

Letter: Paclitaxel- versus limus-coated balloons in the treatment of ISR



Anders Jonsson¹, MD; Keith G. Oldroyd^{1*}, MD; Xiang Chen², MEng

**Corresponding author: Biosensors Europe, Rue de Lausanne 29, 1110, Morges, Switzerland.*

E-mail: kgoldroyd@gmail.com

We congratulate Sagris et al on their meta-analysis of limus- versus paclitaxel-coated balloons (PCBs) in the treatment of in-stent restenosis.¹ In the discussion section, they state “...among the studies included in our analysis, it was only the REFORM trial that failed to show non-inferiority for angiographic outcomes for biolimus DCBs compared with PCBs. Possible factors explaining these discrepancies include the inclusion of both BMS and DES-ISR in the REFORM study, as well as variations in the quality and manufacturing process of the biolimus A9-coated balloon”.¹

We consider it extremely unlikely that “variations in the quality and manufacturing process of the biolimus A9-coated balloon” contributed to the failure of the REFORM trial² to meet its primary endpoint. We can confirm that the design of the 1st-generation biolimus A9-coated balloon (BCB; Biosensors International) tested in the REFORM study was extensively validated through design verifications, Good Laboratory Practice-compliant preclinical studies, and long-term shelf-life studies. This BCB’s robust routine manufacturing quality control included key attributes such as drug content, release profile, and coating uniformity; these were strictly evaluated to ensure consistency and to minimise variations in product performance. As outlined in the REFORM study manuscript,² a more plausible explanation for the failure to show non-inferiority for the primary endpoint of angiographic % diameter stenosis at 6 months was suboptimal drug transfer and/or tissue retention resulting in tissue levels of biolimus that were not therapeutic throughout the whole of the initial healing period following intervention. This, in turn, may have been related to the specific crystalline formulation of the drug/excipient matrix used in this 1st-generation BCB.²

The meta-analysis conducted by Sagris et al also included the BIO ASCEND ISR trial which tested a 2nd-generation

BCB against the same comparator as in the REFORM trial, namely the SeQuent Please NEO PCB (B. Braun).³ In this study, the 2nd-generation BCB was non-inferior to the PCB for the primary endpoint of late lumen loss at 9 months. Clinical outcomes were also equivalent and, based on this study, the device is now commercially available in China and several other countries in the Asia-Pacific region. The main design change in the 2nd-generation BCB was a modification of the manufacturing process that resulted in smaller crystals of biolimus with faster dissolution and an approximate doubling of the tissue concentrations of biolimus compared to the 1st-generation BCB. This highlights the critical role of drug excipients and coating formulations in determining the efficacy of drug-coated balloons. For the avoidance of doubt, the same rigorous quality control processes were employed for the 2nd-generation BCB as for the 1st-generation device.

Authors’ affiliations

1. Biosensors Europe, Morges, Switzerland; 2. Biosensors International, Singapore

Conflict of interest statement

A. Jonsson is a full-time employee of Biosensors Europe. K.G. Oldroyd is an external consultant for Biosensors Europe. X. Chen is a full-time employee of Biosensors International.

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