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Restenosis after drug-eluting stenting – a call for action

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Percutaneous coronary intervention (PCI) has become the dominant revascularisation modality for patients with obstructive coronary artery disease. This development has been facilitated by advances in catheterisation techniques, antithrombotic therapy, and stent technology[1-3]. Drug-eluting stents (DES) in particular were a breakthrough technology. The high efficacy of DES enabled the expansion of transcatheter treatment to patients with complex disease patterns, such as multivessel and left main stem disease[4].

Current-generation DES are a mature technology with low rates of treatment failure. However, although the rate of restenosis after DES is low, it is not negligible. A systematic review of 158 randomised trials with different stent technologies showed median rates of clinical restenosis (target lesion revascularisation) with DES of 4.00 (2.05-6.40) per 100 patient years[5]. These observations must be tempered by the knowledge that even in so-called "all-comer trials" the majority of patients may not be represented. In fact, in clinical practice the incidence is probably somewhat higher. Registry studies with systematic angiographic surveillance have shown rates of binary restenosis of more than 10%[6].

When it occurs, DES restenosis is more frequently focal as compared with bare metal stent restenosis. This can be explained by the fact that the overall high efficacy of DES in suppressing neointimal hyperplasia means that focal mechanical factors, such as stent underexpansion or fracture, often play a dominant role. Focal mechanical factors represent double jeopardy: not only is the mechanical deficiency itself a risk for restenosis but the lack of contact with the underlying vessel wall inhibits effective delivery of the antiproliferative drug.

The time course of restenosis after DES is an issue of some interest. Although clinical trials comparing outcomes of patients randomised to treatment with DES or bare metal stents generally do not show evidence of more "late catch-up" restenosis with DES[7], studies with sequential angiographic surveillance during follow-up show differences in the time course of changes in luminal diameter with DES compared with bare metal stents. Whereas late lumen loss after bare metal stenting tends to peak within six months[8], late lumen loss after DES implantation seems to increase steadily – albeit at a low level – up to two or even five years[9,10].

The reasons for this temporal difference in late lumen loss are poorly defined. It may be due to a generalised right shift in vessel healing after DES implantation. Alternatively, it may reflect distinctive underlying pathophysiological processes. Indeed, autopsy evidence and studies with intravascular imaging interrogation suggest that the development of *de novo* atherosclerosis

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– also known as neoatherosclerosis – within the implanted stent may be more frequent or occur earlier after DES implantation[11]. This can be mechanistically explained by the increased permeability of the neointima after DES as compared with bare metal stent implantation[12].

Against this background, in the current issue of AsiaIntervention, Flavia Belloni and colleagues investigate differences in characteristics and outcomes of patients with DES restenosis according to the time interval between stenting and presentation with restenosis[13].

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In the setting of a multicentre restenosis registry, 129 patients were studied, 61% of whom had early restenosis – defined as restenosis occurring within nine months – as compared to 39% with late restenosis occurring beyond this time point. Interestingly, the baseline characteristics of patients in both groups were quite similar; the single statistically significant difference – patient presentation at the time of initial stenting – must be cautiously interpreted due to the risks of multiple testing.

In a second step, the authors examined outcomes of patients treated for DES restenosis. Patients were treated with either repeat stenting with DES (60%) or angioplasty with drug-coated balloons (40%). This is in line with both evidence from clinical trials[14] and recommendations from clinical practice guidelines[15]. Here, three observations are noteworthy. First, no clear difference was observed in outcomes according to whether the restenosis was early or late. Second, diabetes mellitus was the only independent predictor of recurrent adverse events after repeat intervention. Further efforts at understanding the interaction between diabetes and restenosis are warranted, and investigation using novel techniques for the quantification of advanced glycosylation end products may be a fruitful approach[16]. Third, the overall outcomes after treatment for restenosis were less than satisfactory, with one in five patients having another adverse event during follow-up.

This latter finding is consistent with earlier reports, which show that DES restenosis, when it occurs, is a more challenging condition to treat compared with bare metal stent restenosis[17]. The reasons for this remain to be elucidated and should be the subject of future study. Two broad explanations may be proposed. First, it is possible that a subset of patients exhibits hyporesponsiveness to the drugs or hypersensivity to the polymer coatings used on DES[18]. This might trigger a more aggressive type of neointimal hyperplasia that is more challenging to treat. Second, differences in the general restenosis substrate may play a role, with tissue types more frequently found in DES restenosis – such as neoatherosclerosis – more resistant to treatment than classic neointimal hyperplasia. In both respects, in the present study, it would have been very interesting to have had some insight into the appearance of the restenotic tissue with intravascular imaging, ideally with high-resolution optical coherence tomography.

Overall, the findings of Belloni and colleagues shed light on the challenges that exist in relation to managing DES restenosis. The unsatisfactory outcomes of patients treated for DES restenosis represent a genuine unmet clinical need. The magnitude of the problem is likely to increase in the coming years as more and more patients are treated by transcatheter approaches. Real progress in clinical outcomes may require a three-pronged approach: better understanding of the specific pathophysiological processes at play, investigation of novel treatment approaches, both local and systemic, and tailoring of treatment to the individual patient based on the cause of restenosis and the characteristics of the neointimal tissue identified by intravascular imaging. We call on the community for a concerted effort to address this neglected issue.

Conflict of interest statement

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