Recurrent restenosis in drug-eluting stents: Still looking for the best treatment?

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This is a commentary on the article "Long-term outcomes following drug-eluting balloons vs. thin-strut drug-eluting stents for treatment of recurrent restenosis in drug-eluting stents" [1] published in this issue of the *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*). The article is a sub-analysis from the DEB-DRAGON registry that compared thin-strut drug-eluting stents (DES) vs. drug-eluting balloons (DEB) in treatment of recurrent in-stent restenosis (R-ISR). The authors showed in that sub-analysis that thin-strut DES were superior regarding the target vessel revascularization.

In-stent restenosis (ISR) is defined as angiographic diameter stenosis of more than 50% in the stented segment or 5 mm on either side of the stent. R-ISR is defined as new-diameter stenosis of more than 50% within 5 mm of the previously treated in-stent restenosis lesion [2] or, in other words, failure of at least two revascularization procedures in the same stent segment [3]. The prevalence of R-ISR is not clear, but the incidence of ISR range between 3%–20% according to different studies [4].

The mechanism of ISR can be classified into patient-related mechanisms, i.e. the presence of underlying calcification and vessel tortuosity, and operator-related, i.e. operator-related mechanisms, i.e. stent under-sizing or under deployment or inadequate lesion preparation [5, 6]. R-ISR is suggested to be due to exaggerated intimal hyperplasia.

Treatment of ISR is mentioned in the European Society of Cardiology (ESC) revascularization guidelines as follows "DES and DEB are equivalent in treatment of ISR (class I, level of evidence A)" [7]. But there is no clear mention of the R-ISR. The Waksman classification considered R-ISR as the type V restenosis, and coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) with a high-pressure balloon and intravascular brachytherapy or drug coated balloons (DCB) were the recommended treatment options [8].

The main advantage behind DEB is local drug delivery without potential hazards of adding new metal that may induce more inflammation and may initiate more restenosis in the newly deployed stent. Another theory postulates that DEB may allow for more room for negative remodeling and may prevent further restenosis [9]. On the other hand, thin-strut DES has an advantage mainly when the causes of ISR are mechanical, such as stent fracture. This dilemma explains why both options have the same level of evidence in the ESC guidelines [7].

Different studies assessed these different treatment modalities in both ISR and R-ISR, Alfonso et al. [10] may have been the first to assess the concept of R-ISR treatment in 21 patients all of whom were treated with further DES implantation. They showed a 90% 1-year survival rate, and only three patients had restenosis. In this small group, the authors showed good safety and relative long-term efficacy of DES in treatment of R-ISR. They also emphasized the importance of good lesion preparation as they reported residual waist after the third stent implantation in six patients even if the stent was inflated at high pressure.

Later, in 2013, Kubo et al. [11] compared the balloon angioplasty (BA) to DES implantation in treatment of R-ISR in which DES

showed marked superiority. A year later, in 2014, Clever et al. [12] tested using DEB in treatment of r-ISR even before it was available in Europe. They tested it in 28 lesions in patients for whom surgery was not an option, so they called the test a compassionate use of DEB (exploratory use, in our opinion), and DEB showed a good safety and efficacy profile as only 2 of 28 lesions required revascularization later on. "Compassionate" use was obvious, especially in the case of a 70-year-old woman, which they reported. The patient had a DES in a bare-metal stent (BMS) in the left anterior descending (LAD) coronary artery followed by DES in DES. Then she presented with another total occlusion of LAD, and due to the long segment of LAD r-ISR and previous multiple stents, CABG was not an option, so she was treated with 2 DEBs and her clinical follow-up was as she was doing very good with her daily activity.

Kawamoto et al. [3] compared DES and DEB in treatment of r-ISR, and they showed the superiority of DES only in the acute lumen gain after the procedure but similar clinical outcomes.

In the DEB-DRAGON registry [13] that compared long-term outcomes of thin struts DES vs. DEB in treating ISR, there was no significant difference in target lesion revascularization between the two treatment options. In clinical trials, for example, the RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloons vs. Everolimus-Eluting Stents) trial by Alfonso et al. [14], they compared everolimus-eluting stents (EES) and DEB in treatment of restenosis, and they showed the superiority of EES in preventing further revascularization.

These conflicting results leave laid the foundations for further research with stricter definitions, especially with regard to the concept of thin-strut DES! The authors in the article in the *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*) included new-generation DESs with different struts' thickness ranging from 60 µm to 80 µm. A comparison of such diverse types of DESs, with different thickness, would be interesting to look for how the difference in strut thickness may affect the outcome.

The concept of using a different type of drug while choosing the DES platform to treat ISR was not consistently considered, and it may have a theoretical benefit. Standarization with either routine predilation with complaint balloons or non-compliant balloons may be limited by the type of the study being retrospective — but lesion preparation techniques may also affect the outcome.

Looking into the future with newly available methods that may help for better lesion preparation such as intravascular lithotripsy together with the newly available data from the peripheral intervention that showed the increased risk of death associated with the use of paclitaxel DEB in femoropopliteal artery intervention [15] highlight the importance of continuous research and advancement to find more effective ways to treat such complex group of patients.

Article information

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