

# Optimal interventional strategy for the treatment of coronary in-stent restenosis

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In-stent restenosis (ISR) has been an important issue in the era of percutaneous coronary intervention (PCI) since the first bare metal stent (BMS) was applied to clinical settings. BMS substantially reduces acute vessel closure and restenosis after PCI by attenuating early arterial recoil and contraction, two major limitations of plain old balloon angioplasty (POBA). Thereby, it has been considered as a major advancement over POBA. However, ISR caused by neointimal hyperplasia after stent implantation hampers the benefit of BMS by increasing the rate of target lesion revascularization (TLR) or target vessel revascularization (TVR). With the innovation of stent technology, drug-eluting stents (DES) designed to inhibit excessive neointimal growth was produced and anticipated to reduce the incidence of ISR. Indeed, the RAVEL trial (1), a double-blind randomized study comparing sirolimus-eluting stent with its non-coated counterpart, reported no restenosis in the sirolimus stent group, and 23.4% of the patient in the BMS group developed binary restenosis ( $P < 0.001$ ) at 6-month follow-up. Despite of these promising results, there's still a certain proportion of ISR occurring after DES implantation due to the expansion of indications for PCI to complex coronary lesions in high-risk patients. Meanwhile, the advent of DES brought new challenges for the interventional cardiologists, such as the higher rate of late stent thrombosis and more bleeding events due to prolonged duration of dual anti-platelet therapy (DAPT). According to the type of stents previously implanted, ISR is classified as BMS ISR and DES ISR. As the literature (2,3) mentioned, 20% to 53%

BMS ISR present as unstable angina and 3.5% to 20% as myocardial infarction (MI); The proportion of DES ISR manifesting as unstable angina and MI is 16% to 66% and 1% to 20% respectively. Given the clinical and prognostic importance of ISR, the debate on the optimal strategy to prevent and treat ISR is far from over.

The current treatment options for ISR include POBA, drug-eluting balloon (DEB), repeated DES implantation, radiation therapy and local drug delivery. Among these modalities, POBA, DEB and DES are widely studied. To date, the most appropriate therapeutic strategy for ISR remains poorly identified. In recent issue of *JACC: Cardiovascular Interventions*, Lee *et al.* (4) performed a network meta-analysis of 11 randomized, controlled trials, trying to comprehensively compare among POBA, DEB and DES for the treatment of ISR. Their study enrolled 11 RCTs including 2,059 patients with BMS ISR or DES ISR.

There are several important points of this meta-analysis. First, it showed that both DEB and DES are superior to POBA in the prevention of TLR or major adverse cardiovascular events (MACE). On angiographic outcome analysis, the rate of binary restenosis for DES or DEB is significantly lower than POBA. Second, the efficacy of DEB and DES is comparable, whereas in terms of safety, DEB showed a nonsignificantly lower risk of MI or all-cause mortality when compared with DES. Third, DEB had the highest probability of being ranked as the first treatment option for ISR with the lowest risk of TLR, MI, all-cause mortality and MACE. While, DES had the highest probability of being ranked as the second option for the

treatment of ISR in terms of TLR, all-cause mortality and MACE. In terms of MI, DES showed the lowest probability to reduce the risk of MI after treatment for ISR. Overall, these results are in agreement with our previous analyses that have compared DEB angioplasty with conventional balloon angioplasty or DES implantation for the treatment of coronary ISR (5,6).

Two factors should not be ignored when we interpret the results of this study. First, the trials enrolled in the analysis include two types of ISR population: BMS ISR and DES ISR. Can we simply compare the efficacy and safety of different treatment options without considering the type of ISR? A multicenter randomized trial (7) comparing DEB with POBA in patients with BMS ISR and DES ISR found that in DEB treated group, recurrent restenosis occurred in 1.1% of patients with BMS-ISR and in 9.1% of patients with DES ISR ( $P=0.04$ ). Late lumen loss was lower in patients with BMS ISR than in patients with DES ISR ( $0.05\pm 0.28$  vs.  $0.18\pm 0.38$  mm;  $P=0.03$ ). These results suggest that DES ISR is associated with poorer outcomes compared with BMS ISR. Therefore, it may not be appropriate to take BMS ISR and DES ISR as an undistinguished ISR population to compare different ISR treatment modalities. Second, DES studied in the enrolled trials includes sirolimus-eluting stent, paclitaxel-eluting stent and everolimus-eluting stent (EES). As we know, stents coated with different drugs have different properties with regard to the prevention and treatment of ISR. As Kastrati *et al.* (8) demonstrated in their randomized trials, sirolimus-eluting stent had an insignificantly lower rate of angiographic restenosis ( $P=0.19$ ) and a significantly lower rate of TVR ( $P=0.02$ ) compared with paclitaxel-eluting stent. Another clinical trial (9) comparing the efficacy of EES with that of DEB in patient with BMS-ISR revealed that both EES and DEB provide excellent clinical outcomes with a very low rate of clinical and angiographic recurrence. However, in late angiographic findings, EES was shown to be superior to DEB. For this reason, exclusively concluding DES as the second option for the treatment of ISR without considering the type of DES is likely to mislead real-world clinical practice, especially when the new generation stents are showing promising prospect in term of prevention and treatment of ISR (10,11).

It has been widely recognized that ISR and stent thrombosis are two major reasons for revascularization failure. Therefore, reducing the incidence of ISR after stent implantation without increasing the rate of late stent thrombosis has been a great challenge for today's

interventional cardiologists. As DES has developed from the first generation to the third generation, it is quite promising that the rate of ISR will be substantially reduced without compromising safety benefit. The SPIRIT trial and its subsequent trials (12,13) comparing the second generation stent EES with its bare metal counterpart and other DES demonstrated that EES was superior to its bare metal counterpart in terms of reducing ISR rate and was shown to have a significant advantage over the first generation stent PES with regard to TLR, combined cardiac endpoints and stent thrombosis. Recently, results from a multicenter Italian experience (11) revealed that the implantation of bioresorbable vascular scaffold for the treatment of coronary ISR is technically feasible and associated with favorable mid-term clinical results. As the technology of stents advances rapidly, evidence-based application of new generation DES to de novo coronary lesions may effectively prevent the occurrence of ISR in the age of the third generation DES. Choosing an optimal strategy when ISR occurred after stent implantation has been another great challenge facing interventional cardiologists. American College of Cardiology/American Heart Association/Society for Cardiovascular Intervention (ACCF/AHA/SCAI) guidelines for PCI (14) recommends BMS ISR to be treated by DES (class I, Level of evidence: A) and DES ISR by POBA, BMS or DES. However, the real-world clinical practice is far more complicated than what the guidelines recommend. A comprehensive consideration of previously implanted stent types, lesion types and patients' sensitivity and tolerance to DAPT should be made to determine the optimal therapeutic strategy for each individual patient.

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### Footnote

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