Rev Esp Cardiol. 2018;71(8):606–607

Editorial

Predicting Recurrent Restenosis After Drug-eluting Balloon: A First Step Toward Personalized Treatment

Predicción de reestenosis recurrente tras angioplastia con balón farmacoactivo: un primer paso hacia el tratamiento personalizado

Raffaele Piccolo[a] and Philippe Kolh[b,*]

[a] Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy
[b] Department of Biomedical and Preclinical Sciences, University of Liège, CHU Sart Tilman, Liège, Belgium

Article history:
Available online 12 March 2018

In 2017, we celebrated the 40th anniversary of percutaneous coronary intervention (PCI), which currently represents the preferred revascularization method in most patients with obstructive coronary artery disease, although coronary artery bypass grafting remains indicated for patients with complex coronary artery disease and acceptable surgical risk.[1,2] However, despite continual progress for 4 decades in terms of safety and efficacy, there is no evidence proving eradication of restenosis after coronary stent implantation.[3] Indeed, in the largest registry of data on systematic surveillance angiography between 6 and 8 months, restenosis still occurred in about 12% of patients receiving new-generation drug-eluting stent (DES), even though the overall proportion has constantly decreased over time with the transition from bare-metal stents to early-generation and new-generation DES.[4] In addition to requiring an unplanned revascularization procedure and additional cost burden, restenosis may also increase the risk for death by more than 20% during long-term follow-up.[5] Out of more than a dozen strategies developed for the treatment of restenosis, spanning from coronary artery bypass grafting to bioresorbable vascular scaffolds,[6] the use of paclitaxel-eluting balloons (PEB) represents one of the most attractive options by delivering antiproliferative drugs at the site of neointimal hyperplasia and avoiding at the same time a second metallic layer indwelling in the coronary vessel.[7] Despite these potential advantages, PEB result in a slightly higher diameter stenosis, roughly 10%, at follow-up angiography when tested against repeat DES, which should be taken into account if one considers that a reduction in stent lumen diameter of 50% or more represents the threshold for defining angiographic restenosis.

In a recent article published in *Revista Española de Cardiología*, Cassese et al.[8] reported an individual patient-data analysis from 6 randomized trials that used PEB (SeQuent Please, B Braun, Melsungen, Germany) in their experimental arm. A total of 546 patients randomly allocated to PEB were pooled and about 89% underwent follow-up angiography between 6 and 9 months. The principal findings of the study were that recurrent restenosis was present in every fifth patient and that independent correlates of recurrent restenosis were lesion length (for every 5-mm increase in lesion length, there was a 58% higher risk for restenosis) and vessel diameter (for each 0.5-mm reduction in vessel diameter, the risk for restenosis increased by 42%).

How should we interpret the results from this brilliant analysis by Cassese et al.? First, the study indicates that 20.8% of patients treated with PEB will redevelop restenosis. While this means that only 2.4% of a general patient population undergoing PCI will experience recurrent restenosis, absolute estimates are striking. In fact, with an estimated population of 510 million in the European Union and 2300 PCI procedures performed per million inhabitants per year,[9] more than 50 000 patients per year are expected to experience recurrent restenosis in Europe alone. As a consequence, recurrent restenosis, while uncommon in relative terms, represents a clinically relevant issue in absolute numbers. In addition, these data may even be underestimated because pooled trials were performed by experienced operators with expertise in the treatment of restenosis. Second, long restenotic lesions and small vessel disease were identified as the 2 main risk factors for recurrent restenosis. These findings have important clinical implications for clinical practice and may provide the basis for a personalized approach to the initial treatment of restenosis. Indeed, PEB may be avoided in these 2 settings, which are also frequently intertwined, while the use of new-generation DES, representing the standard of care in PCI setting, may be preferred. In this respect, refinements in DES technology allowed the introduction of dedicated new-generation DES for small vessel disease with acceptable late loss and low rates of binary restenosis.[10,11] As such, a stent-based strategy can be pursued for vessels with reference diameter of 2.00 mm or more. This observation is also in keeping with the results of a network meta-analysis suggesting that DES provide better angiographic results than PEB in patients with small vessel disease.[12] If PEB remain the preferred option for long lesions or small vessel disease, then adequate lesion pretreatment with cutting or scoring balloons should be considered. In a randomized trial of 252 patients with DES restenosis, neointimal modification with scoring balloons moderately improved the efficacy of PEB by increasing diameter

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* Corresponding author: Department of Biomedical and Preclinical Sciences, University of Liège, Sart Tilman B 35, 4000 Liège, Belgium.
E-mail address: philippe.kolh@uliege.be (P. Kolh).

https://doi.org/10.1016/j.rec.2018.01.013

stenosis by about 5% and decreasing rates of restenosis by 14% at angiographic follow-up.[13]

In conclusion, the analysis by Cassese et al.[8] represents a crucial first step toward a personalized treatment of in-stent restenosis. The identification of lesion subsets less suitable for treatment with PEB is key in order to improve the algorithm of therapy for in-stent restenosis. Ultimately, it is interesting to highlight that none of the pooled studies had enough statistical power to assess correlates of recurrent restenosis. As such, the study is an example of how collaborative group policies and data sharing are relevant to improve knowledge on disease and treatments and, eventually, patients care.

CONFLICTS OF INTEREST

None declared.

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