

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



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We would like to thank our colleagues for their interest and positive comments¹ on our meta-analysis, “Head-to-head comparison of limus-versus paclitaxel-coated balloons in the treatment of in-stent restenosis: a meta-analysis”,² which are both informative and encouraging for future research endeavours on the efficacy and safety of drug-coated balloons (DCBs). Considering the failure of the REFORM study (2025)³ to meet its primary non-inferiority endpoint, one plausible explanation for this finding may be the inclusion of both bare metal stent in-stent restenosis (BMS-ISR) and drug-eluting stent (DES)-ISR within the same analysis. It is now well recognised that DCBs may demonstrate different efficacy and safety profiles in these distinct clinical settings. BMS-ISR is typically characterised by more homogeneous neointimal tissue with greater smooth muscle cell density, a predominantly synthetic smooth muscle cell phenotype, more diffuse restenotic patterns, and relatively infrequent neoatherosclerosis. In contrast, DES-ISR is more commonly associated with hypocellular, proteoglycan-rich tissue, a predominantly contractile smooth muscle cell phenotype, more focal or stent-edge restenosis, and a higher prevalence of neoatherosclerosis.⁴ The DAEDALUS study (2020)⁵ also demonstrated that DCB angioplasty and repeat stenting with DES were similarly effective and safe in the treatment of BMS-ISR, whereas DCB angioplasty appeared less effective compared with DES implantation in the setting of DES-ISR. So, while suboptimal drug transfer has been proposed as a contributing factor, it may also be important to consider the potential impact of lesion heterogeneity, which could differentially influence treatment response and thereby affect the overall non-inferiority assessment.

We agree that suboptimal drug transfer is an important contributing factor. Regarding pharmacokinetics, paclitaxel

is highly lipophilic, achieving rapid tissue uptake and durable retention. However, concerns have been raised in light of the drug “flake-off” phenomenon during catheter transition and potential vascular inflammation, which remains a point of ongoing investigation regarding long-term vessel healing. Limus, on the other hand, is less lipophilic, resulting in slower tissue uptake and less durable retention. However, this is balanced by its favourable safety profile, including reduced vascular inflammation and better endothelial healing. The emerging option of biolimus A9 (Biosensors International) – a sirolimus derivative – presents enhanced lipophilicity compared to other limus agents, while retaining its rapamycin-inhibitory properties.² However, as our colleagues mentioned, the effectiveness of limus drug delivery is highly dependent on the balloon’s delivery system, requiring advanced coating technologies to ensure adequate drug delivery and retention.

We fully acknowledge the high level of rigour involved in the industrial development of the balloon platform, and we appreciate the detailed clarification provided regarding the comprehensive validation processes underpinning the 1st-generation biolimus A9-coated balloon. Variations in manufacturing highlight the differences in how the drug-device system is engineered to achieve effective transfer and retention within the vessel wall. As such, this multidimensional perspective may also help reconcile the differences observed in the REFORM study³ compared with BIO ASCEND ISR,⁶ where refinements in formulation and delivery technologies, along with the inclusion of more homogeneous patient populations and a larger sample size, appear to have contributed to improved outcomes. The 2nd-generation biolimus DCB is a very promising device, awaiting commercial availability in Europe as well.

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Conflict of interest statement

M. Sagris has no conflicts of interest to declare.

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