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Sirolimus nanoparticles: (Delivering) a new hope in stentless percutaneous coronary intervention?

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Drug coated balloon (DCB)-only strategy is increasing adopted in coronary interventions due to its stent-free platform that provides several advantages over durable metallic stents. These include eliminating an additional layer of stent, minimizing the risk of late stent thrombosis and allowing for shorter duration of dual antiplatelet therapy. Current DCB usage is still limited to specific clinical settings such as in-stent restenosis (ISR) and small vessel disease (SVD). Most manufactured DCBs at present use paclitaxel, a potent antiproliferative drug that binds irreversibly to microtubules and exert local inhibitory effects on smooth muscle cell proliferation. [1] Paclitaxel is suitable for drug delivery and distribution by stent-free devices due to its highly lipophilic profile and tight binding properties to various cell constituents. Even though clinical trials showed acceptable efficacy and safety outcomes among paclitaxel coated balloons (PCB), we were still unable to demonstrate its superiority over drug eluting stents (DES). [2,3] Sirolimus, on the other hand, inhibits cell proliferation by binding to mammalian rapamycin and blocking the cell cycle at G1 and S phases. [4] Pre-clinical animal model testing using novel phospholipid encapsulated sirolimus nanocarriers coating on balloon-only catheter demonstrated efficient transfer of sirolimus to all layers of the vessel wall, achieving high tissue concentration of drugs that persisted for days after application. [5]

In this issue of *Cardiovascular Revascularization Medicine*, *Dani S.* et al. reported the 12-month clinical outcomes of the novel Magic Touch sirolimus-coated balloon (SCB) (Concept Medical Research Private Limited, India) for the treatment of de-novo coronary artery disease and ISR lesions in the Nanoluté registry. Sirolimus is encapsulated in nanocarriers and coated on the hydrophilic surface of the balloon. The nominal dose of sirolimus on a 3.00/15 mm balloon is 180 μg (~1.27 μg/mm^2). The device is available from 10 to 40 mm in length and from 1.50 to 4.00 mm in diameter. The Nanoluté registry is a single arm, prospective, multicentre, all-comers, post-market clinical registry that was conducted in India. The investigators enrolled 332 patients (356 lesions) treated with 394 SCB for stable coronary artery disease or acute coronary syndrome [ISR: 46.1%, SVD - defined as reference vessel diameter (RVD) <2.75 mm: 43.1%]. Primary endpoints were (i) procedural success and (ii) device-orientated adverse cardiac events [DOCE, defined as a composite of cardiac death, target lesion revascularization (TLR) and target vessel myocardial infarction (MI)] at 12 months. High rate of procedural success was obtained (99.7%), with bailout stenting required in only 6.6% of lesions. The overall DOCE and TLR rate at 12 months was commendably low at 4.2% and 3.6% despite high rates of diabetes mellitus (46.6%). However, the investigators combined both settings of ISR and SVD in the overall outcome analysis. There were 9 events reported in patients with ISR and 5 events in patients with de-novo CAD.

SCB may offer a new approach to the treatment of ISR besides the use of conventional plain balloon angioplasty, PCB or repeat stenting. The Virtue SCB (Caliber Therapeutics, New Hope, Pennsylvania) was studied recently in the SABRE trial (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis). [6] The study device delivers 12 μg/mm^2 of sirolimus nanoparticles concurrently with angioplasty through precise micropores in the balloon using a liquid formulation, and was able to maintain a therapeutic dose of 1 ng/mg of sirolimus through 28 days post procedure. It comes in 15–25 mm in length and 2.50–3.50 mm in diameter. The SABRE trial was a single arm, prospective, multicentre study that enrolled 50 patients with ISR that were successful predilatated with residual stenosis of ≤40%. Angiographic follow-up at 6 months showed in segment late lumen loss of 0.31 ± 0.52 mm that met superiority to historical plain balloon angioplasty. Target lesion failure and TLR rates at 12 months were both at 12.2%. Both the Nanoluté registry and SABRE trial were similar in that they were single arm studies with inherent limitations. As compared to the Nanoluté registry, SABRE trial had higher rates of target lesion failure and TLR, and most of the events occurred in patients treated for DES-ISR rather than bare metal stent (BMS) ISR. It was postulated that DES-ISR may be more challenging to treat and was associated with worse outcomes as compared to BMS-ISR. [7] Around half (46.1%) of patients in the Nanoluté registry were treated for ISR lesions but the investigators did not specify if the lesions were BMS- or DES-ISR. In the RIBS IV trial

