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In-stent restenosis: the gold standard has changed

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KEYWORDS

- in-stent restenosis
- drug-eluting balloon

Abstract

In-stent restenosis remains an important issue even in the drug-eluting stent (DES) era today. In recent years, drug-eluting balloons (DEB) have emerged as a potential alternative to the treatment of in-stent restenosis. Paclitaxel was identified as the primary drug for DEB because of its rapid uptake and prolonged retention. Non-stent-based local drug delivery using DEB maintains the antiproliferation properties of DES, but without the limitations of DES such as subacute stent thrombosis, stent fractures, prolonged antiplatelet therapy and more importantly, avoiding a "stent-in-a-stent" approach. The first major impact of drug-eluting balloon (DEB) in the management of bare metal instent restenosis was the "PACCOCATH ISR I" randomised trial, comparing the efficacy of drug-eluting balloon versus uncoated balloon. The six months angiographic results showed a binary restenosis of 5% and 4% MACE in the drug-eluting balloon group, compared with 43% binary restenosis and 31% MACE, in the uncoated balloon group (p=0.002 and 0.02). The second major DEB trial is the "PEPCAD II Trial", comparing the efficacy of the SeQuent Please DEB with the Taxus drug-eluting stent in the treatment of bare-metal stent instent restenosis. At 6-month follow-up, in-segment late lumen loss was 0.38±0.61 mm in the DES group versus 0.17±0.42mm (p=0.03) in the DEB group, resulting in a binary restenosis rate of 12/59 (20%) versus 4/57 (7%; p=0.06). At 12 months, MACE rates were 22% in the Taxus group and 9% in the DEB group (P=0.08). The TLR at 12 months was 15% in the Taxus group and 6% in the DEB group (p=0.15). Based on these two pivotal trials, the European Society of Cardiology Guidelines for Percutaneous Coronary Intervention (2010) recommended that DEB should be considered for the treatment of in-stent restenosis after prior bare-metal stent. This was accorded a class 2 IIa indication, with a level B evidence.

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Introduction

In-stent restenosis remains an important issue even in today's drug-eluting stent (DES) era. The mechanisms for DES in-stent restenosis are mainly divided into three major issues:

The first issue involves "biological factors" resulting from drug resistance, hypersensitivity and polymer toxicity.

The second major issue is due to "mechanical factors" secondary to stent fractures, polymer peeling and non-uniform drug appreciation.

The third major issue concerns "technical factors" such as stent under-expansion and incomplete stent coverage as a result of gaps between stents and geographic miss.

In-stent restenosis

The patterns of angiographic restenosis after bare-metal stent implantation had been previously described[1]. It was shown that the Mehran ISR class was an independent predictor of TLR, emphasising the prognostic relevance of angiographic features after stent failure. Mehran et al showed that at 1-year follow-up in patients undergoing percutaneous coronary intervention for bare-metal stent ISR, a significantly higher rate of TLR occurred with more complex levels of ISR classification (class I 19%, class II 35%, class III 50% and class IV 83%, p <0.0001).

Although restenosis is relatively uncommon after drug-eluting stent (DES) implantation, it can still affect a significant number of patients[2-5]. In-stent restenosis has been considered difficult to treat and these patients are at higher risk for recurrence[1,6]. Compared with brachytherapy, sirolimus-eluting stents and paclitaxel-eluting stents had been shown to result in superior clinical outcomes for treatment of restenosis within bare-metal stents (BMS)[7,8].

In DES in-stent restenosis, several registries and small randomised trials found no difference between sirolimus and paclitaxel stents for the prevention of a subsequent DES restenosis. The Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-stent Restenosis 2 (ISAR-DESIRE-2) study[9] randomised 450 patients with restenosis after sirolimus-eluting stenting to repeat stenting with sirolimus versus paclitaxel-eluting stents. Subsequent revascularisation rates were similar at 16.1% versus 14.6%, respectively (p=0.52). The angiographic binary restenosis was 19.0% with sirolimus-eluting stent group and 20.6% with paclitaxel-eluting stent group (p=0.69).

