



Paclitaxel Drug-Coated Balloons in Peripheral Artery Disease: Who's Trying to Shoot the Football Star?



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Over the last decade, the outcomes of endovascular treatment of peripheral artery disease (PAD) have improved significantly, and nowadays, percutaneous revascularization is recommended either as a consistent alternative to surgery, or even as first-line therapy, according to different guidelines [1,2]. Drug-coated balloons (DCB) are emerging as one of the most interesting therapeutic strategies in this setting.

Indeed, there are several different DCB marketed in Europe, and few of them in the US. The literature offers a significant amount of data on the short- and mid-term outcome of these devices, but a real comparison between them is not available yet. For this reason, reviews like the one by Shanmugasundaram and colleagues [3] are a useful tool to shed some light on this class of devices. This article offers a comprehensive and up-to-date review of the current "state of the art" on DCB for the treatment of PAD, covering all fields of application of this technology, from aorto-iliac to femoro-popliteal disease, both in native vessels and in-stent restenosis. The article covers both positive and negative outcomes of the main available studies. It provides also a dedicated section on the recommended procedural steps for a successful implantation [4], and it will certainly catch the interest of the reader who wants to better understand this technology.

On the other hand, it is important to highlight that the study is not a systematic review, as it lacks the methodology required by dedicated guidelines (i.e., PRISMA), and it does not provide any meta-analysis of reported data. This, normally, should be considered a major limitation of the paper. In this case, however, it offers the chance to highlight the current situation that research is living in this field.

In recent years, methodology of research has changed significantly. Even though historically the main aim of investigators was gathering large amounts of information, now this is no more a critical issue: data are abundant, and they are relatively easy to collect. The real added value relies in their quality and in their organization. A landmark of this change is the interest in the so-called "big data", which were considered a revolution in the early 2000s, while now interest has dropped significantly. In fact, a huge flow of unorganized data occurs when their

quality is uncertain. That's the added value of systematic reviews, and the reason of their appeal to editors.

However, what should be the main shortcoming of the paper turns out to be the index of the main issue affecting the field of percutaneous interventions for PAD, and probably of many fields of medicine: the need for standardization, obtained through well-conducted and well-designed studies, with well-defined population and endpoints, so that results may be comparable. Only when such a condition will be fulfilled, stronger recommendations will be possible, with a real improvement in patient care.

DCB are just an example of this issue. Indeed, multiple studies provided plenty of data on the performance of this class of devices, and nowadays there is general agreement that DCB achieve better outcomes than plain old balloon angioplasty, both in terms of long-term angiographic and clinical results, as patency rates, late lumen loss and rates of device-related events, respectively. This was confirmed by a meta-analysis published in 2016 [5]. Indirect comparisons with trials on stents suggest a similar performance [6], with the theoretical advance for DCB to avoid the permanent deployment of metal struts in highly flexible regions, which may increase the risk for stent fracture and restenosis. Thus, the European Society of Cardiology 2017 guidelines on the management and treatment of PAD [2] recommended the use of DCB with a level of evidence A (evidence supporting DES is rated B).

Nevertheless, trials had significant differences in terms of design, study population, and devices. Thus, some negative results were obtained in isolated trials: an increase in all-cause mortality with the In. Pact Admiral paclitaxel DCB (Medtronic, USA) in the IN.PACT SFA trial, which was judged as non device-related by the internal event adjudicating committee [7], or the increase in leg amputation rate with the In. Pact Amphirion DCB (Medtronic, USA) in the IN.PACT DEEP trial [8]. These unfavorable outcomes were ascribed to potential selection bias, procedural flaws or problems related to a specific device, which cannot be extended to the entire class.

Now, a smart reader may argue that only a few months ago, a meta-analysis [9] of 28 randomized trials (4663 patients) on the use of

paclitaxel-coated devices (including stents) for the treatment of femoro-popliteal PAD detected a significant increase in long-term all-cause mortality. This article created panic in the arena: some doctors refused to use these devices, with a few US hospitals exposing the poster "DCB-free cath lab"!

Notably, 3 trials, BASIL-3 (three arms, randomized, BMS vs. paclitaxel-coated balloon vs. paclitaxel-eluting stent for superficial femoral artery disease), and SWEDEPAD 1 and 2 (paclitaxel-coated balloon for the treatment of intermittent claudication and chronic limb ischemia, respectively), recently interrupted their enrollment until further investigations would shed light on this critical finding. Additionally, the US Food and Drug Administration has published a warning note on these devices.

How is it possible that two different reviews came to such divergent conclusions? It is a firm opinion of our group that the meta-analysis from Katsanos clearly suffers from severe methodological deficiencies that do not justify its title, conclusions, and the consequent behavior of some physicians and companies that considered paclitaxel one of the messengers of the devil. These flaws include the lack of patient-level data, the merging of DCB and stents and the lack of long-term data for most trials included (100% at 1 year, 43% at 2 years and only 10% at 4-5 years).

Moreover, earlier this year, at the Leipzig Interventional Course meeting (Leipzig, Germany) an independent patient-level study on the In.Pact DCB including 1980 patients showed no signs of late mortality increase with paclitaxel through 5 years, independently from the dosage of drug administered.

In the end, our position is to keep on using paclitaxel DCB in the peripheral arena due to consistent good outcomes at short- and long-term follow-up. However, we eagerly expect by physicians and companies involved in scientific research the following behavior: 1) to collect further patient-level analyses with all marketed devices, 2) to proceed with ongoing studies (it is of debatable ethicality to abruptly stop the enrollment without strong adverse evidence), and 3) to push for further improvement in the DCB technology, including the use of different carriers and drugs.

Meanwhile, this should be a lesson for everyone doing clinical research. Before putting devices on the market, long-term data and well-conducted clinical trials should be always pursued.

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