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EDITORIAL COMMENT

New Drug-Coated Balloons on the Horizon

The Quest for a Good Balance Between Safety and Efficacy*

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"It is the right means to choose, and not the excess or the defect, for the right means is as the right reason says."
—Aristotle, in Ethica Nicomachea[1]

The quest for the best treatment for patients with coronary artery disease (CAD) should nowadays consist of a holistic approach to the global atherosclerotic risk profile, instead of the search for the best device to treat 1 or more lesions. A perfect angioplasty in a stable patient will rarely affect their survival status if not corroborated with adequate lifestyle adjustments, tailored therapy, and clinical follow-up—waiting for the results of genetic modification studies.

Current guidelines and practices recommend the implantation of drug-eluting stents (DES) as the final treatment of significant CAD lesions, based on randomized clinical trials with persistent good clinical outcomes. However, one may argue that: 1) DES are associated with a remaining risk of target lesion failure, which never stops even after 10 years;[2] and 2) real-world CAD patients often suffer from diseases and lesion settings that are usually excluded from clinical trials, so the performance of a DES seems lower in this high-risk population.

During the past 15 years in Europe and Asia, a new therapy has emerged that delivers antirestenotic drugs on a balloon and avoids the implantation of permanent prostheses. Drug-coated balloons (DCBs) became available for patients with CAD and increased in use and popularity. Since their introduction, several trials have addressed their role compared with stents in defined lesion settings, including in-stent restenosis, small coronary vessels, and all-comer populations.[3,4] Unfortunately, only a minority of clinical trials could provide strong clinical evidence for the ubiquitous utilization of this device, and the field is marching toward randomized clinical trials to establish such comparisons.

So far, all European Community-approved DCBs have eluted either paclitaxel or sirolimus. Devices eluting paclitaxel are the most studied in both the coronary and the peripheral fields because they were the first to be invented with the ease of applying crystalline paclitaxel on balloon surfaces. The overall clinical performance of this class of devices is good, with a high safety profile and no harm signal in any study. However, some in vitro and animal studies have shown a cytotoxic effect of this drug on the tunica media of the vessel wall following direct application and a higher risk of distal embolization of particulates in benchtop models.[5]

On the other hand, sirolimus-eluting DCBs, which came into the market later, have a less robust clinical background. This drug, however, has a potent anti-inflammatory and antiproliferative effect with a larger therapeutic window and no cytotoxicity. Yet, some studies question its antirestenotic effect compared with paclitaxel-eluting DCBs, at least from an angiographic standpoint.[6] Another important aspect of drug coated balloon (DCB) technology is the need to carefully understand target lesions and prepare them before drug application to prevent clinical failures. Although this approach might be perceived as time-consuming and not widely adopted,

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especially in busy catheterization laboratories, the patient's benefit regarding clinical outcomes is of great value for preserving vessel vasomotricity and leaving nothing behind.[7] Last, more data are still needed on the performance of DCBs in the complex lesion setting, which is the current frontier of interventional cardiology and where the clinical research is heading.

With this background in mind, can we do more in the catheterization laboratory, especially for the sickest patients? Can we address complex coronary lesions without the need for long-term implants? And if so, which is the ideal drug to prevent recurrences? One path would be to start with devices that try to answer these questions and the challenges using well-designed animal studies. In this issue of *JACC: Basic to Translational Science*, Kawai et al[8] used a novel DCB that was coated with a synergistic low dose of paclitaxel and sirolimus in a novel formulation in which both the drugs were co-encapsulated into biodegradable nanoparticles (SirPlux Duo). SirPlux Duo encapsulates paclitaxel and sirolimus in a 1:9 ratio into nanoparticles that enable the sustained release of the 2 drugs. In the study by Kawai et al,[8] the dual-drug combination of SirPlux Duo DCB was evaluated using a complex study design, including in vitro cell culture assessment and in vivo animal vascular models with direct comparison with 2 commercially available paclitaxel-DCBs. The findings were quite interesting: 1) in vitro studies confirmed the synergistic effect of the 2 drugs, although at a lower level of paclitaxel; 2) SirPlux Duo exerted a more potent antiproliferative effect as compared with paclitaxel-DCBs, especially in the intima, along with lower injury scores in the media; and 3) downstream myocardium tissue injury was higher with paclitaxel-DCBs as compared with the study device.

The take-home message of this study is that if these data can be confirmed by human studies, we could consider an alternative to single-drug DCBs, using a device that elutes both drugs, taking the best from each one. The complexity of our patients/lesions deserves a more profound and balanced approach to finding the right tool for the right patient. A dual-drug combination with modern technology and drug dosages could overcome some limitations of currently available devices and define the path to overcoming an aggressive atherosclerotic burden.

This writer is not unaware of the concerns that have been voiced with respect to the adverse side effects of paclitaxel-coated balloons. However, the potential of the new SirPlux Duo technology to encapsulate paclitaxel within nanoparticles, theoretically lowering the risk of paclitaxel crystal embolization, is a potentially important advance. Moreover, the paclitaxel on this device is loaded on the balloon at a lower concentration, which appears to be sufficient to inhibit smooth muscle cell proliferation, possibly potentiated by the synergistic effect of sirolimus. We are not sure whether the SirPlux Duo DCB will overcome the limitations of current DCB technologies, which will require additional testing in clinical studies. The ongoing first-in-human study will also shed light on the angiographic performance of the SirPlux Duo DCB in an atherosclerotic model, which will be an important second step toward a better understanding of the properties of the SirPlux Duo DCB.

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