Editorial

Polymer-Free Drug-Eluting Stents – an inVEST(A)ment for the Future?

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Coronary stent thrombosis following stent implantation is best classified according to the time point post index intervention at which it occurs. Early stent thrombosis (< 28 days) is typically related to lesion and procedural characteristics as well as individual response to antiplatelet therapy and, aside from the increased complexity of treated lesions, its incidence is unlikely to be affected by the adoption of drug-eluting stent (DES) technology. Late stent thrombosis (>28 days), on the other hand, appears to be linked to a process of delayed arterial healing and its incidence may be related to the type of stent implanted. While the etiology of such delayed healing is multifactorial, the persistence of permanent polymer in the coronary milieu after its useful function (i.e. drug-release control) has been served may play a central role[1].

Against this background significant advances have already been realized in the development of DES platforms devoid of permanent polymer. The main challenge associated with these nascent stent technologies lies in the conservation of optimal antirestenotic efficacy – a process strongly related to the control of release kinetics of the active drug. Among potential approaches thus far explored are: (i) utilization of self-degrading biopolymer[2,3]; (ii) substitution for other more biocompatible vehicles for delaying drug-release (e.g. hydroxyapatite) (iii) employment of mechanical methods to enhance polymer-free loading and delay drug release (microporous stent surfaces, drug reservoirs)[4,5]; and (iv) compensation for some erosion of antirestenotic efficacy by incorporation of a second active drug targeted at an additional element of the restenotic response cascade (e.g. probucol[6], estrogen[7], pimecrolimus[8]).

The report of Chamié et al.[9] is the latest study to emerge from a research group that has been prominently involved in DES innovation since the inception of this technology. The VESTAsync stent described by the investigators is a notable addition to next generation DES devices. Of its 3 core components, both the stent backbone (thin-strut 316L stainless steel) and the active agent (sirolimus) are widely proven elements of contemporary DES platforms. The microporous hydroxyapatite nanocoating, on the other hand, is a novel stent constituent. Hydroxyapatite is a naturally occurring form of calcium apatite with the chemical formula $Ca_{10}(PO4)_6(OH)_2$. It comprises up to 70% of bone tissue, is a large component of tooth enamel and also plays a role in vascular calcification. It has extensively-proven biocompatibility in orthopedic and dental surgery. In addition to allowing drug-loading, it may also be associated with thromboresistant and anti-inflammatory effects[10]. While its role as a DES component seems promising, long-term experience with its use in vascular prosthetics remains limited. An additional noteworthy feature of the VESTAsync platform is the utilization of a substantially reduced sirolimus dose (55 μm/cm^2). While sirolimus is acknowledged to have a relatively wide therapeutic index, the usage of lower loading dosages might possibly facilitate improved re-endothelialization[11]. In actual fact, the release kinetics of a drug may be more important for efficacy than the total loading dose.

Specifically in terms of antirestenotic efficacy, the VESTAsync device seems to be associated with an early (4-month) mean late luminal loss (LLL) around 0.30 mm – which is in the range of that of the Taxus DES when consideration of the treated lesion characteristics is included[12]. This degree of LLL may be expected to be somewhat higher as lesion complexity increases[13]. In terms of comparison versus Cypher, the VESTAsync is associated with a lesser extent of neointimal hyperplasia suppression at both 4 and 12 months (though for reasons of small sample size the findings are not statistically significant). This is most likely related to less favorable sirolimus release-kinetics over the first 10 days (see Figure 4 of Chamié et al.[9]). Although the VESTAsync stent takes longer to discharge 80% of its

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drug-load (60 days as compared to 30 days with Cypher), half of the drug is released within the first 10 days. In the ISAR-TEST-3 randomized trial we experienced a similar phenomenon: a more rapid release of sirolimus in the first 10 days resulted in an inferior performance efficacy compared to the Cypher stent; whereas a retardation of sirolimus release (via the incorporation of a biodegradable polymer) resulted in a similar antirestenotic efficacy to Cypher (Figure 1)[2].

A degree of ongoing LLL beyond 4-months is seen with both stents. Although small in absolute terms such "late luminal creep" is nonetheless a consistent feature of DES technology – something not seen in the bare metal stent era. For example, in a large cohort of DES-treated patients with complex lesion morphology we found a mean *delayed* LLL of 0.12 mm between 6-8 months and 2 years[14]. This may be regarded as further indirect evidence of systematic delayed healing; persistent vessel wall inflammation is the central driving force behind ongoing neointimal hyperplasia. Of interest, in our study, this effect seemed attenuated in platforms devoid of durable polymer. The disconnect between angiographic LLL and the intravascular ultrasound parameter of percentage intimal hyperplasia obstruction (%IH) is also worthy of comment, though perhaps best interpreted in light of the recent report from the same authors suggesting late loss as a more accurate predictor of target lesion revascularization than %IH[15], as well as other reports suggesting only modest correlation between angiographic and intravascular measures of restenosis[16].