Lee et al[10] showed that the use of sirolimus-eluting stents for treatment of in-stent restenosis was effective, with a low incidence of re-restenosis and a favourable long-term outcome. Post-DES restenosis, however, was associated with poorer outcomes than post-BMS restenosis, suggesting that these two types of lesions have different biological responses after sirolimus-eluting stent implantation. Lee et al also showed in their study that despite the shorter lesion length, the MACE rate was also significantly higher in the post-DES than in the post-BMS restenosis group. These findings show that the DES "sandwich" technique for the treatment of DES restenosis was associated with a high risk of treatment failure, indicating that different approaches should be considered when restenosis occurs within a DES[11].

Drug-eluting balloon

In recent years, drug-eluting balloons (DEB) have emerged as a potential alternative to the treatment of in-stent restenosis. Paclitaxel was identified as the primary drug for DEB because of its rapid uptake and prolonged retention. Non-stent-based local drug delivery using DEB maintains the antiproliferation properties of DES[12,13], but without the limitations of DES such as subacute stent thrombosis, stent fractures and stent malapposition.

The advantages of DEB include: (a) homogeneous drug transfer to the entire vessel wall unlike stent based technology with non-homogeneous drug transfer; (b) rapid release of high concentrations of the drug sustained in the vessel wall; (c) the absence of polymer could decrease chronic inflammation and the trigger for late thrombosis; (d) the absence of a stent allows the artery's original anatomy to remain intact, notably in cases of bifurcation lesions stenting which can result in "stent jailing" of the side branch vessel and (e) with local drug delivery, dual antiplatelet therapy is required for only one month instead of one year in DES stent in stent approach for in-stent restenosis.

The first major impact of drug-eluting balloon (DEB) in the management of bare metal in-stent restenosis was reported by Scheller et al[14]. In the randomised, double-blind, multicentre Paclitaxel-Coated Balloon catheter for In-stent Restenosis (PACCOCATH ISR I) trial, 52 patients with a clinical evidence of stable or unstable angina and a single bare metal restenotic lesion in stented coronary artery were investigated. The primary endpoint was angiographic late lumen loss in-segment. Secondary endpoints included binary restenosis and major adverse cardiovascular events (MACE). Patients were randomly assigned to either paclitaxel-coated balloon (3 ug/mm^2) or uncoated catheter (Bavaria Medizin Technologie, Oberpfaffenhofen, Germany). At six months, the in-segment late lumen loss was significantly less in the coated balloon group (p=0.002). The coated balloon group had 5% binary restenosis and 4% MACE compared with 43% and 31% respectively, in the uncoated balloon group (p=0.002 and 0.02).

PACOCATH ISR I and II pooled data, after complete 2-year follow-up, confirmed these results[15]. A total of 108 patients were enrolled in both studies. At 1-year follow-up, the in-segment late lumen loss was 0.80 for the uncoated balloon group and 0.11 in the DEB group (p=0.001). The in-segment binary angiographic restenosis was 50% in the uncoated balloon group and 6% in the DEB group (p=0.001). Notably, the one year event free survival for the uncoated balloon group was 69% compared with 96% in the DEB group (p=0.01). The favourable DEB group results were sustained, even up to the two year follow-up, which showed a MACE of 11% in the DEB group and 46% in the uncoated balloon group (p=0.001).

PEPCAD II was a prospective, randomised, multicentre, 2-arm phase II pilot study[16]. The objectives were to examine the safety and efficacy of the SeQuent Please DEB in the treatment of bare-metal stent ISR in native coronary arteries for procedural success and preservation of vessel patency, compared with the Taxus DES. The primary endpoint was angiographic late loss at six months, and the secondary endpoints were procedural success (<30%), 6-month

binary restenosis rate, and MACE at one and three years. Ninety-seven percent of the patients treated, were in Mehran class I, II and III in-stent restenosis. At 6-month follow-up, in-segment late lumen loss was 0.38±0.61 mm in the DES group versus 0.17±0.42 mm (p=0.03) in the DEB group, resulting in a binary restenosis rate of 12/59 (20%) versus 4/57 (7%; p=0.06). At 12 months, MACE rates were 22% in the TAXUS group and 9% in the DEB group (p=0.08). The TLR at 12 months was 15% in the Taxus group and 6% in the DEB group (p=0.15). The one year event free survival showed a very favourable 90.9% in the DEB group and 78.5% in the Taxus group (p=0.08). The conclusion of the PEPCAD II ISR trial was that SeQuent Please DEB for treatment of bare-metal stent in-stent restenosis was safe and had a high procedural success. The SeQuent Please DEB was superior to the taxus stent in the treatment of bare-metal stent in-stent restenosis and avoided a "stent-in-stent" approach. More importantly, there was a reduction in the duration of dual antiplatelet therapy to one month in the DEB group compared to one year in the Taxus group.