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(Restenosis Intra-Stent of Drug-Eluting Stent: Drug Eluting Balloon vs. Everolimus-Eluting Stent), TLR at 12 months was significantly higher in PCB (13.0%) as compared to only 4.5% in everolimus DES in patients treated for DES-ISR, [8] with superior late angiographic results with DES treatment. Although these results suggest that the anti-restenotic properties of new generation DES may be more effective than PCBs, it may also indicate that PCBs are less effective in treating DES-ISR than BMS-ISR. In the RIBS V trial (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent) studying PCB versus everolimus DES in BMS-ISR, TLR at 12 months was only 6.0% in the PCB arm. [9] Unfortunately, the absence of a comparator treatment in the Nanoluté registry clouded by the lack of information on DES- or BMS-ISR subgroups treated does not allow us to draw any reasonable conclusion regarding SCB effect on ISR.

PCBs had consistently showed similar clinical outcomes as compared to first- and second-generation DES in the treatment of SVD. The BELLO trial (Balloon Elution and Late Loss Optimization) reported low TLR (4.4%) and major adverse cardiovascular events (MACE, 7.8%) rates at 6 months in patients treated with PCB, outcomes that were comparable with first generation paclitaxel DES. [2] The recently published BASKET-SMALL 2 study (Basel Kosten Effektivitäts Trial – Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions) found that PCB was non-inferior to paclitaxel DES and second-generation everolimus DES with MACE rate of 7.3% at 12 months. [10] Even in very small vessel disease (vessel diameter 2.0 mm), PCB consistently showed similar outcomes as contemporary DES (PCB 12-month TLF: 7.0%, TLR: 4.7%). [11] In the Nanoluté registry, investigators considered a diameter of <2.75 mm as SVD, which may not be uniformly accepted. The mean device diameter for the overall cohort was 2.69 ± 0.45 mm but the mean vessel diameter and device diameter for patients in the SVD group were not reported in the study. There is still considerable variability in current clinical trials in defining what is SVD. The BELLO trial defined SVD as vessel diameter of <2.8 mm, whereas the BASKET-SMALL 2 used a reference vessel diameter of <3.0 mm. Because of the poorer performance of DCBs in larger vessels, a vessel diameter < 2.5 mm may be a better threshold to define SVD and should be used as a standard cut-off value in studies. [12] Moreover, with SVD, ischemia may remain clinically silent due to the limited amount of myocardium supplied. As there was no routine angiographic follow up in the Nanoluté registry, this could have accounted for their low event rates.

