

In-stent restenosis: local drug delivery with a stent or balloon?

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The emergence of drug-eluting stents (DES) has led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents (BMS) (1). Consequently DES have become the preferred strategy in contemporary percutaneous coronary intervention (PCI) (2). Although rates of ISR are at historical low levels, optimal management remains an important issue as PCI for ISR is associated with a worse prognosis than *de novo* coronary interventions (3).

In this issue of *JACC Cardiovasc Interv*, Lee *et al.* attempt to identify the optimal management of ISR through their Bayesian network meta-analysis comparing local drug delivery, either with a stent or a balloon, and plain balloon angioplasty (POBA) for the treatment of ISR (4). Other treatments for ISR such as vascular brachytherapy, cutting balloon and rotational atherectomy were not included in this analysis.

An advantage of a network analysis is that it allows the authors to compare the effectiveness of DES, drug-eluting balloon (DEB) and POBA with each other, although only one trial compared the three arms directly. A traditional meta-analysis would not have allowed adequate assessment of the comparative effectiveness of the three treatment options. Further, it allows the treatments to be ranked in order of effectiveness.

In this analysis, 11 trials with 2,059 patients were included with a heterogeneous population of ISR of both BMS and DES. The primary endpoint was target lesion revascularisation (TLR), which emphasises a clinical rather than angiographic endpoint. This is relevant as the individual randomised controlled trials were not powered to detect a clinical difference.

Several findings have arisen from this meta-analysis.

Firstly, at 6-month follow-up, both DES and DEB were associated with lower risk of TLR than POBA. Compared to POBA, DEB treatment had an odds ratio of 0.22 (95% credible interval of 0.10-0.42) and DES treatment had an odds ratio of 0.24 (credible interval of 0.11-0.47). Second, when compared against each other the risk of TLR was similar between DEB and DES (odds ratio 0.92, 95% credible interval 0.43-1.9). Third, there was no significant difference between treatment arms in mortality or myocardial infarction, though both DES and DEB were superior to POBA in reducing major adverse cardiovascular events. Fourthly, DEB and DES were equivalent but superior to POBA in reducing the risk of binary stenosis ($\geq 50\%$ stenosis) on angiography follow-up at 6-9 months. Lastly, DEB has the highest probability of being ranked as the treatment of choice for ISR.

The results of this meta-analysis reinforce the latest international guidelines which give DES and DEB (without differentiation) a class I (level of evidence A) recommendation for the treatment of ISR (2). We believe the suggestion that DEB technology may be the preferred treatment option in ISR is premature. A network analysis can result in a coherent ranking of treatment strategies, however in Lee's analysis DEB and DES treatment could not be differentiated, even if DEB had a higher probability of being "ranked first".

We believe the technology of DEB should be named drug coated-balloon (DCB) since the balloons are not eluting drug, rather, they are coated with drug and the mechanism of action is different to DES. Theoretically the use of DEB technology in the treatment of ISR is appealing as an extra layer of stent is avoided and dual antiplatelet

duration may be shorter.

Second generation DES are the gold standard of contemporary PCI (5). The analysis included first generation DES like TAXUS that are inferior to second generation DES as was demonstrated in Ribs IV, a randomised trial showing superior clinical and angiographic outcomes in patients with ISR treated with everolimus-eluting stents compared to DEB (6). Two contemporary studies involving second-generation stents were not included in this analysis (7,8). Late catchup at 18 months was seen with the paclitaxel-coated balloon (8).

A recent published comprehensive network meta-analysis included the RIBS IV trial as well as therapies for ISR (9). It showed that POBA, vascular brachytherapy, rotational atherectomy and BMS were not suitable treatments for ISR. Furthermore, its conclusion was consistent recommending either DES or DEB for the management of ISR. However, these meta analyses are an exercise in statistics for a complex biological process mixing technologies and mechanistic situations. A heterogeneity array of studies may point to a wrong conclusion.

In summary, Lee's analysis adds evidence supporting the use of either DEB or DES for the management of ISR from previously inserted bare-metal or DES. With the thinner struts of second generation DES, most patients can be treated with a second DES; the DEB probably falls short. The BVS (bioabsorbable vascular stent) offers promise with the capability of eliminating the stent layer. We must await needed randomised trials to ascertain the optimal management of ISR.

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Footnote

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