, Yu B, Kakuta T, Jang IK. Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. *Circ Cardiovasc Imaging*. 2012;5:660-6.