Optimal lesion preparation is essential in using DCB as a treatment strategy. The German consensus group suggested proceeding with a DCB-only strategy if results were acceptable after pre-dilatation without major dissection and/or residual stenosis of >30%. [13] An earlier PICCOLETTO study had to be terminated prematurely due to higher incidence of major adverse cardiac events and angiographic restenosis in patients treated with PCB as compared to paclitaxel DES. Inadequate lesion preparation was proposed as a major factor accounting for the higher event rates in the PCB arm. [14] In the BELLO trial, pre-dilatation was performed almost routinely in the PCB group after randomization. In the Nanoluté registry, it is mandatory for all patients to undergo lesion pre-dilatation with either a semi-compliant or non-compliant balloon. However, patients could be excluded from receiving SCB in the first place if they were inadequately pre-dilated. In addition, due to the nature of the study (single arm, non-randomized), the type of devices used to treat the target lesions prior to enrolment into the registry was entirely up to the discretion of the primary operator, and this poses as serious selection bias. Another important consideration with the use of DCBs is the rates of bailout stenting. The Nanoluté registry and the SABRE trial reported much lower bailout stenting rates at 6.6% and 6.0% respectively compared to what was reported in prior DCB registries (of 6.0–36.5%). [15,16] The low DOCE rates in the Nanoluté registry could be in part attributed to the substantial experience of the operators with the use of DCBs as reflected by the low bailout stenting rates. Therefore, it is incredibly difficult to tease out the effect of the operator from the efficacy of the study device alone. In fact, more questions remained unanswered: was the low clinical event rate solely due to the efficacy of the novel sirolimus nanocarrier technology, or was it due to a combination of other factors including the skill of the operators, exclusion of difficult lesions that were not successfully pre-dilated, a broad definition of SVD, a higher proportion of BMS- rather than DES-ISR treated, or undetected subclinical ischemia in SVD?

Although the Nanoluté registry adds new evidence in the evolving DCB field, especially in the real-world setting, most DCB studies at present included small patient population with mixed lesions and short follow up duration. As more SCBs enter the market, will limus balloons using nanoparticle technology eventually take over the DCB realm dominated by paclitaxel much like the DES story? In order for that hope to emerge, the interventional community deserves more robust data beyond registries with adequately powered, multicentre, worldwide, randomized controlled trials against PCB and contemporary DES that may help to expand the role of DCBs beyond ISR and SVD.

References

[1] Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997;96:636–45.
[2] Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. J AmColl Cardiol 2012;60:2473–80.
[3] Loh JP, Waksman R. Paclitaxel drug-coated balloons: a review of current status and emerging applications in native coronary artery de novo lesions. J Am Coll Cardiol Interv 2012;5:1001–12.
[4] Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001;104:852–5.
[5] Lemos PA, Farooq V, Takimura CK, et al. Emerging technologies: polymer-free phospholipid encapsulated sirolimus nanocarriers for the controlled release of drug from astent-plus-balloon or a stand-alone balloon catheter. EuroIntervention 2013;9:148–56.
[6] Verheye S, Vrolix M, Kumsars I, et al. The SABRE trial (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis): angiographic results and 1-year clinical outcomes. J Am Coll Cardiol Interv 2017;10:2029–37.
[7] Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. J Am Coll Cardiol 2014;63:2659–73.
[8] Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). J Am Coll Cardiol 2014;63:1378–86.
[9] Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A prospective randomized trial of drugeluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. J Am Coll Cardiol 2015;66:23–33.
[10] Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease (BASKETSMALL 2): an open-label randomised non-inferiority trial. Lancet 2018;392:849–56.
[11] Sim HW, Ananthakrishna R, Chan SP, et al. Treatment of very small de novo coronary artery disease with 2.0 mm drug-coated balloons showed 1-year clinical outcome comparable with 2.0 mm drug-eluting stents. J Invasive Cardiol 2018;30:256–61.
[12] Serra A. Value of drug-coated balloons in small-vessel disease: have they come of age? JACC Cardiovasc Interv 2018;11:2393–5.
[13] Kleber FX, Rittger H, Bonaventura K, et al. Drugcoated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. Clin Res Cardiol 2013;102:785–97.
[14] Cortese B, Micheli A, Picchi A, et al. Paclitaxel coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICOLETTO study. Heart 2010;96:1291–6.
[15] Unverdorben M, Kleber FX, Heuer H, et al. Treatment of small coro-nary arteries with a paclitaxel-coated balloon catheter. Clin ResCardiol 2010;99:165–74.
[16] Zeymer U, Waliszewski M, Spiecker M, et al. Prospective 'real world' registry for the use of the 'PCB only' strategy in small vessel de novo lesions. Heart 2004;100:311–6.