Based on these two pivotal trials, the European Society of Cardiology Guidelines for Percutaneous Coronary Intervention (2010) recommended that DEB should be considered for the treatment of in-stent restenosis after prior bare-metal stent. This was accorded a class 2 IIa indication, with a level B evidence.[17]

Other emerging DEB, with preliminary data in the treatment of bare-metal in-stent restenosis are FreePac drug-eluting balloon (Invatec/Medtronic) and the PanteraLux DEB (Biotronik).

With regards to DEB in the treatment of DES in-stent restenosis, we still lack randomised trial data for its usage. Several trials involving the use of drug-eluting balloons in patients with DES in-stent restenosis, are currently conducted, to address this issue. Some of these trials are:

(1) ISAR DESIRE 3 trial[9] which will register 375 patients with limus-DES restenosis and randomised to three treatment arms; namely, 125 patients to taxus stents, 125 patients to paclitaxel balloons and 125 patients to uncoated balloons.

(2) The Valentines trial is an open label multicentre registry, involving 27 countries and recruited more than 300 patients with bare-metal stent and DES in-stent restenosis, treated with the DIOR paclitaxel drug-eluting balloon (Eurocor). The recruitment was completed in Feb 2010 and results will be available in 2011.

(3) The RIBS IV trial is a multicentre Spanish randomised trial which will recruit 310 patients with DES in-stent restenosis and randomised 155 patients to SeQuent Please DEB and 155 patients to Everolimus-eluting stent. A six to nine month angiographic follow-up is planned, together with a 12 month clinical follow-up for MACE.

(4) The PEPCAD DES trial is a German multicentre randomised trial, recruiting 120 patients with DES in-stent restenosis. Sixty patients will be randomised to SeQuent Please DEB treatment and 60 patients to uncoated balloon.

Habara et al[18] reported the results of SeQuent Please DEB versus DES therapy in the treatment of 369 patients with 469 sirolimus-eluting stent in-stent restenosis lesions in Japan. The angiographic binary restenosis was 14.3% in the SeQuent Please group and 21.9% in the DES group (p=0.21). The TLR however, was 8.2% in the SeQuent Please group and 19.4% in the DES group (p=0.042).

Mathey et al[19] reported the German Consensus recommendation for in-stent restenosis treatment. Predilatation of ISR lesion should be first done with a conventional balloon shorter than the stent and 0.5mm size smaller than the reference vessel diameter. The balloon should be inflated at nominal pressure. This should be followed by a second conventional balloon, shorter than the stent, with a balloon vessel ratio of 0.8 to 1.0, and inflated up to 12-16 atmospheres. Depending on the outcome of the second balloon inflation, the choice of a DES or DEB is then made. If a major dissection is encountered, with a TIMI flow less than III, or a residual stenosis of 30%, than a DES should be deployed. No DEB should be used in this situation. If a good angiographic result is achieved, after the second balloon inflation in the predilatation of the ISR lesion, then DEB should be used to treat the ISR lesion. The DEB should extend 2 to 3 mm beyond the predilated area in order to avoid a geographic miss. The balloon vessel ratio should be 0.8 to 1.0 and DEB inflation kept at 8 atmospheres, for at least 30 seconds.

Clinical consideration and unresolved issues

There are several types of drug-eluting balloons available for percutaneous coronary intervention. Like drug-eluting stents, not all drug-eluting balloons are the same. Only drug-eluting balloons of proven clinical efficacy in randomised trials, should be used in clinical practice. The current recommendation from the ESC is for the use of drug-eluting balloons in bare-metal stent in-stent restenosis. The use of drug-eluting balloons in DES in-stent restenosis is still unresolved and we await the results of randomised trials to guide us in this issue in the not too distant future.

Conflict of interest statement

The author has no conflicts of interest to declare.

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