A number of limitations should be acknowledged in discussing the generalizability of the authors' current findings. Firstly, although the choice of the Cypher stent as comparator may be particularly apposite in view of its widely-proven excellent antirestenotic efficacy, the comparison is limited by its non-randomized nature and by the drawbacks inherent in the use of a historical control group. Secondly, the lesions studied may be regarded as typical "vanilla lesions" – i.e. non-complex coronary stenosis. The reported findings may be regarded as proof of efficacy under ideal settings rather than of clinical effectiveness in a real-world situation. Confirmation of antirestenotic efficacy in large numbers of patients with real-world lesion complexity will determine the role of this device in the future armamentarium of the interventional cardiologist. Thirdly, though long-term safety is the main motivation behind the development of a technology such as this, this report does not address this issue. The more interesting results will be those in larger patient cohorts with clinical follow-up beyond 2 years. Nevertheless, even allowing for a marginally lower suppression of neointimal hyperplasia with VESTAsync than the current market leaders, the potential trade-off in terms of enhanced long-term safety (and potentially a reduced duration of dual antiplatelet therapy) is attractive and

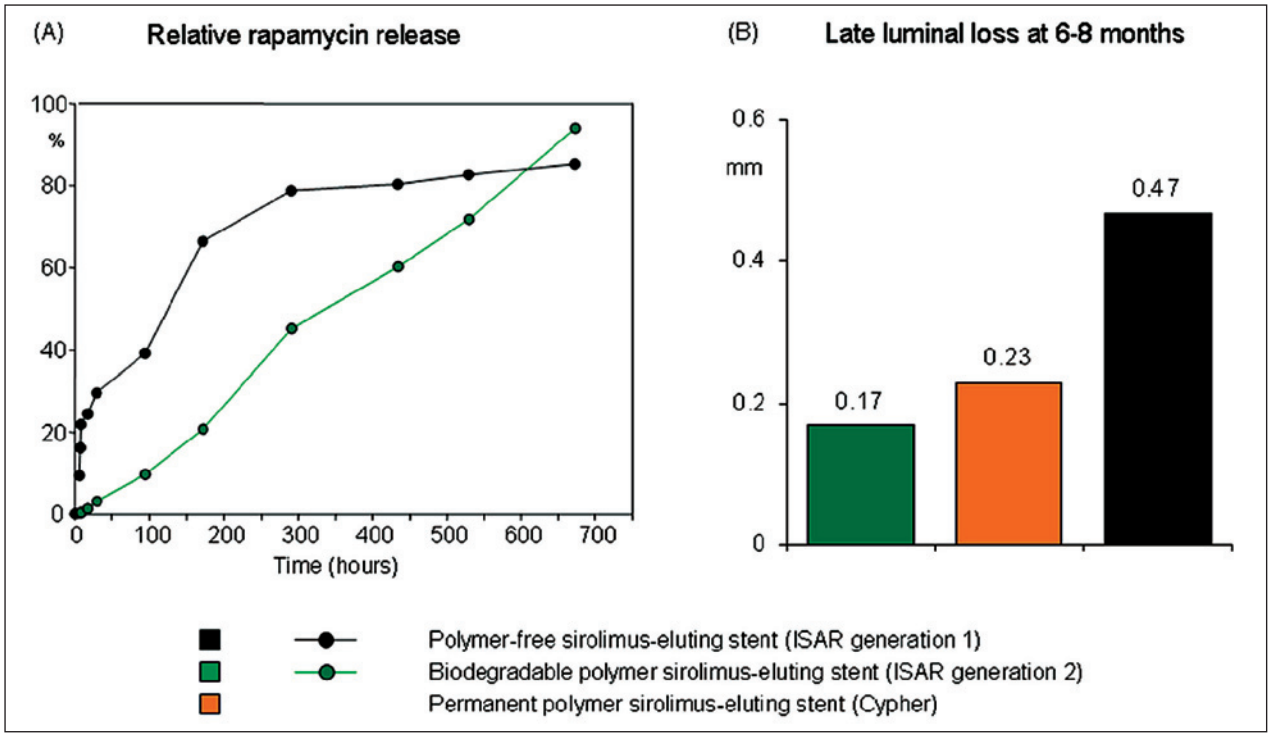

Figure 1 - Drug release kinetics and antirestenotic efficacy in the ISAR-TEST-3 study. A: Drug-elution curve of polymer-free and biodegradable polymer sirolimus-eluting stents. B: Antirestenotic efficacy of polymer-free and biodegradable polymer sirolimus-eluting stents compared with permanent polymer sirolimus-eluting stent.

may well prove preferable for both patients and physicians.

Drug-eluting stents are most certainly a *work-in-progress*. The higher antirestenotic efficacy associated with DES technology allows more room for maneuver in comparison with bare metal stents when it comes to refinements aimed at improving patient and operator outcomes. Although polymer-free platforms offer potential for improved safety outcomes as compared with first generation DES devices, there remain many more paths to be explored before we can be fully satisfied with contemporary stent technology.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare in respect to this manuscript.

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