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EDITORIAL COMMENT

Expanding the Role of Drug-Coated Balloons in Treating De Novo Coronary Artery Disease

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Technological innovations continue to improve percutaneous coronary interventions (PCIs). The introduction of stents alleviated the risk for elastic recoil and flow-limiting dissections after plain old balloon angioplasty. Subsequently, the development of stents coated with antiproliferative drugs such as paclitaxel and sirolimus resulted in a considerable reduction of in-stent restenosis. Nonetheless, in-stent restenosis after drug-eluting stent implantation still occurs in around 3% to 20% of patients depending on the population that is studied.[1] Therefore, drug-coated balloons have emerged as an effective alternative to drug-eluting stents for the treatment of in-stent restenosis and de novo small-vessel coronary artery disease.[2,3]

To be efficacious, a drug-coated balloon should have the following characteristics: 1) retain sufficient antiproliferative drug while being advanced to the bloodstream to the target lesion; 2) transfer an effective dose of antiproliferative drug to the tissue wall during a 30- to 60-second inflation period; and 3) the antiproliferative drug should then be retained in the vessel wall long enough to suppress neointimal hyperplasia. Drug-coated balloons incorporate an excipient that helps retain the drug on the balloon until it is inflated at the target site, where it facilitates drug delivery into the tissue. Most currently available drug-coated balloons are coated with paclitaxel. Paclitaxel is highly lipophilic and possesses potent antiproliferative properties making it effective in preventing neointimal proliferation. Nonetheless, differences in paclitaxel dose, the type of excipient used, and the process used to apply the coating to the balloon may have important implications for the efficacy of paclitaxel-coated balloons (PCBs).

A recent study comparing a sirolimus-coated balloon to an iopromide-based PCB in de novo small vessels failed to show noninferiority for the sirolimus-coated balloon in terms of 6-month net lumen gain, illustrating that there can be important differences in efficacy between different types of drug-coated balloons.[4] This study compared balloons coated with sirolimus against paclitaxel, but given the various intricate steps in manufacturing a drug-coated balloon, it cannot be taken for granted that there is a class effect with PCBs. Careful evaluation of the efficacy of novel drug-coated balloons even when coated with the same drug is therefore germane.

A novel shellac plus vitamin E excipient may offer an alternative to the commonly used iopromide-based PCBs. Vitamin E reduces plasminogen activator inhibitor-1, which is activated after local vascular injury caused by balloon inflation.[5] This prevents neointima formation, potentially reducing the risk for restenosis. Previously, this novel shellac plus vitamin E-based PCB has been found noninferior compared with an iopromide-based PCB for the treatment of in-stent restenosis,[6] but its efficacy in the treatment of de novo coronary artery disease has not yet been studied.

In this issue of *JACC: Asia*, Shin et al[7] report the quantitative angiographic outcomes of a randomized trial with a noninferiority design comparing 2 PCBs with different excipients (a shellac plus vitamin E-based PCB [Genoss Co Ltd] and an iopromide-based PCB [SeQuent Please NEO]). The studied population consisted of 204 patients with chronic coronary syndrome or stabilized acute coronary syndrome and de novo coronary artery disease, defined as a single lesion with more than 50% diameter stenosis. After

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successful predilation, patients were randomized 1:1 to undergo PCI with either of the 2 PCBs. Based on the study conclusions, the shellac plus vitamin E-based PCB demonstrated comparable angiographic outcomes to the reference iopromide-based PCB. The late lumen loss at 6 months did not significantly differ between the 2 PCBs (0.06 ± 0.38 mm with the shellac plus vitamin E-based PCB vs 0.09 ± 0.36 mm for the iopromide-based PCB), and the complication rate in terms of dissections and bail-out stenting was comparable. Although not powered for clinical outcome, both PCBs demonstrated similar target vessel failure rates.

This trial is well-constructed with adequate power to demonstrate noninferiority for the angiographic outcome of late lumen loss, including a reasonable noninferiority margin of 0.15 mm, and with blinded assessment of angiographic endpoints. However, results should be interpreted in the light of certain considerations. First, the study was powered to demonstrate angiographic noninferiority, but the sample size and follow-up period are too small to draw conclusions on clinical outcomes. Second, the lesions included in the study did not undergo hemodynamic testing and were treated based on visual estimation of a diameter stenosis of >50%. Including functional assessment of stenosis severity would allow for a better selection of patients who would benefit from PCI on functional outcome. Third, the study was limited to treatment of relatively straightforward lesions, with only a single lesion treated per patient, meaning that results cannot be directly extrapolated to more complex lesions. Fourth, the authors describe that acute lumen gain directly after balloon inflation is associated with net lumen gain after 6 months. This implies that adequate balloon angioplasty—the basis of drug-coated balloon treatment—is crucial in obtaining satisfying angiographic outcome at follow-up. However, intracoronary imaging was used in less than one-half of the patients. Imaging-guided drug-coated balloon treatment results in larger balloon diameters and higher inflation pressures, leading to higher acute lumen gain and lower late lumen loss.[8] Therefore, incorporating intracoronary imaging to guide PCB treatment could lead to better angiographic outcomes.

In general, the indications for drug-coated balloon treatment continue to expand. The novel shellac plus vitamin E-based PCB has now indicated adequate angiographic results for in-stent restenosis as well as de novo coronary artery disease. In addition to these established indications, the potential of PCBs extends to the treatment of nonobstructive vulnerable plaques, which pose an increased risk for future adverse cardiovascular events. A recent pilot study demonstrated that PCB treatment of vulnerable coronary plaques leads to plaque stabilization by reducing the lipid burden.[9] The use of a shellac plus vitamin E excipient in PCBs could have particular benefits in the prophylactic treatment of nonobstructive vulnerable plaques as the excipient might facilitate plaque stabilization, while the improved drug retention could allow more targeted therapy in these high-risk lesions. Further understanding into the mechanistic effects of this novel excipient on the arterial wall and endothelial function will be crucial in expanding its therapeutic potential.

In conclusion, this trial demonstrated comparable angiographic outcome of a novel shellac plus vitamin E-based PCB compared with the benchmark iopromide-based PCB for the treatment of de novo coronary artery disease. Future randomized studies will have to demonstrate noninferiority on clinical outcome and to explore additional treatment indications.

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