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New light on second-generation drug-eluting stent restenosis

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Although technological developments have dramatically decreased its occurrence, restenosis after coronary stenting remains an important clinical problem even with new-generation drug-eluting stents (DES). Restenosis was once seen as a uniform entity with a single histological substrate: neointimal fibrous hyperplasia, a non-specific histological response to vascular injury observed after coronary interventions. The advent of high-resolution intracoronary imaging with optical coherence tomography (OCT) opened a new dimension in the evaluation of stent restenosis, allowing a detailed assessment of the neointimal tissue and revealing its varied nature[1]. A whole palette of restenotic tissue patterns became evident, leading to a completely new vision of restenosis as a heterogeneous entity with different causes and features depending on the stent type, time from stent implantation and other factors.

In this issue of EuroIntervention, Song et al compare the OCT characteristics of early (<1 year) versus late (>1 year) restenosis occurring in second-generation drug-eluting stents. This retrospective study evaluated all patients who underwent follow-up angiographic and OCT evaluation in two US centres and defined restenosis as an in-stent MLA <3 mm^2 by OCT[2].

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The manuscript provides new insights into the varied nature of the restenotic process and its different morphology depending on the time of occurrence. The authors conclude that heterogeneous restenotic tissue and minimum stent area (MSA) <4 mm^2 seem to be more related to early restenosis while the development of neoatherosclerosis is a process more relevant for late restenosis in second-generation DES.

The lack of a common nomenclature with standardised definitions makes the comparison of the multiple studies using OCT in the evaluation of stent restenosis complex **(Table 1)**. Furthermore, marked differences in the OCT structure of the obstructive tissue are frequently found within a single stent, complicating the analysis of the observations.

In the present study, a heterogeneous OCT pattern of in-stent restenosis was more common in early presenters, while some previous studies in bare metal stent (BMS) and first-generation DES more commonly described the heterogeneous pattern in the late phase **(Table 1)**. This difference can be related to the definition of heterogeneous pattern, which is not uniform in the literature, with some studies including certain types of neoatherosclerosis.

Early restenosis was associated with an MSA <4 mm^2 in this population. However, the early restenosis group had a smaller vessel size (distal reference lumen area 3.8 vs. 4.7 mm^2) and therefore the presence of a higher proportion of stents with a minimum area <4 mm^2 is not surprising. A small stent area can be related to either stent underexpansion or stent implantation in a small vessel. Therefore, use of a single stent area value without considering the reference vessel size has serious limitations and does not allow proper detection of stent underexpansion as a cause of restenosis.

The authors found neoatherosclerosis in 24.6% of lesions with a trend towards increased frequency in late presenters, especially intra-stent calcification. The prevalence of neoatherosclerosis in this population is lower than that reported in previous studies of first-generation DES restenosis evaluated with OCT. This could be attributable to DES type; however, recent pathological data have shown no significant difference in the prevalence of neoatherosclerosis between first- and second-generation DES[3]. The discordances in neoatherosclerosis frequency in the different OCT studies and in comparison with pathology are more probably related to the limitations in the assessment of this entity with OCT. Pathological correlations have shown the potential overestimation in the diagnosis of neoatherosclerosis with OCT, especially regarding thin-cap fibroatheroma detection. Neoatherosclerosis develops earlier in DES than in BMS and its prevalence increases with time from stent implantation, as shown in the present report in agreement with previous OCT studies in first-generation DES. Duration of implant has previously been described as a predictor of neoatherosclerosis together with other factors such as DES use or chronic kidney disease[4].

The major limitation of the present paper is the definition used for restenosis (MLA <3 mm^2 by OCT). Using a single cut-off point to define restenosis risks overdiagnosis depending on vessel size; stents implanted in small vessels can have an MLA <3 mm^2 without

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Table 1. Findings of different studies evaluating stent restenosis with OCT depending on time from stent implantation.

Author	Year	Study aims	Stent type	N total	Early ISR <1 year	Late ISR >1 year	Very late ISR >3 years	Main findings
Takano	2009	To validate neointimal changes in BMS during an extended period following their implantation	BMS	41	20	NA	21	Neointima within the BMS often transforms into lipid-laden tissue during an extended period of time. Expansion of neovascularisation from peristent to intraintima contributes to the neoatherosclerosis development
Habara	2011	To compare the morphological characteristics of early versus very late ISR in BMS	BMS	83	39	NA	43	Very late ISR had a predominantly heterogeneous pattern while early ISR had a predominantly homogeneous pattern
Nagoshi	2013	To distinguish tissue components of in-stent restenosis in DES and BMS	BMS 1st generation DES	122	NA	NA	NA	The OCT appearances of the neointima in ISR were significantly different between BMS and DES. Backscatter and signal intensity were significantly higher with BMS
Ino	2013	To compare the neointimal tissue appearances between early and late ISR after implantation of an SES	1st generation DES	48	30	18	NA	Atherosclerotic progression of neointima was more commonly seen in late ISR compared to early ISR
Goto	2013	To investigate in-stent neointima characteristics according to stent type and restenotic phase	BMS DES (1st and 2nd generation)	59	30	29	NA	Vascular healing pattern varies between stent type and restenotic phase. The predominant patterns were homogeneous in the BMS early phase, lipid-laden intima in the BMS late phase and heterogeneous mixed-signal band in the DES late phase. Heterogeneous restenosis was more common in the early phase in DES than BMS.
Habara	2013	To gain insights into the mechanisms and time course of DES restenosis	1st generation DES	87	44	22	21	OCT characteristics of DES restenosis varied at different time points. TCFA-like pattern and intraintima microvessels increased from the early to very late stage. Speckled pattern was more common in the early phase
Jinnouchi	2017	To evaluate the differences in tissue characteristics between the different phases of ISR after 2nd generation DES implantation	2nd generation DES	53	30	23	NA	OCT characteristics of 2nd generation DES restenosis varied at different time points. Early ISR was mainly caused by neointimal hyperplasia while late ISR was mainly due to neoatherosclerosis

restenosis. The angiographic analysis with less than 50% diameter stenosis in both groups demonstrates that the lesions evaluated were not stenotic and emphasises the limitations of this definition.

In summary, the study by Song et al shows that the OCT structure of restenosis in second-generation DES is related to the duration of the implant. These findings are similar to previous studies with first-generation DES and emphasise the new vision of restenosis as a heterogeneous entity with a variety of causes and mechanisms potentially requiring different treatment strategies. In this regard, OCT has offered a new scope in the evaluation of restenosis *in vivo*, providing a level of detail never before attained. The lack of a common nomenclature and standardisation of the definitions together with the complex correlation between OCT patterns and histological features are challenges for the application of this technology in restenosis evaluation in clinical practice[5]. However, it offers great potential to identify restenosis causes and guide treatment. Further research is needed to determine whether the different restenotic patterns defined by OCT can respond differently to the treatment options currently available.

Conflict of interest statement

N. Gonzalo is a speaker at educational events with Abbott Vascular. J. Escaned is a consultant and speaker at educational events with Abbott Vascular. N. Ryan has no conflicts of interest to declare.

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